Phototherapy in the treatment of skin disease in Scotland

Original clinical research contributing to our knowledge of how best to administer UVB phototherapy as a treatment for psoriasis, and a description of the Scottish phototherapy audit (funded by the Clinical Resource and Audit Group of the Scottish Office).

A thesis submitted to the University of Glasgow for the degree of Doctor of Medicine (MD) by Robert Stewart Dawe, MB,ChB (Glasgow), MRCP(UK) in July, 2001.

Based on work carried out while based at the Photobiology Unit, Department of Dermatology, Ninewells Hospital and Medical School, Dundee.

Abstract

This thesis discusses some aspects of the use of ultraviolet rays to treat skin disease. The early history of dermatological phototherapy in Scotland is summarised as an introduction to the more recent developments described in a chapter on the Scottish phototherapy and photochemotherapy audit of 1996/1997 (funded by the Clinical Resource and Audit Group, the Scottish Office). This audit revealed some aspects of the phototherapy service that could be improved, and identified areas of particular importance for future research.

Following the audit, recommendations to guide those prescribing and administering phototherapy were produced. A major aim of the audit was to identify important aspects of phototherapy practice for which there was evidence on which to base recommendations, and where such evidence was not available, to identify areas for future research. Clinical audit cannot itself provide the evidence on which to base best practice, and this thesis contains original research designed to provide information on which we can answer three questions identified as important during the audit.

Firstly, what type of UVB phototherapy lamp is most effective: the narrow-band (311-313nm) TL-01 lamp, or the broad-band UVB lamp? Whereas the original studies designed to answer this question left some doubts, these studies being small, and having various other flaws, a meta-analysis conducted as part of this thesis gave a clear answer. TL-01 UVB is much more effective than broad-band UVB.

The second included study was a randomised, controlled study that has contributed to deciding the optimal treatment frequency for TL-01 UVB phototherapy of psoriasis. Although 5x weekly treatment cleared psoriasis slightly more quickly than 3x weekly treatment, the difference in speed of

clearance was too small to warrant the significantly greater frequency of acute erythema during treatment, and the greater number of exposures and dose required.

The final question, answered by a randomised, controlled trial, in conjunction with a systematic review of the previous literature, was: for chronic plaque psoriasis, is TL-01 UVB or psoralen-UVA photochemotherapy to be preferred? The study conducted for this thesis showed TL-01 UVB to be more effective. Heterogeneity in findings of the studies addressing this question highlighted the importance of the particular treatment regimens selected for comparison, but the overall conclusion was that TL-01 UVB is the first choice of these two therapies for patients presenting with moderately severe and severe chronic plaque psoriasis.

A series of recommendations based on review of the published literature, when appropriate incorporating the findings of the studies described in this thesis, were produced. This thesis, as a whole, illustrates aspects of the synergistic roles of clinical audit, systematic literature review, and original clinical research in strengthening the evidence base supporting clinical practice in phototherapy.

Author's declaration

I declare that I have personally performed the major part of the work relating to this thesis. My contribution to collaborative studies is described on the following pages (pages v and vi). Co-authors of, and other contributors to, collaborative studies are acknowledged in the list of accompanying reprints and photocopies (pages xix and xx), and under Acknowledgements (page vii). Publications arising from the work included in this thesis, and other publications referred to and directly related to the topics of this thesis, are attached at the end, and listed on pages xix and xx. I confirm that the entire thesis has not been previously published or submitted for any higher degree.

Robert S. Dawe

My contribution to collaborative studies

I was the primary author of all the studies included in this thesis, and wrote the thesis as a whole. Others contributed, particularly to the two clinical studies described in Chapter 4 and Chapter 5. I describe below my contribution to each of the main components to this thesis.

A brief history of dermatological phototherapy in Scotland (Chapter 1)
My contribution: sole author

The Scottish phototherapy and PUVA audit (Chapter 2)
My contribution: major involvement in planning how to conduct this; sole involvement in actual conduct of survey (visiting all participating centres personally and collecting data), and in graphical and statistical analyses, and interpretation of findings; wrote up the report, including recommendations (Chapter 6), myself (with advice from Professor J. Ferguson and Professor R.M. MacKie)

Meta-analysis of studies comparing narrow-band with broad-band UVB phototherapy for psoriasis
My contribution: sole author (conceived idea, designed study, conducted reviews and analysis, and wrote it up). Since, others have made helpful comments on this part of the thesis.

A comparison of 3x and 5x weekly TL-01 UVB phototherapy for chronic plaque psoriasis
My contribution: joint idea (with co-authors listed in citation of published report on Page xix) to perform study; major contribution to design; primary researcher on Ethics Committee submission (and later discussions with members of Ethics Committee performing a review of approved studies conducted in Tayside [acknowledged in T. Smith. *Ethics in medical research,*

Cambridge University Press, 1999]); shared with co-authors in patient recruitment, and conduct of assessments throughout study; personally performed all statistical analyses, including initial interpretation of findings, and wrote initial versions of abstract and paper.

A comparison of TL-01 UVB phototherapy and bath-PUVA for chronic plaque psoriasis

My contribution: joint idea (with co-authors listed in citation of published abstract on Page xix) to perform study; designed study; primary researcher on Ethics Committee submission; shared with co-authors in patient recruitment and assessments for first half of the study (I moved to work in Glasgow before completion of this phase of the study); personally performed all statistical analyses, including initial interpretation of findings, and wrote initial versions of abstract, and of submitted (not yet published) paper.

Development of recommendations for phototherapy practice (Chapter 6)

My contribution: review of literature; wrote first draft recommendations.

Overview of the roles of audit, research on the literature, clinical research, and guideline development in phototherapy (Chapter 7)

My contribution: all views expressed in this chapter are my own (but I hope shared by others). As a source of references to the 18th century history of evidence-based medicine I found the monograph by Ulrich Tröhler (Tröhler 2000) particularly helpful.

Acknowledgements

Professor J. Ferguson, Dundee, and Professor R.M. MacKie, Glasgow acted as advisers, and commented on sections of the thesis, and encouraged me to keep at it. Professor J. Ferguson provided the opportunities to conduct the studies included in this thesis.

I thank all the dermatologists, nurse phototherapists, and physiotherapists throughout Scotland who welcomed me to their departments for the audit (Chapter 2).

Every member of the Photobiology Unit involved in treating patients attending for phototherapy and PUVA contributed to the studies described. Amongst the nursing staff, S. Yule was involved in recruitment and assessments of participants in the clinical studies included, and assisted with audit data entry. R. Hodgson, senior nurse in the phototherapy unit, discussed many aspects of phototherapy and PUVA with me, and taught me much of what I know about the practical administration of phototherapy. Amongst the medical physics staff who contributed particularly to the studies described, and who supervised my learning how to measure cubicle irradiances consistently for the audit, are D. Watson and L. Fullerton. M. Hughes, dermatology department secretary, helped me in my struggles with computing technology.

The others who contributed to the clinical studies that form part of this thesis are acknowledged as authors of publications in the list of accompanying reprints and photocopies.

S. Twaddle, health economist, Glasgow, provided useful comment on my cost effectiveness assessments included in Chapter 2.

List of Contents

Chapter 3.   Evidence on which to base recommendations: a meta-analysis of controlled trials comparing narrow-band (TL-01) UVB with broad-band UVB for psoriasis

Chapter 6.   The Scottish phototherapy and PUVA audit: evidence-based recommendations

Chapter 7.   Discussion

List of Tables and Illustrations

List of Accompanying Reprints and Photocopies

Relevant publications are bound as an Appendix after the end of this thesis. They are listed below:

Publications based on studies forming major parts of this thesis:

Dawe RS, Wainwright NJ, Cameron H, Ferguson J. Narrow-band (TL-01) UVB phototherapy for chronic plaque psoriasis: 3x or 5x weekly treatment? *British Journal of Dermatology* 1998; **138**: 833-9.

Dawe RS, MacKie RM, Ferguson J. The Scottish phototherapy audit: the need for evidence-based guidelines? *British Journal of Dermatology* 1998; **139, Supplement 51**: 17.
(Abstract only. Report circulated to all centres participating in the audit; overview of this audit for publication in preparation)

Dawe RS, Cameron H, Yule S, Man I, Wainwright NJ, Ferguson J. A comparison of TL-01 UVB and bath-PUVA for chronic plaque psoriasis. *British Journal of Dermatology* 2000; **143, Supplement 57**: 15.
(Abstract only. A manuscript has been submitted, and is currently under editorial review)

Other relevant publications to which I have contributed significantly:

Dawe RS, Russell S, Ferguson J. Borrowing from museums and industry: two photoprotective devices [letter]. *Br J Dermatol* 1996; **135:** 1016-7.

Dawe RS, Ferguson J. Prolonged benefit following ultraviolet A phototherapy for solar urticaria. *British Journal of Dermatology* 1997; **137**: 144-8.

Cameron H, Dawe RS. Subcorneal pustular dermatosis (Sneddon-Wilkinson disease) treated with narrow-band (TL-01) UVB phototherapy. *British Journal of Dermatology* 1997; **137**: 150-1.

Dawe RS, Cameron H, Lowe JG. PUVA for diffuse cutaneous reticulohistiocytosis. *British Journal of Dermatology* 1998; **138**: 720-1.

Wainwright NJ, Dawe RS, Ferguson J. Narrow-band ultraviolet B (TL-01) phototherapy for psoriasis: which incremental regimen? *British Journal of Dermatology* 1998; **139**: 410-14.

Man I, Dawe RS, Ferguson J. Artificial hardening for polymorphic light eruption: practical points from ten years' experience. *Photodermatology Photoimmunology & Photomedicine* 1999; **15**: 96-9.

Cameron H, Dawe RS. Photosensitizing drugs may lower the narrow-band ultraviolet B (TL-01) minimal erythema dose. *British Journal of Dermatology* 2000; **142**: 389-90.

Clark C, Dawe RS, Evans AT, Lowe G, Ferguson J. Narrowband TL-01 phototherapy for patch-stage mycosis fungoides. *Archives of Dermatology* 2000; **136**: 748-52.

Abbreviations

BCC	Basal cell carcinoma
CI	Confidence interval
CRAG	Clinical Resource and Audit Group of the Scottish Office
MED	Minimal erythemal dose
5-MOP	5-methoxypsoralen
8-MOP	8-methoxypsoralen
MPD	Minimal phototoxic dose
MRA	Minimal residual activity (used to describe minimal disease persisting despite treatment, usually used of psoriasis)
NHS	National Health Service of United Kingdom
PLE	Polymorphic light eruption
PUVA	Psoralen-Ultraviolet A photochemotherapy
Re-PUVA	Combination therapy with systemic retinoids and PUVA
Re-TL-01	Combination therapy with systemic retinoids and TL-01
SCC	Squamous cell carcinoma (in this thesis refers to SCC of skin, unless otherwise qualified)
SIGN	Scottish Intercollegiate Guidelines Network
TL-01	Philips Lighting® "Tube lamp number 1": as there are no other 311 to 313 nm narrow-band UVB lamps available, "TL-01 phototherapy" is used as a synonym for "narrow-band (311 to 313nm) UVB phototherapy"
TMP	3'4'5' trimethoxypsoralen
UVA	Ultraviolet A
UVA I	Ultraviolet A 1, that is long-wavelength (340-400nm) UVA
UVB	Ultraviolet B

Preface

Over three thousand patients are treated, for a variety of skin diseases, with phototherapy in Scotland every year. This thesis includes clinical research and audit designed to improve the safety and effectiveness of this treatment.

The thesis starts with a historical review of phototherapy to treat skin disease. This includes a discussion of adverse effects, particularly skin cancer. Chapter 2 reports the survey of current phototherapy practice conducted during 1996 and 1997, as part of the Scottish phototherapy and PUVA (psoralen-ultraviolet A) photochemotherapy audit. The discussion of the audit findings is followed by Chapters 3, 4 and 5 which describe research conducted to answer important clinical questions concerning ultraviolet B (UVB) phototherapy and PUVA for psoriasis.

Chapter 3 is a meta-analysis of studies comparing narrow-band UVB with broad-band UVB for psoriasis. Chapter 4 is based on a study designed to ascertain the optimum frequency for narrow-band UVB phototherapy of chronic plaque psoriasis. Chapter 5 reports a study comparing the efficacy of PUVA with UVB as chronic plaque psoriasis treatments. These last two studies were designed to contribute to the evidence-base for guidelines designed to improve the Scottish phototherapy service.

Chapter 6 includes recommendations for phototherapy and PUVA use, based on findings of the survey of current practice (Chapter 2) and a review of published studies. The quality of evidence for each recommendation is assessed.

The concluding Chapters 7 and 8 discuss the contributions of both clinical audit and research towards improving the efficacy and safety of phototherapy and photochemotherapy. Some priority areas for future research are suggested.

Chapter 1

A history of phototherapy, with emphasis on its early use in Scotland; phototherapy and psoralen-UVA photochemotherapy (PUVA) for psoriasis; the realisation that PUVA is associated with a significantly increased risk of skin cancer; and the introduction of narrow-band (TL-01 fluorescent lamp) ultraviolet B. This forms the background to, and explains the reasons for, the Scottish phototherapy and photochemotherapy audit described in Chapter 2.

Introduction and definitions

Phototherapy, the therapeutic use of non-ionising electromagnetic radiation, includes treatment with several ultraviolet B (UVB), ultraviolet A (UVA), and visible light lamps. The term can also be used more broadly to include psoralen photochemotherapy, involving the administration of one of several available psoralens, followed by ultraviolet (usually UVA) irradiation.

Every year, more than 3000 Scottish patients receive a course of phototherapy for skin disease. Phototherapy is effective for controlling the common, chronic diseases psoriasis and atopic dermatitis. Patients with many other, less common, conditions also benefit. It is important that phototherapy is used appropriately. If it is not and, for example, an ultraviolet B (UVB) treatment regimen that is not optimally effective is used, the consequences are serious. Not only may individual patients needlessly continue to suffer from their disease, but also resources, otherwise available to treat others, are wasted. Additionally, how we use these treatments can influence the risk of adverse effects, including skin cancer.

A short history of ultraviolet phototherapy in Scotland

In 1895, Finsen first treated lupus vulgaris with artificial lamps, emitting predominantly UV-B wavelengths. Sunlight exposure had been prescribed for multifarious ailments since ancient times (Rollier 1923; Humphries 1926a) but the development and use of more reliable, artificial sources became possible following the introduction of public electricity supplies (Hedley 1896). Reliable lamps made it possible to experiment in the treatment of a diversity of diseases with lamps with differing characteristics (such as wavelengths emitted), and to compare the effects of different phototherapy regimens.

By 1902, localised treatment with the Finsen carbon-arc lamp was a recognised treatment for lupus vulgaris. Some Scottish patients requested referral to the Finsen Institute in Copenhagen, although (unlike the Danish patients whose treatment was government-funded) they had to pay (Clark 1901).[1] A year later Dr MacIntosh, Medical Electrician at the Western Infirmary in Glasgow, reported his experience of treating lupus vulgaris with a carbon arc lamp, obtained through funds donated by local industry in recognition of the centennial celebrations (MacKintosh 1902). Over the next 25 years artificial ultraviolet radiation was increasingly used for this and other indications, and a variety of lamps (different types of carbon-arc and mercury vapour lamp) became available in the major Scottish cities. In the absence of a national health service, there was little co-ordination in the introduction of phototherapy equipment. A variety of different lamps were used, some designed for phototherapy, and others initially used for other purposes such as street lighting (Percival 1982).[2]

Early phototherapy lamps

Lamps powered by mains electric current could then, as now, be divided into three main types: 1) incandescent lamps with a continuous solid connection between the electrodes, such as tungsten filament bulbs, 2) arc lamps in which

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1   "Your letter duly received, and I shall with pleasure tell you all I can about Finsen's, and the treatment here, ...
      "...in August we go to a new institution, money having been provided by the government now that the cure has proved more than an experiment. ..." (Extracts from a letter by a lupus vulgaris patient to her doctor in Dumfries.)

2   "Walker [then Professor of Dermatology in Edinburgh] and I then visited the Street Lighting Department [of Glasgow Corporation] and inspected some dismantled carbon arc street lamps, selected four which we thought were least dilapidated, agreed a price of £1 per lamp, arranged for them to be delivered to the Edinburgh Royal Infirmary...." (Recollections of a visit to Glasgow to attend a BMA meeting and to purchase lamps – probably in 1923 or 1924. The lamps were in use by the end of 1924.)

the unenclosed electrodes were separated, and 3) mercury vapour lamps in which the current passed through gaseous mercury held in a quartz chamber between two liquid mercury electrodes. For phototherapy, the latter two lamp types were used (Humphries 1926b; Rosewarne 1928a). Arc lamps differed according to the make-up of the carbons or irons used, and the length of the gap between electrodes. Arc lamps, particularly those with tungsten electrodes (Rosewarne 1928a; Burdon-Cooper et al. 1931), produced unpleasant fumes, but were possibly more effective than mercury vapour lamps, at least for lupus vulgaris (Aitken 1946). The fragile quartz cases of the early mercury vapour lamps tended to become dirty, and were expensive to replace when broken during cleaning. Most modern phototherapy sources are fluorescent lamps, which are mercury vapour lamps with a coating to the chamber which absorbs the radiation produced and re-emits it. The composition of this phosphor coating determines the wavelengths produced.

Indications

The report of a meeting of the Forfarshire Medical Association held in 1927, published in the British Medical Journal (Anonymous 1927b),[3] gives an idea of the diversity of conditions then treated with phototherapy. In a book written a few years later, Robert Aitken, Lecturer in Dermatology and Physician in Charge of the Dermatological Light Departments at Edinburgh Royal Infirmary and Leith General Hospital, described his experience of

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3   Dr Milln, Medical Electrician, reported that phototherapy worked well in skin conditions, especially carbuncles and furunculosis, for which the "results of ultra-violet radiation were almost uncanny". However, he warned: "Claims were being made for ultra-violet rays in almost all diseases, but it would be well to see that this most beneficial form of treatment did not fall into disrepute through exaggerated statements." Dr J. Hunter, Dundee's Chief Tuberculosis Officer, favoured open carbon arc therapy. Dr J.B. MacDonald, of Dundee Eastern Hospital, described his 6 months experience using a mercury vapour lamp for marasmus and rickets. Dr John Kinnear described what is, to the best of my knowledge, the first recorded use of an artificial ultraviolet source for prophylactic treatment of a photodermatosis, a case of "summer eruption due to sunlight cured by small doses of ultra-violet rays." Dr A.R. Moodie discussed ophthalmological uses.

phototherapy for many dermatological, and other, diseases (Aitken 1930a). Like others (Rasch 1926-27),[4] he warned against over-reliance upon phototherapy, and the tendency to uncritically accept anecdotal evidence of its efficacy.

Most agreed upon the value of phototherapy for lupus vulgaris (Hall 1925; Aitken 1930a), although there were differences of opinion regarding the most appropriate lamp (Sibley 1920; Sollux Company 1937). Many, including Whitfield (Whitfield 1907), regarded phototherapy as the treatment of choice, and preferable to X-rays.[5] Other dermatological indications included psoriasis, childhood dermatitis - perhaps particularly of flexural pattern (Cassie 1927) - pityriasis rosea, vitiligo and alopecia areata. A manual by a lamp-manufacturing company (Sollux Company 1937) lists multiple indications: including, amongst the other non-dermatological ones, agranulocytosis, common cold, diphtheria carriage, neurasthenia, miners' nystagmus, poliomyelitis and whooping cough. Aitken's handbook provides a more critical review, and he was particularly sceptical about its role in treating vitiligo, and also warned that, for alopecia areata, "to speak of it as a specific remedy is to show a lack of knowledge and experience of the disease" (Aitken 1930a).[6]

Phototherapy with carbon arc and mercury vapour lamps was used successfully to treat psoriasis, although some, including Rosewarne (Rosewarne 1928b), favoured using it in conjunction with X-rays. Aitken

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4   "The reason that we see so many of the harmful effects [of light on skin] is partly due to a mistaken conception of light therapy, for many people think that as much light as possible is good for all people and all diseases."

5   "Compared with the Finsen treatment, it may be said that it [X-ray therapy] is much less constantly successful, and when the eradication of the disease is secured, there is almost always left a peculiar, polished atrophy of the skin, often accompanied by the development of telangiectasis. The danger of causing necrotic changes and inflammation is much greater than with the Finsen method. ..."

6   Aitken on alopecia areata: "The disease is very capricious, and the last remedy – and the last doctor – always get the credit for the cure."

conducted a controlled trial (Aitken 1930a),[7] which confirmed the efficacy of twice-weekly carbon arc lamp treatment in some patients. Not all responded, however, and thick plaque disease proved particularly resistant.

Early concern about possible carcinogenicity

The possibility that phototherapy would increase the risk of future skin cancer development was considered in the 1920s. However, not all took this possibility seriously. A speaker at a talk at the Royal Society of Medicine in London stated that "the bogy of carcinoma as a sequel to ultra-violet treatment had been laid to rest by Dr Reyn and Dr Sequeira, both of whom stated that they had never seen such a case" (Anonymous 1927a).

Not everyone accepted this anecdotal evidence of safety and, in Edinburgh, Aitken was concerned by animal studies which showed mercury vapour lamp irradiation to be carcinogenic (Findlay 1928), and a case of multiple solar keratoses apparently induced by mercury vapour lamp treatment prescribed by an unqualified practitioner in Australia (Colquhoun 1927). He believed that lupus vulgaris patients might be at particular risk, because of the prolonged courses of treatments, usually administered daily, required. He favoured carbon arc lamps over mercury vapour lamps not only because of possible greater efficacy, but also because of his greater concern about the risks of adverse effects with mercury-vapour lamps (Aitken 1930b). With the choice of an appropriate "carbon" (which might be impregnated with iron, tungsten or other metal), carbon-arc lamps generally emitted relatively less of the shorter (ultraviolet C and UVB) wavelengths.

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7   "I have tested the effect of the radiations in several cases, smearing the one side of the body with ointment so as to prevent the rays acting on that side, the other side being left without any such protection. There was no doubt that the side receiving the radiations twice a week, with ordinary treatment on other days, paled more rapidly than the side receiving ordinary treatment only."

Phototherapy no longer the treatment of choice for lupus vulgaris

The introduction of calciferol treatment, followed by systemic antimicrobial chemotherapy for tuberculosis, led to the abandonment of phototherapy as the treatment of choice for lupus vulgaris. Also, tuberculosis, perhaps particularly of the skin, was becoming less common (Paul 1964). By the mid-1940s, there was a decline in academic medical interest in UVB phototherapy in Europe, reflected in a down-turn in the number of publications concerning its use for any indication. Phototherapy was still used, but increasingly administered by non-medically trained physical therapists, often working in isolation from those prescribing the treatment. At least one Scottish university hospital dermatology department phototherapy unit was closed some time between 1953 and 1966 (Percival 1982).

Increased interest in phototherapy for psoriasis

Ultraviolet B phototherapy was used for psoriasis in Europe since shortly after its widespread introduction, primarily for lupus vulgaris. However it was generally regarded as not particularly effective and, for this indication, many favoured radiotherapy if psoriasis required treatment other than tar or chrysarobine[8]. In the United States of America, where the introduction of UVB phototherapy was not driven by the needs of the many severely disabled lupus vulgaris patients in Europe, phototherapy was only introduced two decades after its wide availability in Europe. However, early interest in using UVB for psoriasis appears to have been greater in the USA. In particular, Alderson (Alderson 1923) was more enthusiastic than most of his European contemporaries about phototherapy (using a mercury vapour lamp) for this indication. In particular, he noted that his experience was that "recurrences are delayed longer" than after X-ray treatment. Goeckerman (Goeckerman

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[8] This was developed from Goa powder, and contained the active principal dithranol.

1931), who used adjunctive coal tar (in place of the salicylic acid ointment used by Alderson), also endorsed phototherapy for psoriasis. Combined tar and UVB therapy were widely used, and it was not until the 1970s (Petrozzi et al. 1978; le Vine et al. 1979; Eells et al. 1984) that the first controlled studies were conducted, and it was recognised that the tar component of Goeckerman's regimen was unnecessary for effective treatment.

Despite the more cautious reports on phototherapy for this indication from the United Kingdom, psoriasis became the main condition treated following the decline of the lupus vulgaris problem. It was not generally regarded as an especially effective treatment, and was often used in combination with other treatments, including X-rays and topical dithranol. In a report of his experience of setting up a psoriasis treatment centre in Leeds, Ingram (Ingram 1953) described a regimen, involving dithranol application and UVB, he considered effective. Later, a combination therapy based on Ingram's regimen was studied more carefully.

In an observer-masked, randomised controlled trial Bowers and colleagues at the Gloucester Royal Infirmary (Bowers et al. 1966) showed both dithranol and UVB separately to be more effective than controls presumed to have little, if any, therapeutic effect. The combination of these two effective treatments proved better than either alone. Tar baths, customarily prescribed as a preliminary to phototherapy, were not shown to offer any additional benefit. For the purposes of this study a suitable control for phototherapy had to be found. A glass filter preventing transmission of wavelengths longer than 320 nanometres (nm) was used, and this preliminary study confirmed that the UVB of the broad-spectrum (UVB, UVA and visible) output of all the phototherapy lamps then in use was the therapeutic portion. This was the first experimentally derived information on the therapeutic action spectrum for psoriasis.

The development of photochemotherapy

Photochemotherapy involves the interaction between ultraviolet radiation, usually UVA, and a photosensitising chemical, usually a psoralen (linear furocoumarin). The use of plants containing high psoralen concentrations, particularly *Psoralea corylifolea* (a Legume) and *Ammi majus* (an Umbillifer), for white patches on the skin (probably vitiligo) was described in ancient Indian and Egyptian texts (Mosher et al. 1991; Kopera 2000). This use of naturally occuring psoralens (which serve various functions in plants, including protection against leaf infections (Afek et al. 1995)),[9] with sunlight as the ultraviolet source, continues in areas where refined psoralens and artificial ultraviolet sources are unavailable.

In the 1940s, 8-methoxypsoralen (8-MOP) was isolated from Ammi majus by El Mofty (El Mofty 1948). This isolated psoralen was used, with the Sun as an ultraviolet source (El Mofty 1948; Lerner et al. 1953), and then with man-made ultraviolet sources (Parrish et al. 1976), to treat vitiligo.

In 1974, 8-MOP-ultraviolet A photochemotherapy (8-MOP PUVA) was found to be an effective treatment for psoriasis. Parrish et al (Parrish et al. 1974) showed, in a 21 patient paired comparison study, that 8-MOP PUVA was more effective than broad-band UVB at clearing chronic plaque psoriasis. Large multicentre studies in the United States of America (USA) (Melski et al. 1977; Anon. 1979) and Europe (Henseler et al. 1981) found clearance rates to be far higher (85% to 88%) than would be expected for untreated psoriasis, and similar to, or better than, clearance rates with other established therapies.

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[9]   Furocoumarins possess activity against various fungal pathogens, and some insect pests, of plants. The apparent paradox of increased psoralens in some damaged, unrooted plants (for which we would not expect any evolutionary advantage related to possession of endogenous anti-pathogenic substances) may be explained by the fact that psoralens can be break-down products of substances, such as marmesin, that may possess even higher fungicidal activity in the healthy plant.

The 16-centre USA study showed in a randomised, controlled comparison that, in Fitzpatrick skin phototype I to III patients (Gupta et al. 1987), twice-weekly was as effective as thrice-weekly treatment (Melski et al. 1977). Also, maintenance therapy was found to be of limited value. Maintenance PUVA frequencies of once weekly, once every fortnight, and once every 3 weeks were compared with no maintenance therapy. Even once weekly maintenance therapy did not prevent 50% of patients experiencing a flare of psoriasis within a year. The European multicentre study showed no benefit from routine maintenance therapy. This European regimen cleared psoriasis more quickly and with a mean cumulative UVA dose less than half of that recorded for the 16-centre USA study (Henseler et al. 1981). Caution is required in comparing UVA doses recorded in different centres even within one country, as was shown by the Scottish phototherapy and PUVA audit (described in Chapter 2), but this raised the suggestion that the European regimen might prove safer. The main differences between these regimens were the different treatment frequencies (4x weekly in Europe and 2x weekly in the USA), and the fact that most patients treated in the European multicentre study were given an individualised, minimal phototoxic dose-based starting dose instead of the sun-reactive skin type-based regimen used in the USA.

A UK study, which found a combination regimen of daily broad-band UVB, dithranol and tar to clear psoriasis more quickly than thrice weekly PUVA, with starting dose based on skin type, (Vella Briffa et al. 1978), showed PUVA maintenance therapy to be of value (Vella Briffa et al. 1981), although once-weekly maintenance treatment was of no greater value than continuing treatment once every 3 weeks. Following this, many centres in the UK did use maintenance therapy.

Photochemotherapy and skin cancer

A major concern with the use of PUVA is that it increases the risk of skin cancer development. Before its use to treat psoriasis, it was recognised to be mutagenic (Igali et al. 1970; Arlett 1973), and carcinogenic to mouse skin (Griffin 1959). None of the early reports on PUVA use for vitiligo described long-term follow-up to determine whether or not these patients were at increased risk of developing skin cancers. A randomised, double-blinded controlled trial was conducted in a group of patients with skin cancers in Texas to determine whether daily administration of 20mg 8-methoxypsoralen had a protective effect (MacDonald et al. 1963). Neither this study, nor a replicate study conducted in Australia (Hopkins et al. 1963), showed any effect on skin cancer incidence. The low dose of psoralen used in these trials appeared to have some effects: in the Texas study 42/86 8-MOP patients described "sunburn" episodes compared to 27/87 control patients. Follow-up was short (with the main end-point being number of new lesions over 12 months) and it is likely that any increased skin cancer risk might have been missed for this reason. Because of concern about the possibilty it would increase the risk of skin cancer development in humans, it was considered wise to carefully follow-up those treated with PUVA for psoriasis (Bridges 1978).

Follow-up of 1380 participants in the 16-centre USA study of PUVA for psoriasis showed a higher than expected incidence of squamous cell carcinoma of skin (Stern et al. 1984). Further follow-up showed a strong dose-reponse relationship for induction of squamous cell carcinoma, and that many of these were arising on sites not much exposed to sunlight (Stern et al. 1994). Other studies also found PUVA to be carcinogenic (Lobel et al. 1981; Bruynzeel et al. 1991; Chuang et al. 1992). Although the initial reports of other European authors (Henseler et al. 1984; Tanew et al. 1986) raised the possibility that the risk might only be associated with particular regimens, it

is likely that follow-up in those studies that did not find a definite increased risk was not sufficiently long, and not enough high-exposure patients were included, to detect the increased risk, which was even more apparent on meta-analysis of all the English language studies involving at least 150 patients and 5 years follow-up (Stern et al. 1998).

The increased risk of squamous carcinoma of the skin associated, probably causally, with PUVA treatment is not now in doubt. The possibility that PUVA also increases the risk of other cutaneous cancers, including malignant melanoma, has been raised (Stern et al. 1997; Lunder et al. 1998), but a causative association remains less certain.

Development of a new UVB source (TL-01 fluorescent lamps)

Despite concern about the risk of skin cancer with PUVA, and practical problems with its administration (which shall be discussed in Chapter 2), it was generally recognised as more effective than UVB (Kenicer et al. 1981; Williams 1991), and regarded as the second-line treatment of choice for psoriasis. A major change has occurred with the development of a new UVB phototherapy lamp.

Narrow-band (TL-01) phototherapy (**Figure 1.1**) was introduced in 1984, after therapeutic action spectrum studies suggested that it ought to clear psoriasis more effectively than broad-band UVB (Parrish et al. 1981). Initial use demonstrated that it could clear psoriasis (see **Figure 1.2** for example). Several studies published since its introduction concluded that TL-01 UV-B is indeed more effective than broad-band UV-B, and its use has greatly increased, replacing broad-band UV-B in many centres throughout Europe (Bilsland et al. 1997). Chapter 3 of this thesis describes a meta-analysis of studies designed

to compare the efficacy of TL-01 UVB and broad-band UVB as treatments for psoriasis.

Reasons for the Scottish phototherapy and PUVA audit

In 1991 when the first national survey of PUVA use in Scotland was conducted, and recommendations produced, PUVA was regarded as the second-line treatment of choice for moderately severe and severe psoriasis. Evidence of its association with skin cancer development was concerning. It was largely because of this concern that it was regarded as essential to assess how we were using this treatment.

The next survey of the audit (conducted in 1996 and 1997, and described in the following chapter) was designed to assess whether or not the recommendations of 1991 had been implemented. This time, with the new TL-01 UVB source available and increasingly used, it was decided to survey UVB (in dermatology and physiotherapy departments) as well as PUVA usage.

Figure 1.1 Relative spectral emission from the narrow-band TL-01 lamp (right) and a typical traditional broad-band UVB phototherapy lamp. (From Green et al. 1988).
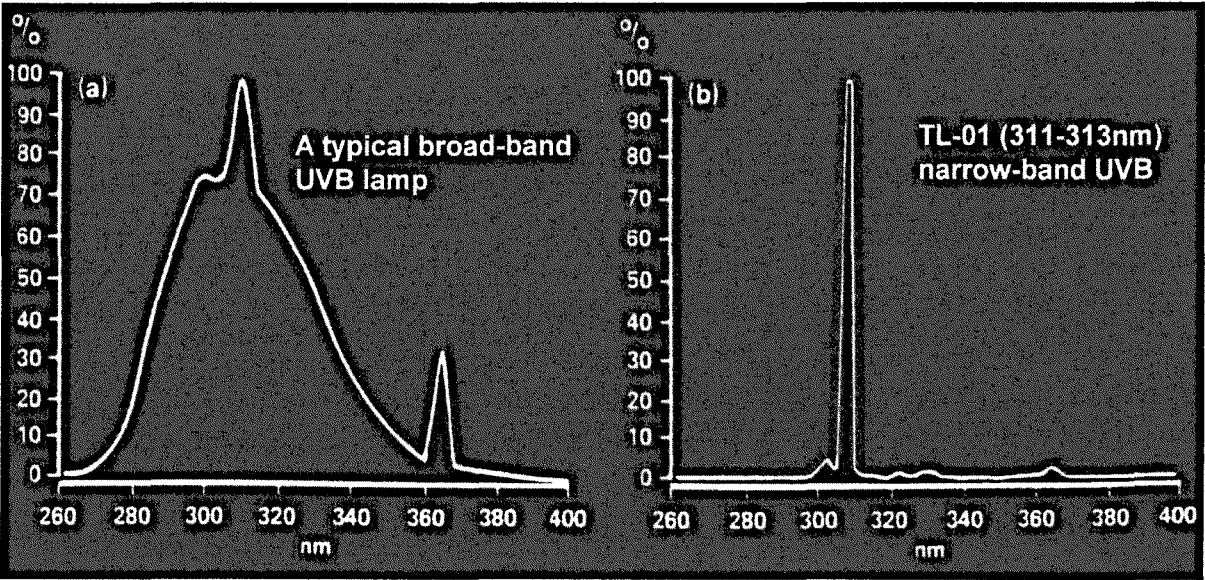
Figure 1.2　　An example of a patient with psoriasis treated with the new TL-01 UVB phototherapy lamps.

At start of treatment course

After 20 treatments

Chapter 2

The Scottish phototherapy and PUVA audit, funded by the Clinical Resource and Audit Group (CRAG) of the Scottish Office.

This Chapter summarises the main findings of the 1991 survey of PUVA use in Scotland (conducted by Dr W. Perkins), and the resulting recommendations. This is followed by a more detailed report of the 1996 to 1997 survey of both phototherapy and PUVA use in physiotherapy and dermatology departments.

The next phase of the audit cycle, the development of recommendations and their implementation will be discussed in Chapter 6, following one chapter describing a meta-analysis of previous studies comparing narrow-band and broad-band UVB for psoriasis, and two chapters describing studies conducted to fill gaps in our knowledge about how best to use phototherapy and PUVA noted during the survey.

The 1991 survey of PUVA practice

In 1991, Dr W. Perkins (then a trainee in dermatology in Glasgow) conducted a survey of PUVA use in Scotland. This first survey of practice, with resultant recommendations, was funded by the Clinical Resource and Audit Group (CRAG) of the Scottish Office department of health. The main findings and recommendations are summarised in **Table 2.1**. Members of the Scottish Dermatological Society discussed these recommendations. Following this initial phase of the Scottish phototherapy and PUVA audit, the Scottish PUVA users' group, consisting of consultants supervising PUVA and phototherapy in each centre, was established.

Regular meetings of the Scottish PUVA users' group were held to help update all members regarding developments in PUVA and phototherapy, and to assist implementation of the 1991 audit recommendations. In 1995 an annual national course for nurse phototherapists was established in Dundee, and has been held every year since. This was followed in 1997 by the photodermatology update course for dermatologists, another development to assist those prescribing and supervising phototherapy in keeping up-to-date, and to encourage the exchange of views and ideas.

Table 2.1

The 1991 Scottish PUVA Audit: main findings and recommendations of audit carried out by William Perkins

Findings

- Wide variation in UVA dosimetry (how meters used; how meters calibrated; which meters used)
- Few centres offer 5-MOP or bath PUVA
- UVA starting dose (for PUVA) only based on MPD in 3 centres
- Several centres customarily use maintenance therapy for psoriasis
- Increasing use of PUVA since 1975
- Limited availability in some geographical areas/ out of government office hours
- In only 9 of 20 centres, is UVB available at the same site as PUVA
- Permanent PUVA records kept in department in only 8 centres

Recommendations

- Named Consultant to oversee service in each centre
- Aim to extend availability
- Aim to have UVB and PUVA available at same site
- Records (PUVA & UVB) to be kept in departments with "risk factors" and cumulative exposures recorded; to allow
- Follow-up of patients regarded as at significantly increased risk of skin cancer as a result of treatment (patients with cumulative exposure to >150 PUVA treatments or >1000Jcm-2 UVA during PUVA)
- UVA metering throughout Scotland should be reviewed and standardised
- A range of psoralens should, ideally, be available in each centre
- Aim to base UVA starting dose on MPD

The 1996/1997 survey of phototherapy and PUVA practice

Survey Methods

- *Information on unit structure, process and outcomes were collected from all Scottish dermatology department phototherapy units and from physiotherapy department-based units. Information for each centre was collated on a structured questionnaire.*
- *UVA and TL-01 UVB dosimetry between centres was compared - cubicle outputs were measured in the same way with the same meters in centres visited.*
- *Data were analysed graphically with, when appropriate, the use of statistical tests to determine the probability of chance accounting for findings of differences between groups.*

All dermatology departments in Scotland were invited to participate. A list of physiotherapy departmental heads was obtained from The Chartered Society of Physiotherapy Scottish Board, and all were written to, to find out who provided a phototherapy service.

Information on aspects of unit structure, process, and outcomes were collected by visiting all dermatology department phototherapy units, and a sample of physiotherapy units. Questionnaires were sent to the remainder of the physiotherapy phototherapy units. Information was collected in dermatology units by interview with appropriate staff (nursing, medical, medical physics) and by review of phototherapy and PUVA notes. Ninewells Hospital UVB (National Light® 1400 meter, spectroradiometrically calibrated against a bank of TL-01 lamps) and UVA (Waldmann® meter, calibrated according to Scottish PUVA dosimetry guidelines) meters were used, as in Ninewells Hospital, to measure stand-up irradiation cubicle outputs - to be compared with outputs used in each centre, and so allow comparison of dosimetry between centres.

At each visit, data were collected, and collated on a structured questionnaire form. It was important that it was a dermatologist (I had 3 years of post-

MRCP clinical training in dermatology, with particular experience in phototherapy and PUVA, when I started the audit) who personally visited each department. It is unlikely that a non-medically qualified audit officer would have been able to adapt the way information was collected in each centre sufficiently to learn as much from the phototherapy staff. Also, it is likely that the audit visits would have been met by some distrust if it was not clear that this was being done by someone whose interests were in patient care and clinical dermatology. Because of marked variation in how records were kept, and in the terminology used for different outcomes, a non-dermatologist would not have been able to obtain useful information from the notes review component of the survey in many centres. Information on unit structure (siting, staffing, equipment), process (treatment indications, phototherapy and PUVA methodology, patient follow-up arrangements) and outcomes (response to treatment and unwanted effects) was gathered. As outcomes, in particular, were recorded in different ways in different departments a coding system to grade outcomes, which could be applied in all centres, was used.[1]

After collection, data were entered onto a computer spreadsheet (Microsoft® Excel Version 5.0) before transfer to a statistics and graphics package (Intercooled Stata for Windows Release 5.0, Stata Corporation 1997) for analysis. Data were analysed graphically (Crombie et al. 1993), using box-whisker plots to examine between centre differences in variables such as number of treatments per course of UVB or PUVA. When appropriate the Mann-Whitney U test or the Kruskal-Wallis test for equality of populations was used to determine the probability that chance accounted for differences

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[1] Codes used when recording treatment course outcomes: 1) - clear/ minimal residual activity/ "much" or "greatly" improved/ ">90% clear"; 2) - moderate improvement/ "better" (but still disease, requiring other therapy); 3) - no better/ slight improvement only; 4) - condition for which UVB or PUVA prescribed worse (whether or not because of therapy); 5) - outcome of course not ascertainable from phototherapy unit notes; 6) - did not attend to complete course.

in values (for example, treatments per course for polymorphic light eruption) between centres (Altman 1991).

Participating Centres

All identified NHS hospital dermatology department phototherapy and PUVA units participated:

> Aberdeen Royal Infirmary & Woolmanhill Hospitals, Aberdeen; Crosshouse Hospital, Ayrshire; Dumfries and Galloway District General Hospital; Inverclyde Royal Hospital, Greenock; Monklands Hospital, Airdrie; Ninewells Hospital and Medical School, Dundee; Perth Royal Infirmary, Perth; Queen Margaret Hospital, Dunfermline; Raigmore Hospital, Inverness; Royal Alexandra Hospital, Paisley; Royal Infirmary, Glasgow; Royal Infirmary, Edinburgh; Southern General Hospital, Glasgow; Stirling Royal Infirmary; Stobhill Hospital, Glasgow; Stonehouse Hospital, Lanarkshire; Stranraer Hospital; Victoria Hospital, Kircaldy; Victoria Infirmary, Glasgow; and Western Infirmary, Glasgow.

Separate physiotherapy department phototherapy units in:

> Arbroath Infirmary; Blairgowrie; Borders General Hospital; Broadford; Dr Gray's Hospital, Elgin; Forfar Infirmary; Golspie; Haddington; Montrose Infirmary; Peterhead; Heathfield Hospital, Ayr; Raigmore Hospital, Inverness; St Johns Hospital, Howden; Stornoway; Stracathro District General Hospital, Brechin; Strathclyde Hospital, Motherwell; Thurso; Vale of Leven District General Hospital, Alexandria; and Wick.

also took part.

Numbers were randomly allocated to each centre for the presentation of results. This centre number (used in the graphs that follow later in this chapter) bears no relation to geographical location of centre or when it was visited, but the same number is used consistently for each centre.

All but one of the dermatology department units (that treated less than 20 patients each year and was only open when a clinic there is running) were visited. Records were available in all except two of the units visited. In one unit the records were kept in main hospital notes, so only a convenience sample of those notes most readily obtained by the unit secretary were reviewed. In another centre a random sample of 25% of the records was examined. For the other units an attempt was made to review all records, although in some it was not possible to examine those of patients currently attending. **Table 2.2** shows the total number of notes and documented treatment courses reviewed. Unless stated otherwise, as where estimates extrapolated from notes reviewed are given, figures based on the notes review component of this survey relate to notes actually examined, therefore underestimating the total numbers of courses and patients treated.

Eight physiotherapy departments were visited, and information was obtained from the other 10 listed above by letter, questionnaire, and telephone. Three other physiotherapy phototherapy departments were identified but did not respond to invitations to participate.

Table 2.2 Notes review

	PUVA	Broad-band UVB	TL-01 UVB
Notes reviewed:	2345	2561	3522
Documented treatment courses:	4531	3625	5499

Results

Dermatology department phototherapy & PUVA units: Structure

- *22 centres had whole-body PUVA facilities and 21/22 compared with 8/15 in 1992 provided UVB on the same site. 19 units offered TL-01 UVB.*

- *Since 1992, 8 new units had opened, and 5 had extended their opening hours to make treatment accessible to more patients. There were still patients in geographically remote areas who could not benefit from these treatments.*

- *Most dermatology department based PUVA/UVB units were within a dermatology outpatient department, treatment centre or ward. Two were in other wards but treatment was supervised by a dermatology nurse.*

- *Only 3 departments still used a combined UVB and PUVA cubicle: all others had separate cubicles for each treatment to allow shorter treatment times, and to minimise the risk of administering the wrong treatment.*

- *In 19 units treatment was administered by nursing staff. Level of staffing, and grade and experience of the nurse in charge, varied between units.*

- *Increasing numbers of UVB courses were administered each year. The number of PUVA courses per year had declined since 1994.*

- *In 1996, 1 in 1580 of the Scottish population completed a course of UVB and 1 in 8455 completed a course of PUVA. There was marked regional variation in the use of UVB and PUVA - it is probable that the number of courses administered yearly by most centres will continue to increase.*

Results

General overview

Twenty-two centres now have whole-body PUVA facilities, compared to fifteen in 1992 **(Figure 2.1)**. All but one (compared to only 8/15 in 1992) provided UVB phototherapy on the same site. In 1992 there were eight dermatology departments with whole-body, stand-up UVB phototherapy units. There were twenty-one units with such cabinets in 1997 **(Figure 2.2)**, with therapy administered by dermatology nurses except in three that were physiotherapy-run but worked closely with dermatology departments. Nineteen of these units had narrow-band (TL-01) UVB lamps, and another two fitted them within the year after this survey.

Patient accessibility of units

This depends on a variety of factors: geographical situation of unit, opening hours, patient's occupation and the local public transport system. Although few patients were known by staff to spend more than 2 hours travelling for each treatment visit, there were exceptions (particularly those dependent on ambulance transport in some areas). Also, in areas remote from the "local" phototherapy unit, there were patients known to medical and nursing staff who would be expected to benefit from phototherapy but who could not be offered it because of their inability to get to the unit. Some who cannot travel for treatment can be treated with inpatient phototherapy but this is not always practicable or appropriate. It is probable that there is more unmet need than those working in phototherapy and PUVA units are aware of. Patients may not seek attention because they are themselves aware that treatment cannot be offered locally. Although waiting list figures were not

specifically collected, some centres lacked the resources to provide treatment as rapidly as they would like: in one centre, in 1996, patients sometimes had to wait over 4 months after referral before starting UVB phototherapy. Other centres had a shorter (or non-existent) waiting list for UVB or PUVA, although patients might still have to wait many months from general practitioner referral before assessment in the outpatient clinic where UVB or PUVA could be prescribed.

Opening hours

Opening hours ranged from 3 hours twice a week to 16 hours seven days a week. Since the 1992 survey, five departments had extended their opening hours. The availability of treatment before and after office-working hours is of particular benefit to some employed patients who might otherwise have to take annual holiday or sick leave to attend. Such extension of opening hours is not, however, universally helpful. Whether or not it is appropriate depends on the area served. One unit, in an area with high unemployment, found little demand for early morning appointments when these were offered.

Siting of dermatology department-based PUVA/UVB units

Ten units were within a dermatology outpatient department or treatment centre, 5 within a combined ward/outpatient centre, 3 in a dermatology ward, and 2 in other wards (but with dermatology nurse supervision of treatments).

Figure 2.1

Whole-body PUVA Centres

1992 ●

New centres open by 1997 +

Figure 2.2

UVB Centres

Units with stand-up UVB cubicles, 1997 ●

Equipment

All but 3 departments used separate cubicles for UVB and PUVA, allowing greater numbers of patients to be treated than if a combined UVB/UVA unit were used, and minimising the risk of accidental administration of the wrong treatment. Eighteen departments offered hand and foot PUVA with separate UVA irradiation apparatus. Equipment in use in 1997 were Waldmann® cabinets (1000, 5000, 8001, 7001), Dixwell® cabinets, cabinets built by Ninewells Hospital Medical Physics department, Waldmann® PUVA 180 and 200 hand and foot/ scalp units, and various locally-built localised UVB treatment units. MPD and MED testing apparatus include locally-built units and (for MPDs) a sunbed and Waldmann PUVA 180 units. One department occasionally used localised high-dose UVA, for pre-tibial myxoedema and morphoea, using a metal halide source. All the other UVB and UVA sources used in dermatology (but not physiotherapy) departments were fluorescent lamps.

Staffing

In 19 departments therapy was administered by nursing staff: with regular staffing ranging from a department with an enrolled nurse a few hours per week to one with at least 2 fully trained nurses, including a G-grade charge nurse, working primarily in phototherapy/PUVA 50 hours a week. The phototherapy/PUVA unit staffing was impossible to determine in many centres, especially those based in a ward, because of the varying proportions of time devoted to other duties in between treating UVB and PUVA patients.

Trends in the use of PUVA and UVB phototherapy

Increasing numbers of UVB courses were being administered each year, and over the previous 3 years there appeared to have been a trend towards fewer courses of PUVA being administered (**Figure 2.3**). Some caution must be taken in looking at these figures as, until recently, many centres kept more detailed records of PUVA than of UVB treatment. Nevertheless, the trends shown in this figure could not be explained by changes in documentation alone. **Figure 2.4** shows the number of courses of UVB and PUVA for psoriasis at four centres that did keep comprehensive combined UVB and PUVA records over the preceding 3 years.

These trends towards greater use of UVB and less use of PUVA were apparent in 13 of the 16 units for which the relevant information was recorded.

Figure 2.3 Documented courses of UVB and PUVA per year (all conditions; all centres)
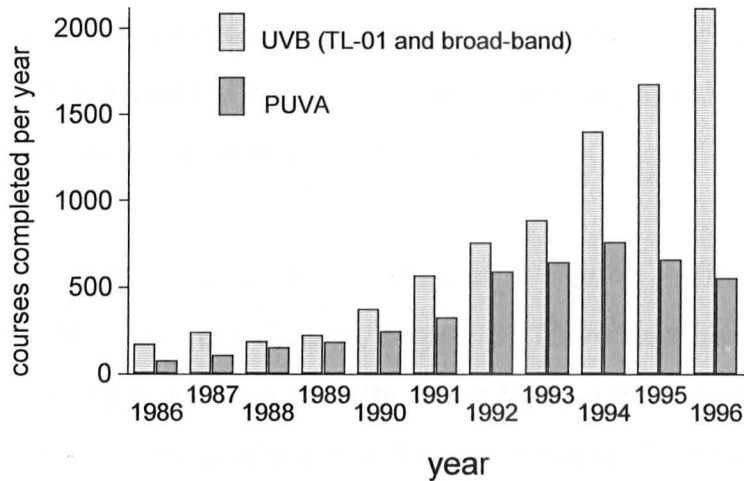
Figure 2.4 Documented courses of UVB and PUVA for psoriasis per year (4 centres with combined UVB and PUVA notes)
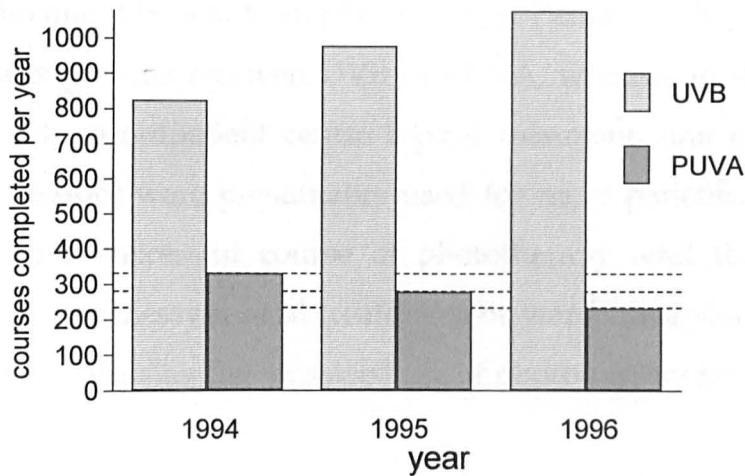
In 1996, 1 in 1580 of the Scottish population completed a course of ultraviolet B (TL-01 or broad-band) and 1 in 8455 completed a course of PUVA.[1] In 1992, 1 in 2825 completed a course of UVB and 1 in 7908 a course of PUVA. The proportion of the population receiving a course of UVB or PUVA varies from region to region. Estimated proportions for two regions (selected as regions in which most UVB and PUVA courses are given in a limited number of centres with good records) are shown in **Table 2.3**.

A far higher proportion of the population in Region A finished a course of UVB or PUVA each year than in Region B. There had been relatively little change in these proportions over the prior 5 years in Region A. In Region B, however, the proportion of the population receiving phototherapy and PUVA rapidly increased. Psoriasis, the main indication for phototherapy and PUVA, affects about 2% of the population (Williams 1997). If we estimate that 1 in 10 psoriasis patients are moderately or severely affected we arrive at a prevalence of 1 in 500 of the population with moderately severe or severe psoriasis who might benefit from phototherapy. Perhaps in Region A many of these psoriasis patients received UVB or PUVA, whereas in Region B other therapies (such as outpatient centre topical treatment, oral cytotoxics, and hospital admission) were presumably used for more patients. Patients who have received a successful course of phototherapy tend thereafter to be reluctant to accept messy topical treatments or ward admission. This may be one of the factors causing the increased use of phototherapy in many centres.

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[1] These figures are extrapolated from data collected during this survey - including estimated numbers for centres with incomplete records, inaccessible records or where only a sample of records were reviewed. Population figures used were taken from *Scottish Health Statistics 1992* and *Scottish Health Statistics 1996* (ISD, NHS Scotland).

Table 2.3   Proportion of the population receiving a course of UVB or PUVA in 2 Scottish regions in 1992 and in 1996.[2]

The estimated proportion of the population with psoriasis receiving each of these treatments is shown in brackets.

	UVB		PUVA	
	1992	1996	1992	1996
REGION A.	1/659 (1/37)	1/582 (1/24)	1/2057 (1/56)	1/2824 (1/98)
REGION B.	1/6118 (1/150)	1/2125 (1/52)	1/24471 (1/583)	1/12275 (1/433)

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[2]   Assumptions made in making these estimates: that each individual patient receives no more than 1 course per year (leading to a, probably small, over-estimation of numbers of patients treated) and that people are only treated in their own region of residence.

Figures in brackets refer to proportion of psoriasis population (assumed to be 2% of general population) treated - only courses documented to be for psoriasis as primary indication considered in these calculations.

National trends in PUVA and UVB use for a selection of conditions

- **Psoriasis remained the major indication for UVB and PUVA, but increasing numbers of UVB courses were given for other conditions, particularly atopic dermatitis and polymorphic light eruption.**

- **For most conditions there was a trend towards increased use of UVB and a decline in the use of PUVA. Palmo-plantar pustulosis was an exception, with a decline in UVB use after a peak in the number of courses for this indication in 1993, reflecting the impression that for this condition PUVA may be more effective.**

Psoriasis

Psoriasis was the main indication for these treatments. As expected a graph of courses per year for psoriasis alone **(Figure 2.5)** was similar to **Figure 2.3** (courses for all indications combined).

Atopic dermatitis

Ultraviolet B phototherapy was increasingly used for this indication **(Figure 2.6)**, although the numbers of patients treated were still few compared to those treated for psoriasis. Thirteen centres used phototherapy for atopic dermatitis and, although one department accounted for half the patients treated, 6 departments treated over 10 patients in 1996. Of 632 UVB courses for atopic dermatitis between 1992 and 1996, 396 were with narrow-band (TL-01) UVB and 236 with broad-band UVB lamps. In one centre, 15 patients were treated with UVA I (340-400nm ultraviolet A) monotherapy.

Figure 2.5 Documented courses of UVB and PUVA
for **psoriasis** per year (all centres)
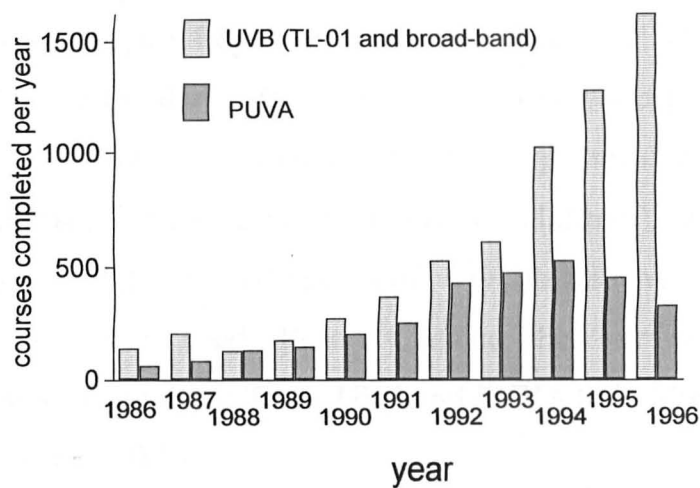
Figure 2.6 Documented courses of UVB and PUVA
for **atopic dermatitis** per year (all centres)
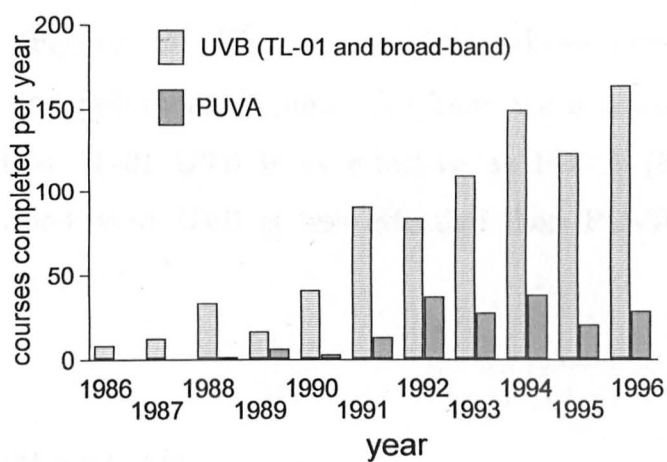
There is open study evidence for the efficacy of TL-01 UVB, broad-band UVB and PUVA for atopic dermatitis (Morison et al. 1978; Falk 1985; Atherton et al. 1988; Ekler et al. 1988; Jekler 1990; George et al. 1993a; Collins et al. 1995; Hudson-Peacock et al. 1996). Although a controlled comparative study has not been done many have the impression that TL-01 UVB is more effective, and less likely to "flare" dermatitis, than broad-band phototherapy. Because of concerns about adverse effects (particularly considering that many atopic dermatitis patients requiring treatment are children), and in the absence of any evidence that it possessed any advantages over UVB phototherapy, PUVA was rarely used. Recently, since this survey was conducted, a controlled study showed TL-01 UVB and PUVA to be similarly effective (Der-Petrossian et al. 2000).

Polymorphic light eruption (PLE)

Increasing numbers were treated with UVB, mainly TL-01 UVB, for this indication (**Figure 2.7**). This suggests that those prescribing prophylactic treatment for polymorphic light eruption were aware of the published evidence that TL-01 UVB is as effective as PUVA (Bilsland et al. 1993), whereas broad-band UVB is less effective than PUVA (Addo et al. 1987; Murphy et al. 1987).

Palmo-plantar pustulosis

For this condition (**Figure 2.8**) the trend was towards increasing numbers of courses of PUVA each year. Although 5 centres had used UVB for this

Figure 2.7 Documented courses of UVB and PUVA for **polymorphic light eruption** per year (all centres)
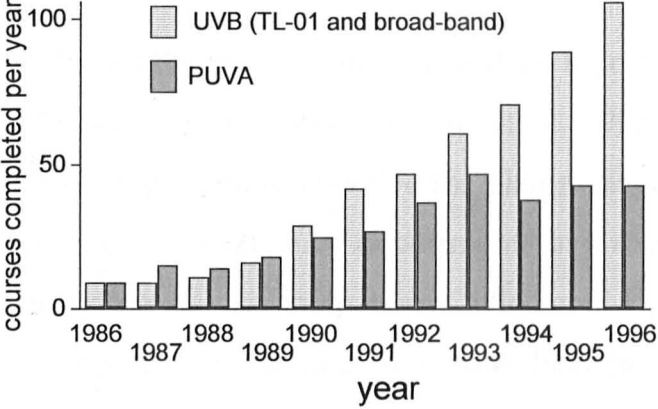
Figure 2.8 Documented courses of UVB and PUVA for **palmo-plantar pustulosis** per year (all centres)
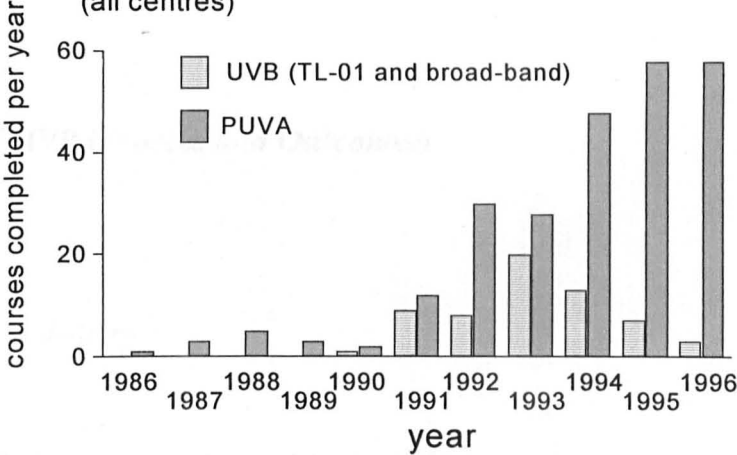
condition, 4 using TL-01 lamps, the decline in the number of courses after a peak in 1993 may have been related to the impression that many of these patients do better with other treatments, such as PUVA.

Mycosis fungoides

Broad-band UVB is effective for early patch stage mycosis fungoides (Milstein et al. 1982; Piccinno et al. 1990; Ramsay et al. 1992; Resnik et al. 1993), although PUVA may be more effective for plaque stage disease (Piccinno et al. 1990; Ramsay et al. 1992). Five departments had tried TL-01 UVB for this indication, including its use for patients who would previously have been offered PUVA. As yet, no comparative studies have been conducted, but TL-01 UVB does appear highly effective for patch stage mycosis fungoides (Clark et al. 2000), although PUVA appears to be more effective for plaque stage disease.

PUVA and UVB (Process and Outcomes)

PUVA methodology

- *Since the 1991 audit, PUVA methodology had become more uniform across Scotland.*
- *All departments provided written and oral information to patients and sought written consent to treatment.*
- *Oral 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP) were available in all units. Bath PUVA was used only occasionally, if available at all: only 4 departments administered >10 courses of whole-body bath PUVA during 1995 and 1996. Of these 4 centres, 2 used trimethoxypsoralen (TMP) and 2 used 8-methoxypsoralen (8-MOP) for bath PUVA.*

- *Pre-treatment checks in all centres included a drug history and examination of normally exposed skin. Liver function tests and lupus serology were checked if indicated by the patient's history.*

- *Duration of recommended wearing of eye protection varies from 12 to 24 hours. Checking of protective spectacles varied from none (but advice to use only approved spectacles and UV-absorbent coatings) to checking that transmission of cubicle UVA through spectacles to a UVA meter was negligible to checking spectacles with a spectrophotometer.*

- *Dosimetry has become much more uniform since the development of the Scottish PUVA Dosimetry Guidelines following the last 1992 survey of practice.*

- *The UVA starting dose is now usually based on minimal phototoxic dose (MPD) determination in 10 units, compared to just 3 in 1991. The standard treatment frequency, for indications except polymorphic light eruption (often treated 3x weekly), was 2x weekly in all units. Incremental regimens varied but most were based on a geometric incremental regimen, with each dose a percentage of the previous dose. Use of topical and systemic adjunctive therapies varied. All used adjunctive retinoids (Re-PUVA) at least occasionally.*

- *Significant between-centre variation in numbers of treatments per course remained. This might in part have been because of differences in patient selection for treatment, but remaining differences in treatment methodology were important.*

Indications

Psoriasis remained the primary indication for PUVA (**Figure 2.9**). It was used for severe or moderately severe psoriasis not adequately controlled by topical therapies. In centres with access to TL-01 UVB this was usually used first, with PUVA only prescribed if TL-01 UVB proved disappointing or provided an unacceptably short duration of remission. Of the other frequent indications for PUVA, the only conditions for which increasing numbers of PUVA courses are prescribed each year are palmo-plantar pustulosis and palmo-plantar psoriasis. Other conditions treated with PUVA are listed, in alphabetical order, in **Table 2.4**.

Figure 2.9 PUVA courses 1992 to 1996 (n= 3225) - the 5 most frequent indications for PUVA. Percentage of courses for each indication is shown.

psoriasis (69%)

palmo-plantar pustulosis/ psoriasis (6.9%)

PLE (6.5%)

atopic dermatitis (4.7%)

mycosis fungoides (2.4%)

other conditions
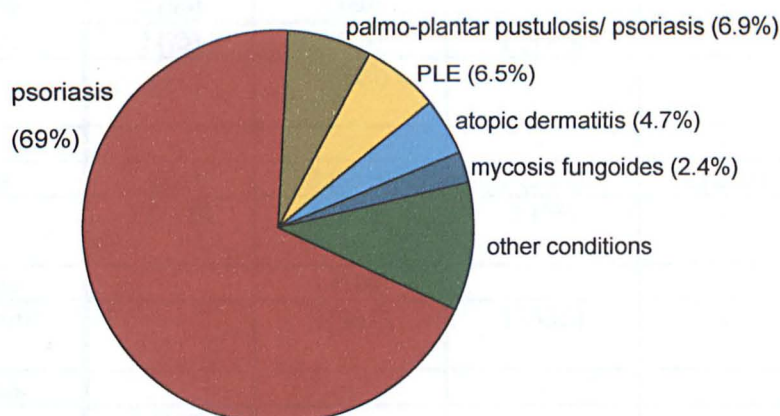
Table 2.4 PUVA courses - outcomes of courses - numbers (percentages)

Condition	Clear/ MRA	Moderate improvement	No change/ minimal improvement	Worse	Outcome not recorded	DNA (did not attend)
Acquired perforating dermatosis	1 (100)	-	-	-	-	-
Actinic prurigo	3 (60)	1 (20)	-	-	1 (20)	-
Alopecia areata	8 (20)	16 (40)	11 (27.5)	1 (2.5)	2 (5)	2 (5)
Angiolymphoid hyperplasia with eosinophilia	-	1 (100)	-	-	-	-
Annular erythemas	-	1 (33.3)	2 (66.7)	-	-	-
Aquagenic pruritus	-	-	-	1 (100)	-	-
Atopic dermatitis	44 (25)	59 (33.5)	17 (9.7)	5 (2.8)	33 (18.8)	18 (10.2)
Cholinergic urticaria	1 (100)	-	-	-	-	-
Chronic idiopathic urticaria	4 (33.3)	4 (33.3)	1 (8.3)		1 (8.3)	2 (16.7)
Chronic superficial dermatitis	16 (53.3)	3 (10)	1 93.3)	-	8 (26.7)	2 (6.7)
Diffuse cutaneous reticulohistiocytosis	1 (100)	-	-	-	-	-
Discoid eczema	-	3 (100)	-	-	-	-

Condition	Clear/ MRA	Moderate improvement	No change/ minimal improvement	Worse	Outcome not recorded	DNA (did not attend)
Epidermolysis bullosa	-	1 (100)	-	-	-	-
Follicular mucinosis	2 (40)	3 (60)	-	-	-	-
Granuloma annulare	2 (25)	2 (25)	1 (12.5)	-	3 (37.5)	-
Hidradenitis suppuritiva	-	1 (100)	-	-	-	-
Ichthyoses	-	-	-	-	3 (75)	1 (25)
Idiopathic pruritus	1 (11.1)	3 (33.3)	2 (22.2)	2 (22.2)	-	1 (11.1)
Idiopathic solar urticaria	1 (12.5)	1 (12.5)	2 (25)	-	4 (50)	-
Insect bite reactions	-	1 (100)	-	-	-	-
Jessner's lymphocytic infiltrate	-	2 (66.7)	1 (33.3)	-	-	-
Lichen amyloidosus	-	-	-	-	-	1 (100)
Lichen nitidus	1 (100)	-	-	-	-	-
Lichen planus	13 (44.8)	6 (20.7)	5 (17.2)	-	4 (13.8)	1 (3.5)
Lichen simplex	-	2 (66.7)	-	-	-	1 (33.3)
Linear IgA disease	2 (100)	-	-	-	-	-
Lymphomatoid papulosis	2 (40)	-	1 (20)	-	1 (20)	1 (20)
Mastocytoses	4 (22.2)	1 (5.6)	2 (11.1)	-	10 (55.6)	1 (5.6)
Mycosis fungoides	47 (46.1)	26 (25.5)	5 (4.9)	1 (1)	17 (16.7)	6 (5.9)
Necrobiosis lipoidica	-	3 (30)	4 (40)	-	1 (10)	2 (20)
Palmar hyperhidrosis	-	-	1 (100)	-	-	-
Papuloerythroderma of Ofuji	-	-	-	-	1 (100)	-
Perifolliculitis capitis abscedens et suffodiens	-	-	1 (100)	-	-	-
Photosensitivity dermatitis/ actinic reticuloid syndrome	1 (50)	-	-	1 (50)	-	-
Pityriasis lichenoides chronica	8 (61.5)	3 (23.1)	-	-	2 (15.4)	-
Polymorphic light eruption	64 (19.3)	45 (13.6)	12 (3.6)	4 (1.21)	200 (60.4)	6 (1.8)
Sezary's syndrome	-	-	-	-	1 (100)	-
Undefined eczemas	14 (41.2)	5 (14.7)	2 (5.9)	1 (2.9)	5 (14.7)	7 (20.6)
Palmar/plantar dermatitis	20 (37)	11 (20.4)	10 (18.5)	3 (5.6)	8 (14.8)	2 (3.7)
Palmo-plantar pustulosis/ psoriasis	54 (20.9)	81 (31.4)	34 (13.2)	6 (2.3)	64 (24.8)	19 (7.4)
Pityriasis rubra pilaris	1 (25)	-	1 (25)	1 (25)	1 (25)	-
Pretibial myxoedema	-	-	1 (100)	-	-	-
Prurigo nodularis	7 (22.6)	15 (48.4)	5 (16.1)	-	3 (9.7)	1 (3.2)
Psoriasiform dermatitis	1 (33.3)	-	-	2 (66.7)	-	-

Condition	Clear/ MRA	Moderate improvement	No change/ minimal improvement	Worse	Outcome not recorded	DNA (did not attend)
Psoriasis	1598 (48.9)	455 (13.9)	171 (5.23)	47 (1.4)	791 (24.2)	208 (6.4)
Scleroderma	-	1 (33.3)	2 (66.7)	-	-	-
Vitiligo	1 (4.55)	6 (27.3)	11 (50)	-	-	4 (18.2)

Consent to treatment and patient information

The referral process for PUVA varied from centre to centre. Usually, the patient was seen in the outpatient clinic and PUVA prescribed, either on a specific referral form (including documentation of previous treatments and any relative contraindications), as used in 6 centres, or by letter or telephone call to the nurse in charge of administering PUVA. In 4 departments patients were referred from the outpatients' clinic to another dermatologist in the phototherapy unit who further assessed the patient before prescribing PUVA.

All departments provided written as well as oral information about PUVA and sought written consent. Information sheets about PUVA described what is involved in administering the treatment, mentioned the most frequent acute adverse effects, and explained the need for protective eye-wear after psoralen administration. Some emphasised the need to avoid pregnancy because psoralens are mutagenic (Lambert et al. 1978; McEvoy et al. 1987), although they may not be teratogenic (Stern et al. 1991; Gunnarskog et al. 1993). Three of the information sheets viewed contained specific mention of increased risk of skin cancer as a chronic adverse effect. Only two departments' information sheets explicitly listed PUVA pain amongst the possible adverse effects.

Psoralens

Psoralens may be administered orally or topically, for whole-body treatment or for localised (usually hands/ feet or scalp) treatment. Oral psoralens were most often used for both whole body and local treatment **(Figure 2.10)**. Oral 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP) were available in all PUVA units. In all centres, 8-MOP was the first-choice psoralen, with 5-MOP used if 8-MOP caused unacceptable gastro-intestinal adverse effects. In

some centres, 5-MOP was also prescribed, apparently successfully, as an alternative psoralen for those who developed PUVA pain during 8-MOP-UVA therapy. The oral psoralen dose was based on patient weight (0.6 mg/Kg for 8-MOP and 1.2 mg/Kg for 5-MOP) in all but one centre which had adopted a surface-area-based psoralen dosing scheme. In practice, similar doses are used for most patients whichever system is used: but low-weight patients may be under-dosed if body-weight alone is used. Some centres avoid this by never prescribing less than 40mg of 8-MOP regardless of body weight. Minimal phototoxic dose determination ensures that whatever dosing schedule is favoured, there is an adequate psoralen skin concentration to interact with UVA.

For whole-body topical PUVA, the psoralens are applied in bath-water. Only 4 centres gave more than 10 courses of whole-body bath PUVA during the previous 2 years (1995, 1996) - two used trimethoxypsoralen (TMP) and two 8-MOP.

Bath PUVA is indicated for patients unable to tolerate oral psoralens (usually because of nausea), those already on multiple oral medications or with hepatic or renal impairment, those with no phototoxic response detectable after 2 or more oral psoralen doses prior to minimal phototoxic dose (MPD) testing, and (particularly when TMP is used - as it requires low UVA doses, leading to short treatment times) claustrophobic patients (Halpern et al. 2000).

There is a hope that bath-PUVA may turn out to be less photocarcinogenic than oral PUVA. Epidemiological data from Scandinavia suggests that TMP bath PUVA may be safer than oral 8-MOP PUVA (Berne et al. 1984; Lindelöf et al. 1992; Hannuksela et al. 1996). However, the latest report from Finland, which showed no more skin cancers than expected in a matched population in 527 TMP-treated patients followed-up for a mean of 10 years, could have

Figure 2.10 Method of psoralen administration 1992-1996

Whole body
2923 courses

topical psoralen

oral psoralen

Local application
426 courses

(13 centres)
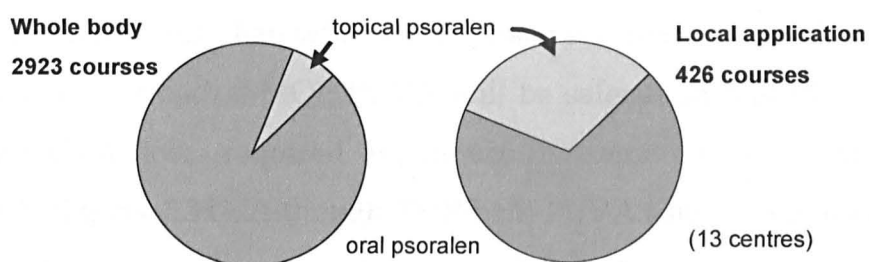
missed up to a seven-fold increased risk because of the, still small, cohort size and relatively short duration of follow-up. There is no evidence that topical 8-MOP, or 5-MOP (Calzavara-Pinton et al. 1997) PUVA is any less, or more, photocarcinogenic than when the psoralen is administered orally. It cannot be assumed that bath 8-MOP PUVA will be safer than oral PUVA, despite the lower UVA doses required to produce the same phototoxic and therapeutic effects (**Figure 2.11**). Although TMP-bath PUVA *may* eventually turn out to be safer, if this occurs the explanation might relate to the particular psoralen used, rather than the mode of administration. Mouse studies have shown topical 8-MOP+UVA to be as carcinogenic as oral 8-MOP+UVA (Griffin et al. 1958) and, in another study, lifelong topical TMP-PUVA caused no mouse skin cancers (Hannuksela et al. 1986)whereas topical 8-MOP PUVA did.

When following-up patients regarded as at risk of skin cancer as a result of PUVA, cumulative treatments may be a more important risk factor than cumulative dose. This is because a high UVA dose given in relatively few treatments may be safer than the same dose spread over more treatments (Gibbs et al. 1985), and because of variation in UVA dosimetry leading to difficulty in meaningful comparison of dose (Jcm^{-2}) reported from different centres (Diffey et al. 1986). Given the lower cumulative UVA doses to achieve the same phototoxic, therapeutic (and, *possibly*, photocarcinogenic) effects if psoralens are applied topically, it is particularly important that the cumulative number of treatments, and not just cumulative UVA dose, is regarded as a risk factor when following-up bath PUVA patients.

Figure 2.11 UVA dose per course for whole-body PUVA for psoriasis (1992 - 1996). The central lines represent median dose, the boxes enclose the interquartile range (IQR). The whiskers enclose the adjacent values (1$\frac{1}{2}$ x IQR) and more extreme outlying values are represented as circles.
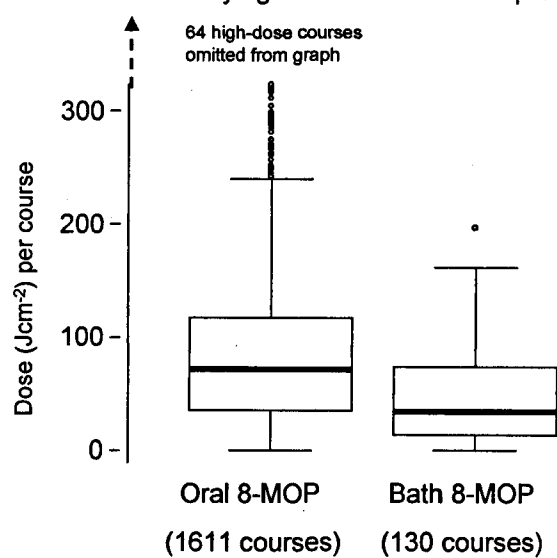
Only 36 of a total of 132 recorded localised PUVA courses administered in 1996, predominantly for hands and/or feet, were documented to involve topical psoralen application. Frequently-used preparations included: 8-MOP emulsion 0.15% applied for 15 to 30 minutes before UVA irradiation, 8-MOP bath lotion made up in a 0.0003% solution applied as a soak for 10 to 20 minutes, and TMP bath solution made up with 1mg TMP in 3 litres applied as 10 minute soak. One centre was assessing an 8-MOP gel. No centre was yet using the newly available preparation, 0.005% aqueous gel of psoralen (the parent compound), which appears promising as a treatment for palmoplantar psoriasis (de Rie et al. 1995).

Pre-treatment checks

In all centres, patients were asked about possible relative contraindications, and examined for any skin malignancies or premalignant lesions. A drug history was also taken in all departments. A total body skin examination was routine in some departments. In others, pressure on clinic time allowed routine examination of normally exposed sites only.

Liver function tests (LFTs) were always carried out if there was a history to suggest possible liver disease. Other departments still checked LFTs routinely for all PUVA patients. Hepatic injury is an uncommon side effect of PUVA (Bjellurup et al. 1979; Pariser et al. 1980; Freeman 1984), and has occurred as an idiosyncratic effect of topical 8-MOP lotion (Park et al. 1994) as well as with oral psoralens. It is generally accepted that, if baseline LFTs are normal, there is no need for routine monitoring of LFTs (British Photodermatology Group 1993). There is no clear evidence in favour of unselective pre-treatment screening for liver biochemistry abnormalities in all PUVA patients, but if a PUVA patient does develop liver dysfunction, it could be helpful to have baseline results.

All centres checked antinuclear factor antibodies (ANAs) for patients with a history of photosensitivity, or who developed a photosensitivity problem (commonly polymorphic light eruption) during treatment. Just over half followed the British Photodermatology Group recommendation that anti-Ro antibodies also be checked in these patients (British Photodermatology Group 1993). Some centres routinely requested ANA tests for all patients prior to starting PUVA. There was a suggestion that PUVA might induce antinuclear antibodies, but it has since been shown that this is not a complication of PUVA for psoriasis (Picascia et al. 1987; Calzavara-Pinton et al. 1994b), and no Scottish departments *routinely* monitor ANAs during treatment.

Only two departments routinely requested a pre-treatment pregnancy test for female patients. The others relied on warning of the potential risks, and giving advice on contraception. If pregnancy occurs during a course of PUVA this treatment is stopped but, as pregnancy outcomes following psoralen exposure have been reassuringly normal (Stern et al. 1991; Gunnarskog et al. 1993), no department would advise pregnancy termination in this situation.

Eye protection

The usual eye protection during treatment was with "UVC-303 treatment goggles", provided by Arthrodax Surgical Ltd., also used during UVB treatment. There was some variation in the advice given after psoralen administration. All advised UVA protective spectacles for at least 12 to 24 hours following oral psoralen ingestion. Two departments distinguished between those regarded as at low risk, advised to wear protection for 12 hours, and those at higher pre-existing risk of cataract (children and atopic dermatitis patients) who were advised to wear protection for all waking hours up to 24 hours after taking psoralens. Advice to bath PUVA patients

was variable: some regarding this as unnecessary and others, cautiously, advising eye protection for 24 hours, on the grounds that topical application can lead to significant plasma (and presumably lens) psoralen levels (Gomez et al. 1995). Since this survey, most departments have adopted the guidelines of a British Photodermatology Group workshop (Halpern et al. 2000), and no longer recommend eye protection routinely to bath PUVA patients.

Any increased risk of cataract in humans as a result of PUVA appears to be low (Cox et al. 1987; Stern 1994), despite concern about a possible risk based on theoretical and animal study grounds. Even in a cohort of patients known not to comply with eye protection advice no excess in cataract incidence was noted (Calzavara-Pinton et al. 1994a). Nevertheless, while the true risk remains uncertain, protective spectacles fulfilling recommended transmission criteria should be advised (Moseley et al. 1988; Diffey 1996). If the patient wishes to wear his or her own sunglasses these must be checked, ideally with a spectrophotometer although reasonable alternatives have been suggested (Diffey 1996). This is especially important because inadequate UVA absorption by sunglasses is potentially a greater hazard than no protection at all, due to pupillary dilatation resulting from visible light-shielding (Deleu et al. 1990). Eye protection of aphakic patients to prevent retinal damage is essential. Fortunately most cataract extractions now are followed by insertion of a UV-absorbing anterior chamber prosthetic lens implant.

UVA administration

Dosimetry

Implementation of the Scottish PUVA Dosimetry Guidelines, following the 1991 PUVA audit, succeeded in making UVA dosimetry throughout the country more uniform: so that a Jcm^{-2} of UVA in one department means

approximately the same as a Jcm^{-2} in another department. **Figure 2.12** illustrates this, with the, still non-standardised, UVB dosimetry for comparison.

Until similar guidelines are established elsewhere we will have to continue to be cautious in our interpretation of Jcm^{-2} quoted in the literature from other countries, but uniform dosimetry in Scotland is a start and, practically, already allows safer transfer of patients between units during a course of PUVA.

Starting dose

This is ideally based on determination of the minimal phototoxic dose (MPD) for each patient. This ensures that sufficient psoralen is present in the skin at the time of irradiation - taking into account individual variation in drug metabolism and any drug interactions. It is also a safety check, ensuring that the starting dose does not cause an acute phototoxic "burn". Also, there is evidence from a Scottish population (Collins et al. 1996b), that use of an MPD-based starting dose allows clearance of psoriasis with a lower cumulative number of exposures than with a skin-type based starting dose.

Ten units in Scotland routinely used an MPD-based starting dose for most patients, and 4 determined the MPD for some patients (those with a photodermatosis or those who are starting a first PUVA course). This is encouraging as in 1991 only 3 centres determined MPDs. **Figure 2.13** shows that more treatments were required for a successful course of PUVA in centres which did not routinely base starting UVA doses on MPD measurement, compared to those that did. This is not controlled trial data and there are many possible explanations for the finding but, we do have evidence that basing starting dose on the individual's MPD leads to significantly fewer

Figure 2.12 <u>UVA dosimetry</u>
1 Jcm^{-2} in each of 14 units converted to "Ninewells Joules"
TL-01 dosimetry shown for comparison
Differences in values in shaded area possibly accounted for by
measurement error alone
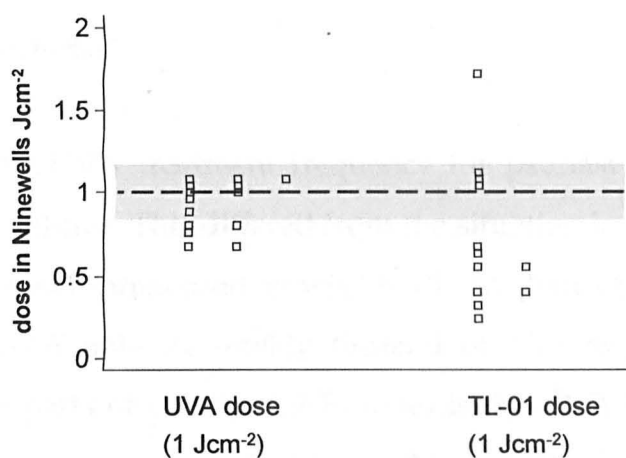
Figure 2.13 PUVA treatments per course for **psoriasis** documented as
leading to **clearance/ MRA** (1992-1996). Centres with starting dose
routinely based on MPD or not.
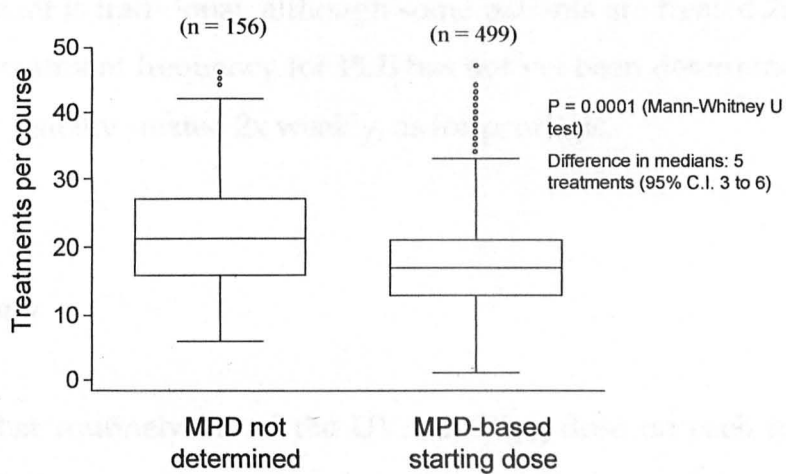
treatments required to achieve clearance (Collins et al. 1996b) and this was likely to be an important factor.

Treatment frequency

The standard PUVA treatment frequency for psoriasis in Scotland was 2x weekly in all centres. This differed from the situation in the UK as a whole in 1991, when most centres used 3x weekly PUVA (Farr et al. 1991). One reason for using PUVA only 2x weekly (instead of 3 or 4x weekly as has been customary in parts of continental Europe) is that PUVA erythema does not reach maximum intensity until at least 72 hours after UVA irradiation. Open study evidence supports the use of 2x weekly PUVA for a UK psoriasis patient population (Sakuntabhai et al. 1993). An "aggressive" 3x weekly regimen, with weekly MPD determination (Carabott et al. 1989), caused uncomfortable erythema episodes too frequently to be appropriate for a Scottish population (Green et al. 1993). Two centres occasionally used a 1x weekly regimen (Cox 1995) for selected patients who would find it difficult, or impossible, to attend more frequently. For polymorphic light eruption, 3x weekly treatment is traditional, although some patients are treated 2x a week. The optimal treatment frequency for PLE has not yet been determined. Other conditions are usually treated 2x weekly, as for psoriasis.

Dose increments

The centres that routinely based the UVA starting dose on each individual patient's MPD, then used increments based on a percentage of previous dose: usually 40% increments reducing to 20% or 10% later during the course, depending upon erythemal response. Other centres had a variety of arbitrary incremental regimens.

Adjunctive therapy

Many centres sometimes used adjunctive tar, dithranol, or calcipotriol. The use of adjunctive retinoids varied greatly between centres. Systemic retinoids combined with PUVA (Re-PUVA) have been shown to minimise the UVA dose required to clear psoriasis (which is expected to reduce the risk of long-term adverse effects), and retinoids may, themselves, exert anti-neoplastic effects (Bertram et al. 1985; Eccles 1985). One centre, which until recently tended to use maintenance therapy more frequently than others, frequently had more than half the patients attending for PUVA on etretinate or acitretin. Because of its shorter biological half-life, isotretinoin was occasionally used as an adjunct (and PUVA sparing therapy) when a retinoid was required for a young woman.

Fewer than 20 patients were documented to have had methotrexate, cyclosporin, hydroxyurea or azathioprine in conjunction with PUVA. One department had tried psoralen-UVB treatment for one, previously treatment resistant, psoriasis patient.

Stopping treatment

Treatment for psoriasis is usually stopped on achievement of clearance or "minimal residual activity". The decision to stop a course of treatment was made in different ways in different centres:

1) some had a protocol allowing the staff administering therapy to stop, with or without clinic follow-up, treatment if clearance was achieved before 20 treatments,

2) in others a doctor reviewed every patient before discharge, and

3) some units had the patient reviewed in clinic after a set number of treatments (often 20) or weeks (often 6). This has the disadvantage of

meaning that some patients are given unnecessary extra exposures, after clearance, because the decision to stop treatment is not made until this review.

For other conditions, in all centres, the patient was usually reviewed by a doctor before discharge. For polymorphic light eruption (PLE) 15 treatments were usually prescribed. Polymorphic light eruption is provoked during about half of all prophylactic treatment courses administered in Dundee (Man et al. 1999). In some departments, however, patients had unusually prolonged "desensitisation" courses, with treatment apparently continued until they stopped having PLE provoked during treatment. In other centres, it was customary to "give up" and stop treatment early if a patient experienced a few episodes of provoked PLE.

Between-centre differences

Use of maintenance PUVA for psoriasis has declined over the years since 1977 (**Figure 2.14**). Another explanation for falling numbers of treatments per course may be that, as treatment regimens have been improved, the number of treatments to attain clearance has fallen. To compare treatments per course between centres, it is important to ensure that changes in PUVA use over time and different mixes of conditions treated are not confounding variables.

Figure 2.14 Whole-body PUVA treatments per course for **psoriasis** for which data available. Median is central line; box encloses interquartile range.

3058 courses - 60 of >120 exposures (of which 70% where at 3 centres) not shown
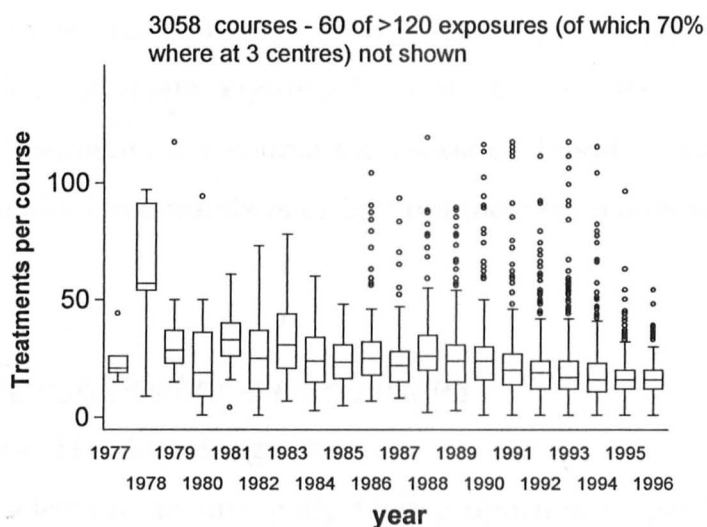
Psoriasis

No Scottish centres now *routinely* use maintenance PUVA for psoriasis. Maintenance treatment was used for mycosis fungoides and, occasionally, for vitiligo or alopecia areata. **Figure 2.15** shows the between-centre variation in number of treatments per course for psoriasis. Possible reasons for centres giving unusually large numbers or low numbers of treatments per course are listed:

<u>Unusually prolonged, multiple treatment courses</u>

- Sub-optimal treatment regimens.

- Patient selection: an unusually high proportion of particularly severely affected, and relatively treatment-resistant, patients referred for PUVA.

- No clear policy on when a course should stop, or a protocol that encourages extra treatments after clearance or MRA is achieved (such as a "standard" 20 treatments before a decision on stopping or continuing treatment is made).

<u>Unusually short, few treatment, courses</u>

- Many patients failing to attend
    - difficulties in travelling to centre (geography, local public
        transport).
    - a perception by patients and/or staff that treatment is ineffective (a
        self-fulfilling prophecy if patients stop treatment early).

- Other therapies, such as UVB and hospital admission, not readily available so patients with relatively mild, and easy to clear, psoriasis are referred for PUVA.

Figure 2.15 Whole-body PUVA treatments per course for **psoriasis** (1992 - 1996) in each centre for which data available. Median is central line; box encloses interquartile range.

P = 0.0001 (Kruskal-Wallis)

2066 courses - for clarity of graph, 41 courses involving >105 exposures not shown. (These very high exposure courses were given at 8 centres - 12 courses at 1 centre)
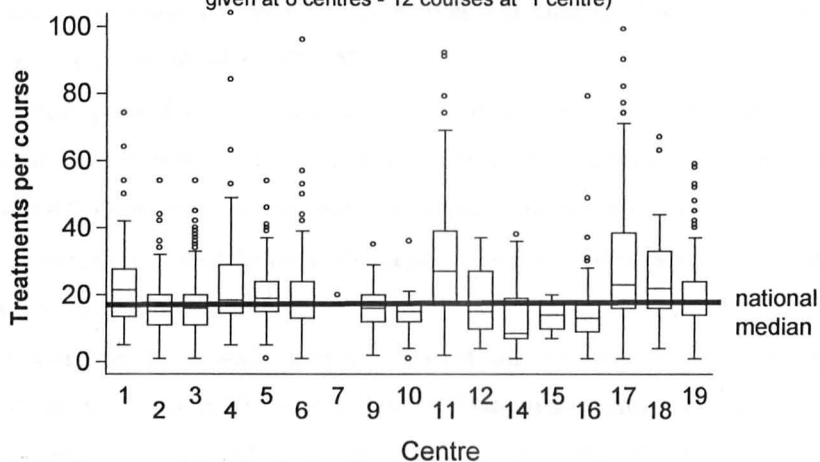
UVB phototherapy methodology

- Whilst psoriasis remained the major indication for UVB, increasing numbers of UVB courses were administered for other conditions, particularly atopic dermatitis and polymorphic light eruption. Most UVB courses administered in Scotland between 1992 and 1997 were narrow-band TL-01 UVB.

- 12 departments provided written as well as oral information to patients and requested written consent to treatment. Baseline lupus serology was checked prior to a first course of UVB in patients with a known photodermatosis, in every centre.

- UVB dosimetry varied widely between centres, making between-centre comparisons of "uncorrected" doses meaningless.

- The UVB starting dose was routinely based on minimal erythemal dose (MED) determination in 5 centres. The method of MED determination varied.

- Treatment frequency varied from 2x weekly to daily. Routinely used treatment frequencies were 2x, 3x and 5x weekly.

- All units encouraged use of appropriate emollients during a treatment course. About half of UVB courses also involved other adjunctive topical treatment. All units using TL-01 occasionally used systemic retinoids with UVB (Re-TL-01).

- There was wide variation between centres in numbers of treatments and dose per course for psoriasis. Similarly, although TL-01 UVB was an effective treatment for psoriasis in all centres using it, there were variations in outcomes between centres suggesting that, with improvements in methodology, some units could treat their patients more effectively.

Indications

Most courses of UVB, whether narrow-band TL-01 (**Figure 2.16**) or broad-band (**Figure 2.17**), administered in Scotland were for psoriasis or atopic dermatitis. TL-01 UVB was more often used for PLE than broad-band UVB. Both UVB sources were still used for acne: the indication for 1% of

Figure 2.16 Narrow-band (TL-01) courses 1992 to 1996 (n= 4243)
- the 5 most frequent indications for TL-01 UVB.
Percentage of courses for each indication is shown.

atopic dermatitis (9.3%)

PLE (8.4%)

psoriasis
(69.2%)

chronic urticaria (1.5%)

acne (1%)

other conditions
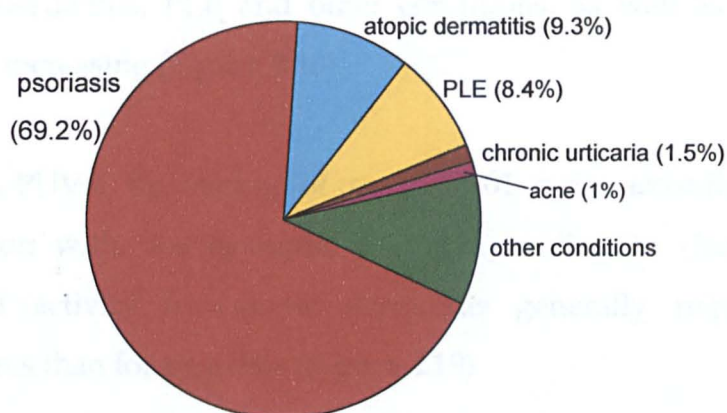
Figure 2.17 Broad-band UVB courses 1992 to 1996 (n= 2601) -
the 5 most frequent indications for broad-band UVB.
Percentage of courses for each indication is shown.

atopic dermatitis (9.1%)

acne (1.2%)

pityriasis lichenoides (1.2%)

psoriasis
(82.2%)

PLE (0.7%)
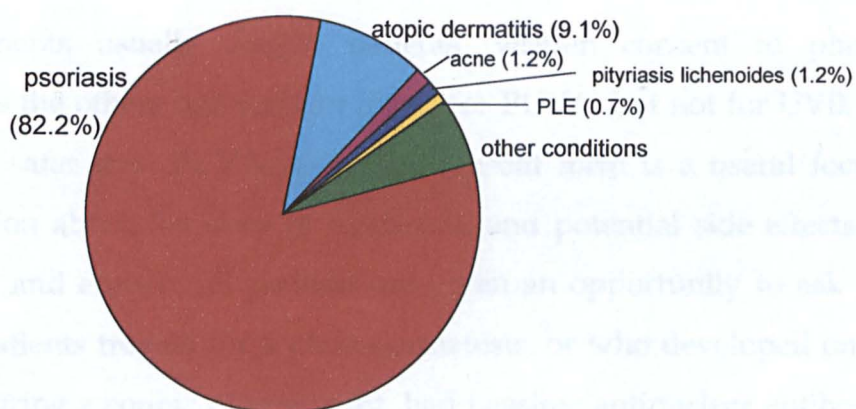
other conditions

courses. A significant proportion of TL-01 courses were for chronic urticaria. Both sources were used for a wide variety of other indications (**Tables 2.5 and 2.6**) but the proportion of courses for these "other conditions" was greater with TL-01. The number of yearly courses of TL-01 administered each year for atopic dermatitis, PLE and other conditions, as well as for psoriasis, was rapidly increasing (**Figure 2.18**).

As with PUVA, the method of use of TL-01 varies according to the treatment indication with, for example, a course leading to clearance or minimal residual activity for atopic dermatitis generally requiring more UVB exposures than for psoriasis (**Figure 2.19**).

Pre-treatment checks

In 12/19 departments a UVB patient information sheet was given to patients, either when the treatment was prescribed or when it started. These departments usually sought patients' written consent to phototherapy whereas the others had consent forms for PUVA, but not for UVB. Although UVB is safer than PUVA, a written consent form is a useful focus for the discussion about the aims of treatment, and potential side effects, with the patient: and ensures all patients are given an opportunity to ask questions. Most patients treated for a photodermatosis, or who developed one (usually PLE) during a course of treatment, had baseline antinuclear antibody (ANA) and anti-Ro and La antibodies checked. Unless specifically indicated for an individual patient, these tests were not, in any unit, repeated for subsequent courses. Some centres had a problem with the apparently over-sensitive ANA assay used by one regional immunopathology service.

Table 2.5   Conditions treated with broad-band UVB - outcomes of courses - numbers (percentages)

Condition	Clear/ MRA	Moderate improvement	No change/ minimal improvement	Worse	Outcome not recorded	DNA (did not attend)
Acne vulgaris	-	8 (24.2)	8 (24.2)	1 (3)	9 (27.3)	7 (21.2)
Actinic prurigo	1 (33.3)	-	1 (33.3)	-	1 (33.3)	-
Alopecia areata	-	-	1 (50)	-	1 (50)	-
Aquagenic pruritus	2 (50)	1 (25)	1 (25)	-	-	-
Atopic dermatitis	50 (18.5)	87 (32.1)	27 (10)	5 (1.9)	71 (26.2)	31 (11.4)
Cholinergic urticaria	-	-	-	-	1 (100)	-
Chronic idiopathic urticaria	-	2 (100)	-	-	-	-
Chronic superficial dermatitis	7 (50)	6 (42.9)	-	-	1 (7.1)	-
Darier's disease	-	-	1 (100)	-	-	-
Discoid eczema	4 (44.4)	3 (33.3)	-	-	1 (11.1)	1 (11.1)
Epidermolysis bullosa	-	1 (50)	1 (50)	-	-	-
Erythrokeratoderma variabilis	-	5 (100)	-	-	-	-
Hidradenitis suppuritiva	-	2 (100)	-	-	-	-
Idiopathic pruritus	2 (13.3)	7 (46.7)	3 (20)	-	23 (13.3)	1 (6.7)
Insect bite reactions	2 (100)	-	-	-	-	-
Keratosis pilaris	-	2 (40)	-	-	-	3 (60)
Lichen planus	2 (50)	-	1 (25)	-	-	1 (25)
Lichen simplex chronicus	-	-	-	1 (50)	1 (50)	-
Lymphomatoid papulosis	-	-	-	-	1 (100)	-
Mastocytoses	-	3 (50)	1 (16.7)	-	1 (16.7)	1 (16.7)
Milia	-	-	1 (100)	-	-	-
Mycosis fungoides	-	-	-	-	1 (100)	-
Necrobiosis lipoidica	-	1 (25)	-	-	1 (25)	2 (50)
Palmo-plantar pustulosis/ psoriasis	-	-	1 (100)	-	-	-
Papuloerythroderma of Ofuji	-	2 (100)	-	-	-	-
Pityriasis alba	-	1 (100)	-	-	-	-
Pityriasis lichenoides chronica	19 (48.7)	5 (12.8)	3 (7.7)	1 (2.6)	9 (23.1)	2 (5.13)
Pityriasis lichenoides varioliformis et acuta	1 (50)	-	-	-	-	1 (50)
Pityriasis rosea	-	1 (25)	-	-	1 (25)	2 (50)
Pityrosporum folliculitis	-	-	-	-	1 (50)	1 (50)
Polymorphic light eruption	50 (54.4)	7 (7.6)	2 (2.2)	3 (3.3)	23 (25)	7 (7.6)
Prurigo nodularis	2 (20)	2 (20)	-	-	6 (60)	-
Pruritus of Hodgkin's lymphoma	1 (50)	-	-	-	-	1 (50)
Pruritus of liver disease	-	-	1 (50)	-	-	1 (50)
Pruritus of renal failure	1 (11.1)	3 (33.3)	-	-	-	5 (55.6)
Psoriasis	153 (34.9)	431 (14.3)	122 (4)	9 (0.3)	1131 (37.5)	274 (9.1)

Condition	Clear/ MRA	Moderate improvement	No change/ minimal improvement	Worse	Outcome not recorded	DNA (did not attend)
Symptomatic dermographism	-	1 (50)	-	-	-	1 (50)
Undefined eczemas	2 (25)	2 (25)	1 (12.5)	1 (12.5)	2 (25)	-
Urticarial vasculitis	1 (50)	1 (50)	-	-	-	-

Table 2.6 Conditions treated with TL-01 UVB courses - outcomes of courses - numbers (percentages)

Condition	Clear/ MRA	Moderate improvement	No change/ minimal improvement	Worse	Outcome not recorded	DNA (did not attend)
Acne	8 (18.2)	13 (29.6)	14 (31.8)	2 (4.6)	1 (2.3)	6 (13.6)
Acne agminata	-	-	1 (100)	-	-	-
Acquired perforating dermatosis	1 (33.3)	-	2 (66.7)	-	-	-
Actinic prurigo	11 (39.3)	1 (3.6)	-	-	16 (57.1)	-
Alopecia areata	1 (14.3)	1 (14.3)	-	-	1 (14.3)	4 (57.1)
Angiolymphoid hyperplasia	-	-	1 (100)	-	-	-
Annular erythema	1 (50)	-	-	-	-	1 (50)
Atopic dermatitis	330 (58.6)	112 (19.9)	30 (5.3)	11 (2)	24 (4.3)	56 (10)
Cholinergic urticaria	1 (33)	-	2 (66.7)	-	-	-
Chronic fatigue	-	-	-	-	-	1 (100)
Chronic idiopathic urticaria	31 (38.8)	22 (27.5)	17 (21.3)	2 (2.5)	2 (2.5)	6 (7.5)
Chronic superficial dermatitis	6 (66.7)	2 (22.2)	-	-	-	1 (11.1)
Cold urticaria	1 (100)	-	-	-	-	-
Discoid eczema	11 (78.6)	2 (14.3)	-	-	-	1 (7.1)
Drug induced photosensitivity	1 (100)	-	-	-	-	-
Erythrokeratoderma variabilis	1 (100)	-	-	-	-	-
Erythropoietic protoporphyria	11 (50)	-	-	-	9 (40.9)	2 (9.1)
"Follicular dermatitis"	1 (50)	-	-	-	-	1 (50)

Condition	Clear/ MRA	Moderate improvement	No change/ minimal improvement	Worse	Outcome not recorded	DNA (did not attend)
Granuloma annulare	4 (50)	3 (37.5)	1 (12.5)	-	-	-
Heat urticaria	-	1 (100)	-	-	-	-
Hydroa vacciniforme	7 (46.7)	1 (6.7)	-	-	7 (46.7)	-
Ichthyoses	5 (71.4)	2 (28.6)	-	-	-	-
Idiopathic solar urticaria	2 (12.5)	1 (6.25)	-	-	11 (68.8)	2 (12.5)
Insect bite reactions	1 (11.1)	8 (88.9)	-	-	-	-
Jessner's lympho-cytic infiltrate	-	1 (50)	1 (50)	-	-	-
Juvenile plantar dermatosis	-	1 (100)	-	-	-	-
Juvenile Spring-time eruption	1 (33.3)	2 (66.7)	-	-	-	-
Keratosis pilaris	4 (50)	1 (12.5)	2 (25)	-	-	1 (12.5)
Kimura's disease	1 (100)	-	-	-	-	-
Lichen nitidus	1 (100)	-	-	-	-	-
Lichen planus	6 (37.5)	4 (25)	3 (18.8)	-	2 (12.5)	1 (6.3)
Lichen simplex	-	2 (100)	-	-	-	-
Mastocytoses	1 (16.7)	1 (16.7)	1 (16.7)	-	3 (50)	-
Mycosis fungoides	13 (72.2)	2 (11.1)	-	-	1 (5.6)	2 (11.1)
Necrobiosis lipoidica	-	-	2 (100)	-	-	-
Palmoplantar dermatitis	21 (42.9)	5 (10.2)	14 (28.6)	1 (2)	4 (8.2)	4 (8.2)
Palmoplantar pustulosis/ palmoplantar psoriasis	13 (21.7)	19 (31.7)	13 (21.7)	1 (1.7)	9 (15)	5 (8.3)
Photosensitivity dermatitis/ actinic reticuloid syndrome	2 (16.7)	2 (16.7)	2 (16.7)	-	6 (50)	-
Pityriasis lichenoides chronica	46 (68.7)	7 (10.5)	1 (1.5)	-	4 (6)	9 (13.4)
Pityriasis rosea	3 (33.3)	2 (22.2)	1 (11.1)	-	-	3 (33.3)
Pityriasis rubra pilaris	-	-	1 (33.3)	-	2 (66.7)	-
Pityrosporum folliculitis	3 (37.5)	2 (25)	9 912.5)	-	2 (25)	-
Polymorphic light eruption	164 (35)	8 (1.7)	9 (1.9)	2 (0.4)	269 (57.4)	17 (3.6)
Porphyrias (not EPP)	1 (50)	-	-	-	1 (50)	-

Condition	Clear/ MRA	Moderate improvement	No change/ minimal improvement	Worse	Outcome not recorded	DNA (did not attend)
Prurigo nodularis	12 (37.5)	5 (15.6)	9 (28.1)	1 (3.1)	3 (9.4)	2 (6.3)
Pruritus (idiopathic)	16 (34.8)	9 (19.6)	12 (26.1)	3 (6.5)	3 (6.5)	3 (6.5)
Pruritus (liver disease)	1 (100)	-	-	-	-	-
Pruritus (renal disease)	6 (66.7)	-	2 (22.2)	-	1 (11.1)	-
"Psoriasiform dermatitis"	13 (65)	1 (5)	2 (10)	-	1 (5)	3 (15)
Psoriasis	2661 (70.7)	305 (8.1)	104 (2.8)	38 (1)	314 (8.3)	343 (9.1)
Scleroderma	-	-	1 (100)	-	-	-
Seborrhoeic dermatitis	3 (60)	1 (20)	-	-	-	1 (20)
Subcorneal pustular dermatosis	1 (100)	-	-	-	-	-
Symptomatic dermographism	2 (50)	1 (25)	-	-	1 (25)	-
Undefined eczemas	4 (66.7)	1 (16.7)	-	-	-	1 (16.7)
Urticarial vasculitis	-	-	2 (100)	-	-	-

Figure 2.18 Courses of TL-01 UVB per year; all centres; since 1986
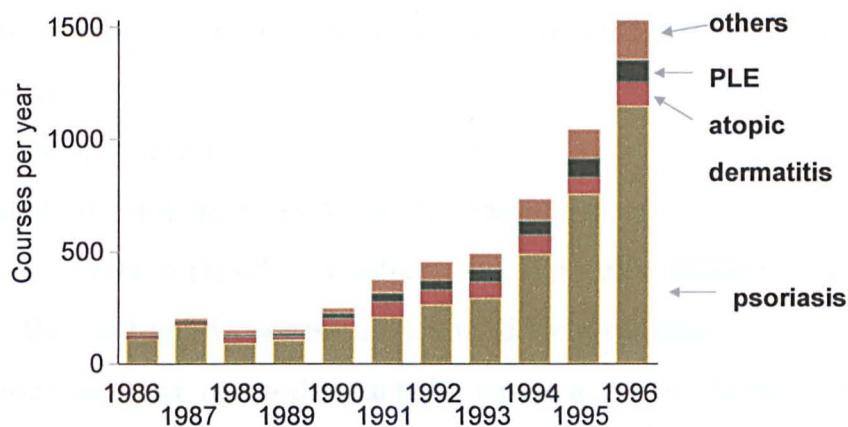
Figure 2.19

UVB (TL-01) treatments per course documented as leading
to clearance/ MRA 1992-1996.

PLE treatment outcomes recorded frequently only for a centre with a policy of giving 15 exposures
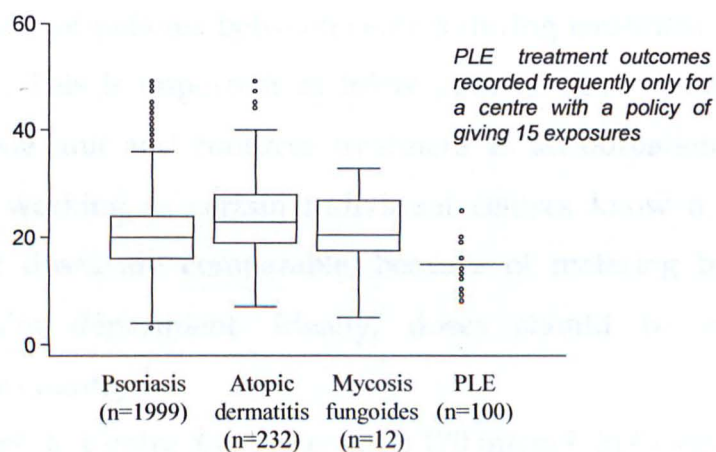
UVB administration

Dosimetry

TL-01 UVB dosimetry varied widely between centres (**Figure 2.20**). Reasons for this included:

1) Different meters, calibrated in different ways

2) Different methods of using the UVB meter, including

    - various direct methods, in which the, carefully protected, person performing the reading measures outputs while in the cubicle.

    - various indirect methods, such as using a meter clamped in the centre of the cubicle, or taking readings from individual lamps and using mathematical manipulations to provide a whole-cubicle output measure.

Such variation in what a mJcm^{-2} of UVB represents in different centres matters because:

1) It makes transfer of patients between centres during treatment difficult to arrange safely. This is important as many patients start treatment as an inpatient in one unit and continue treatment as an outpatient closer to home. Those working in certain individual centres know a few other centres where doses are comparable, because of metering by a single medical physics department. Ideally, doses should be comparable throughout the country.

2) While 25 mJcm^{-2} in Centre X is the same as 170 mJcm^{-2} in Centre Y, to take the most extreme example, there are potential problems of over- or under-treatment if a regimen from one centre is adopted by another if MED-testing is not performed.

3) While such variation in dosimetry exists, even in one relatively small country with a cohesive dermatology community, the UVB doses in quoted in publications must be interpreted cautiously.

Figure 2.20 <u>UVB (TL-01) dosimetry</u>

100 mJcm^{-2} in each of 12 units converted to "Ninewells millijoules"
UVA dosimetry shown for comparison
Differences in values in shaded area possibly accounted for by
measurement error alone
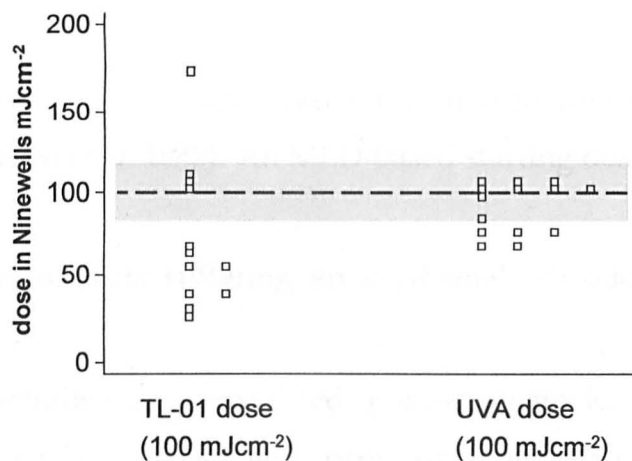
Starting dose

The starting dose of UVB (TL-01) was routinely based on the individual patient's minimal erythemal dose (MED) in 5 out of 17 centres for which this information could be obtained.

Skin phototype is not a reliable proxy for an individual's erythema response to UVB (Rampen et al. 1988). An MED-based starting dose has the advantages that:

1) It prevents patients suffering an erythemal episode following the first treatment.

2) It also excludes an unexpected photodermatosis, for example, MED measurement in a patient with psoriasis showed he also had previously unsuspected solar urticaria, and a patient with atopic dermatitis was only found to be severely photosensitive, with chronic actinic dermatitis, when his MED was determined. If MEDs are not routinely determined such patients are at risk of disastrous consequences if treated using a "standard" dose in a whole-body UVB cubicle.

3) It takes into account any drug causing increased photosensitivity with TL-01 radiation (Cameron et al. 2000a).

4) It avoids setting the starting dose excessively low for the majority (and so impairing treatment effectiveness for them) in order to avoid "burning" in a minority.

In the different centres where the MED was routinely measured, this was done in a variety of ways. Irradiation equipment was either a treatment cubicle, or separate lamp or lamps. Most used a template with squares that could be closed off to administer the MED doses. It is essential that, whichever system is used, the radiometry is the same for the MED irradiation apparatus as for the treatment cubicle.

Ideally, considering the sigmoid shape of the TL-01-erythema dose response curve (Diffey et al. 1991), a geometric series of doses (with each dose being a percentage, usually 140%, of the preceding dose) should be used (British Photodermatology Group 1992), rather than the simple arithmetic series used in some departments. Use of an arithmetic series may result in significant under-estimation of some patients' MEDs, and so compromise the effectiveness of therapy.

Figure 2.21 illustrates the trend to more treatments being required to attain clearance or minimal residual activity in centres not determining the MED. Of course, differences other than policy on MED determination may be important confounding variables. For example, in some centres not checking each patient's MED, UVB may be perceived as less effective (compared to, for example, PUVA) so many UVB patients may be relatively mildly affected (perhaps with guttate psoriasis) leading to an under-estimate of the number of "extra" treatments needed because MEDs cannot be determined.

Treatment frequency

In all except one department (which could only offer treatment twice weekly) the "standard" treatment frequency was 3x weekly. However, individual patients were treated as infrequently as once weekly (only one patient), and as often as 7x weekly. Five to seven times weekly regimens were most often prescribed for inpatients. The optimum treatment frequency for TL-01 UVB for psoriasis (let alone other conditions) is still unknown. For the majority, 3x is preferable to 5x weekly treatment, as shown by the study described in **Chapter 3** (Dawe et al. 1998). Five times a week treatment clears psoriasis only slightly more quickly than 3x weekly treatment: for most patients the extra erythema episodes, greater number of exposures, and higher UVB dose are not worthwhile when clearance only one week quicker can be anticipated. We

do not know whether 2x weekly treatment is as effective as 3x weekly treatment, and whether treatment frequency is a factor contributing to the possible differences between centres shown in **Figure 2.22**. A randomised, observer-blinded trial nearing completion in Dundee compares 2x and 3x weekly TL-01 UVB (Cameron et al. 2000b).

Figure 2.21 TL-01 UVB treatments per course for **psoriasis** documented as leading to **clearance/ MRA** in 1996. Treatment in centres basing starting dose on MED or not.
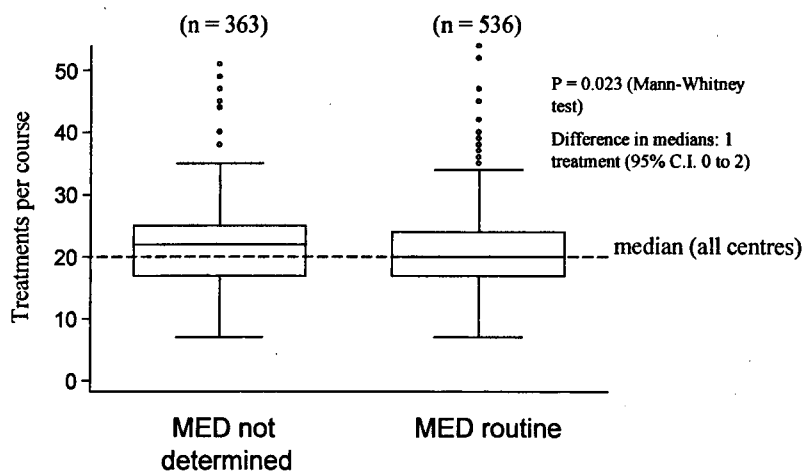
Figure 2.22 TL-01 UVB treatments per course for **psoriasis** documented as leading to **clearance/ MRA** in 1996. Treatment given 2x or 3x/ week.
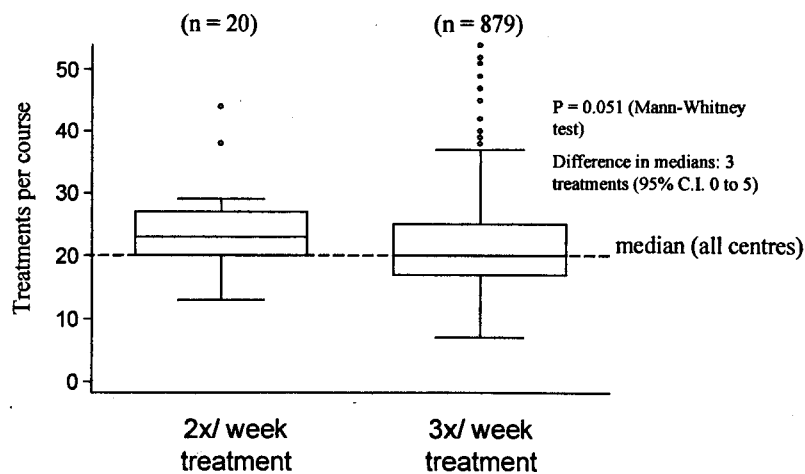
Dose increments

Most of the original studies, confirming the efficacy of TL-01 phototherapy for psoriasis, used 40% dose increments, reducing to 20% or lower depending on each individual patient's erythemal response. Recently it has been shown, in a Scottish patient population, that a lower incremental regimen with 20% reducing to 10% increments is as effective and leads to significantly fewer episodes of well-demarcated erythema (Wainwright et al. 1998). The fact that lower increments are appropriate for UVB phototherapy than for PUVA fits with the shallower erythema-dose response curve for PUVA compared to UVB (Cox et al. 1989).

The most appropriate incremental regimens for atopic dermatitis, and other conditions, still have to be determined. Most treatment units aim to use the same regimen as used for psoriasis for atopic dermatitis but, in practice, because of erythemal episodes and flare-ups of dermatitis, patients often do not tolerate the same increments, and have to be held at the same dose for several treatments during a course.

Adjunctive therapy

All departments encouraged the use of emollients during a course of phototherapy. The majority had no restrictions on emollients except that preparations that act as a sunscreen (Lebwohl et al. 1995), and those which might contain photosensitising perfumes, were discouraged. Some asked patients not to apply an emollient shortly prior to treatment although, as long as appropriate preparations, such as 50:50 white soft paraffin/ liquid paraffin or aqueous cream, are used this advice may be unnecessary. Consistency is most important: no problems should arise if the same emollient is used at the same time prior to each treatment of a course.

In theory, an appropriate emollient might increase effectiveness of psoriasis treatment by reducing refraction of radiation by scale, and so increase the UVB dose reaching psoriasis plaques, while not affecting that reaching neighbouring normal skin. However, when the clinical effect of using coconut oil prior to irradiation was studied it did not lead to more effective psoriasis clearance (George et al. 1993b). The preliminary results of a more recent study suggested that the application of groundnut oil prior to each TL-01 exposure might lead to more rapid initial psoriasis clearing. This study did not, however, examine the effect, if any, on time and exposures to clearance (Hung et al. 1997). Whether or not adjunctive emollients enhance the effectiveness of phototherapy, their use makes most psoriasis patients more comfortable while attending for treatment, and it is essential that those with atopic dermatitis continue frequent emollient use while attending for phototherapy.

Data on use of concomitant topical therapy were sparse in most phototherapy notes, but approximately half of courses involved some form of adjunctive topical therapy other than emollients: tar preparations, dithranol, corticosteroids, or calcipotriol.

There is no benefit in using adjunctive tar preparations with broad-band UVB if a "maximal suberythemogenic" regimen is used (le Vine et al. 1979). We do not know how concomitant tar therapy affects the effectiveness of TL-01 phototherapy. Similarly, data is lacking on the effects of adjunctive dithranol, corticosteroids, and calcipotriol. A study examining the effect of dithranol showed a trend towards benefit from adding dithranol but the study was small and these results may have occurred by chance (Storbeck et al. 1993). Also the TL-01 regimen used may have been sub-optimal as an unusually low starting dose and dose increments were chosen. Calcipotriol plus TL-01 UVB

is more effective than calcipotriol alone (Kerscher et al. 1993), but whether it is any more effective than TL-01 alone remains undetermined.

Most centres sometimes used systemic retinoids in combination with TL-01 UVB (Re-TL-01). Acitretin was the retinoid most frequently used. This combination has been shown to reduce exposures and dose to clearance, but does not lengthen duration of remission if the retinoid is stopped on completion of the UVB course (Green et al. 1992). Fewer than 10 patients in Scotland were documented to have received combinations of UVB and methotrexate, cyclosporin, azathioprine, or hydroxyurea. There is a concern that such combinations may have a synergistic carcinogenic effect similar to that with combinations of PUVA and systemic immunosuppressive drugs (Fitzsimmons et al. 1983; Bos et al. 1989; van de Kerkhof et al. 1997).

Stopping treatment

The comments regarding stopping treatment with PUVA (see **Page 55-56**) also apply here. Although maintenance treatment with broad-band UVB allows some patients with psoriasis to remain clear for longer than if it is not used (Stern et al. 1986), the extra exposures (with accompanying inconvenience, reduction in availability of treatment to others, and probable increased skin cancer risk) make it inappropriate for all but the exceptional, difficult-to-manage patient for whom it may be the least risky of the available alternatives. The efficacy of maintenance TL-01 has not been assessed, although it has been used for a few patients in Scotland. Sixty-seven recorded TL-01 courses extended beyond 50 treatments.

It is easy to decide when to stop a course when complete clearance is achieved. It is more difficult if a few small, thin plaques remain on shins or sacrum (minimal residual activity or "MRA"): generally practice follows that

described in the literature, and 4 to 6 "extra" treatments are given after MRA is reached if clearance is not achieved. The rationale for this is that:

1) if all courses were stopped at MRA, complete clearance would rarely be achieved, and

2) the extra exposures may help in clearing invisible (Farber et al. 1985; Kligman 1991), subclinical psoriasis from apparently normal skin and so reduce the risk of rapid relapse. This hypothesis has not yet been tested.

As with PUVA, some centres have a standard course, often of 20 exposures, which has the disadvantage of encouraging over-treatment of some, and risking under-treatment of other, patients.

Between-centre differences

Figure 2.23 shows the wide variation in number of treatments per course for psoriasis. As shown in **Figure 2.24**, similar differences were still evident if we examined only courses completed in 1996 (in case of changes in practice within centres during the preceding 5 years). Some of the explanations for differences between centres discussed under PUVA **(Pages 56-58)** apply equally to UVB.

Centre 17 used unusually high numbers of exposures for some patients, but (see **Figure 2.25**) tended to use a lower cumulative UVB dose per course. A possible explanation is that the treatment regimen used there was relatively ineffective because unusually low doses were used, and that this resulted in the need for longer courses to achieve improvement, and a few patients required maintenance therapy because they were not completely cleared during the initial course.

Some centres showed the reverse: those with unusually high cumulative UVB doses per course compared to number of treatments might be expected to

have more patients developing undesirable erythema episodes. This would appear to be true for some, but not for all: the exact regimen used, and patient selection for treatment, are important.

There was similar variation between centres in how TL-01 phototherapy was used for atopic dermatitis and for polymorphic light eruption, as illustrated in the graphs showing the range of numbers of treatments per course for those centres for which this data was available (**Figures 2.26 and 2.27**).

Figure 2.23 Whole-body UVB (TL-01) treatments per course for psoriasis (1992 - 1996) in each centre for which data available. Median is central line; box encloses interquartile range.
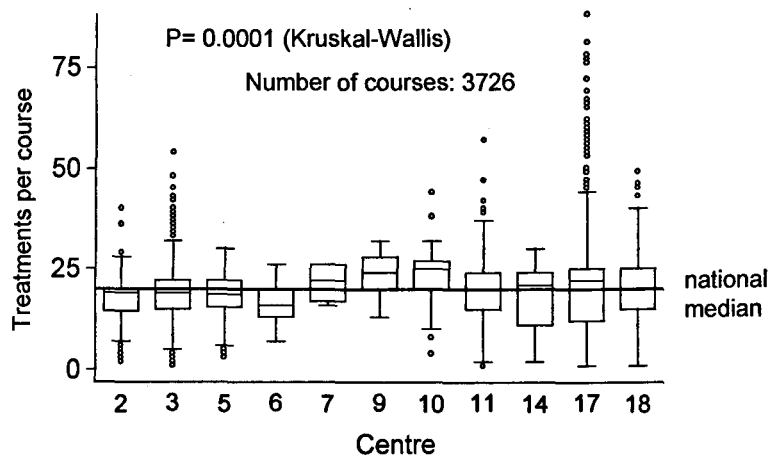
Figure 2.24 Whole-body UVB (TL-01) treatments per course for **psoriasis (1996 only)** in each centre for which data available. Median is central line; box encloses interquartile range.
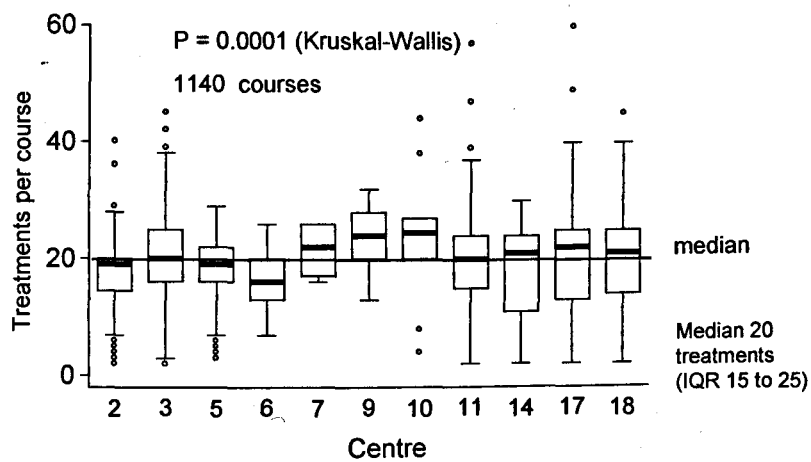
Figure 2.25 TL-01 UVB dose per course for PSORIASIS ;
1992 to 1996. *Doses all converted to Ninewells Hospital
mJcm⁻² to allow between-centre comparisons*
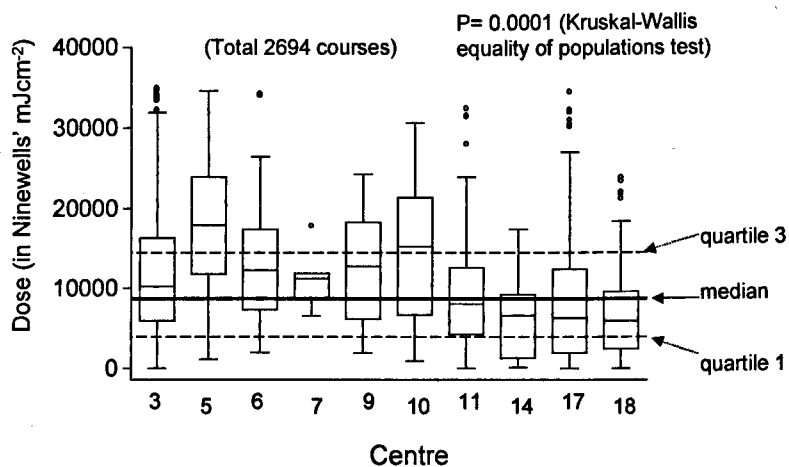
Figure 2.26 Whole-body UVB (TL-01) treatments per course
for **atopic dermatitis** (1992 - 1996) in each centre for which
data available. Median is central line; box encloses
interquartile range.
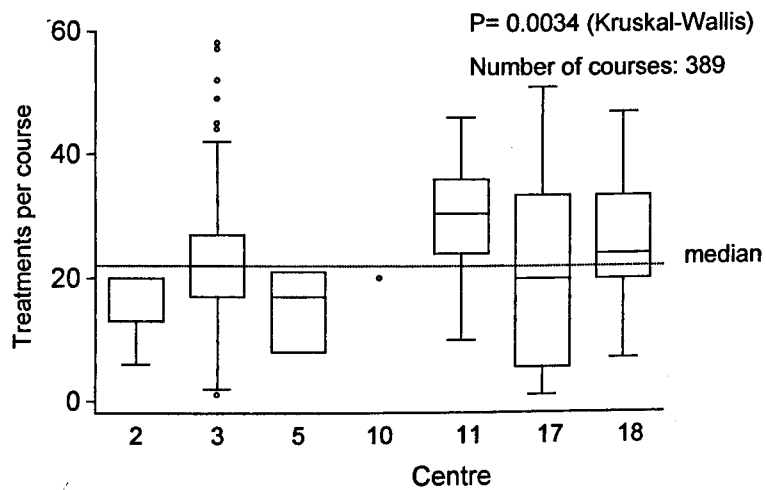
Figure 2.27 UVB (TL-01) treatments per course for **polymorphic light eruption** (1992 - 1996) in each centre for which data available. Median is central line; box encloses interquartile range.

P= 0.0001 (Kruskal-Wallis)

Number of courses: 357
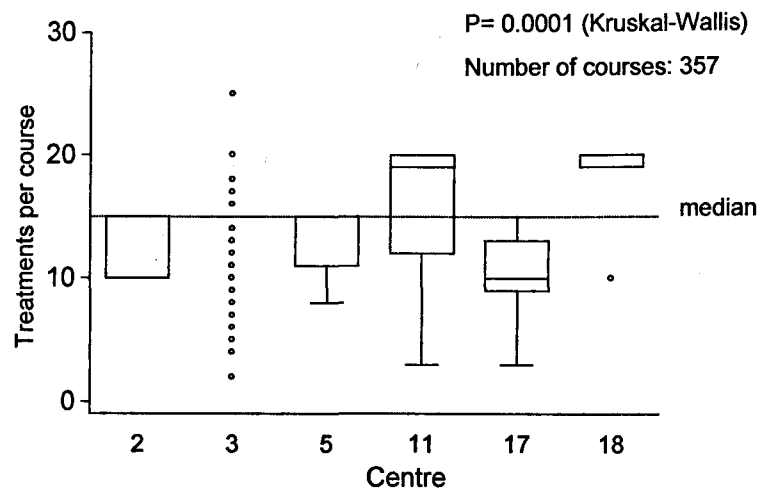
Cumulative UVB exposures

Total cumulative TL-01 exposures for individual patients were being documented by all centres so, in years to come, we will have a far better record of TL-01 UVB use than we had for broad-band UVB. TL-01 UVB has not been available in the centre (Centre 17) in **Figure 2.28** with the most high-exposure patients for as long as it has been in several others. This figure illustrates the effects of different ways of using UVB: this particular centre tended to give more prolonged courses, and frequently repeated courses, to a significant minority of their patients. This may reflect local referral habits: perhaps some of these patients would, in another centre, have received methotrexate or cyclosporin, and the use of prolonged or frequent courses of UVB for some such patients may well be preferable.

How effectively UVB is used may also have an impact on duration of remission, and therefore how frequently courses have to be repeated.

Treatment outcomes

As for PUVA, meaningful direct between-centre comparisons cannot be made because of different patient populations referred for treatment, and wide variation in the completeness of records. In some departments, if no record of outcome was made this appeared to denote a successful course of UVB, but this did not apply in other centres.

In general TL-01 UVB, as used in everyday practice, is highly effective (**Figure 2.29**) for psoriasis. **Table 2.6** lists outcome data for other conditions treated with TL-01 (and **Table 2.5** shows the data for broad-band UVB).

Figure **2.28** Total cumulative whole-body TL-01 UVB treatments per patient for **psoriasis** in each of 11 centres for which data available. Median is central line; box encloses interquartile range.
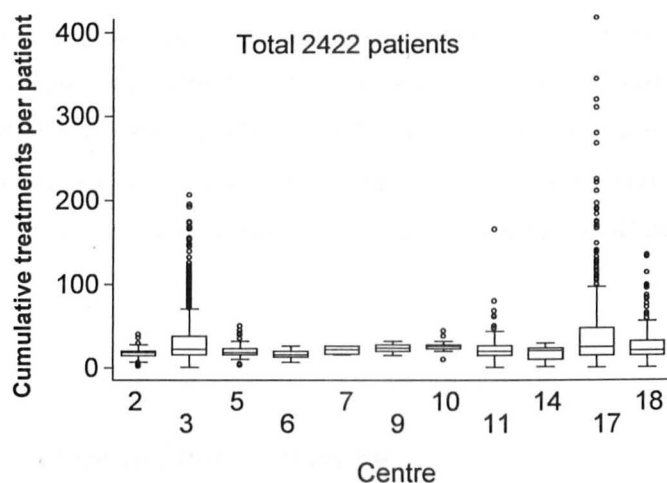
Figure 2.29

Outcome - UVB (TL-01) for Psoriasis
(Centres with >70% outcomes recorded; DNAs and unrecorded outcomes excluded)
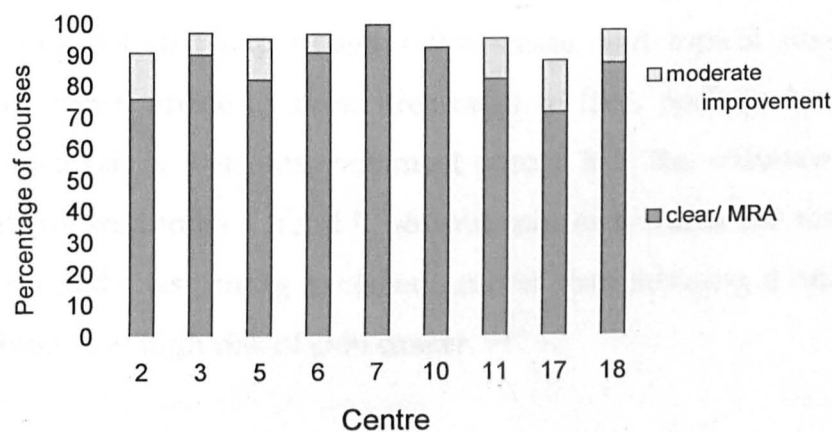
Reducing the risk of chronic adverse effects (PUVA and UVB)

- *Methods used to reduce the risk of chronic adverse effects, particularly non-melanoma skin cancer, included shielding sites not requiring treatment, as well as improving treatment regimens to minimise the number of exposures required to attain clearance. Retinoid-PUVA and retinoid-TL-01 UVB combinations were used for selected patients.*
- *All centres attempted follow-up of patients regarded as at especially increased risk, but only 2 used a computerised database to aid reliable recall of all patients with defined risk factors.*

Precautions before and during therapy

In order to minimise the risk of chronic adverse effects, particularly non-melanoma skin cancer, all centres recommended for occasional patients that only those sites requiring treatment be treated. Many psoriasis patients do not require many treatments to face, and were asked to wear a face-shield (Dawe et al. 1996) during treatments. To protect hands not requiring treatment gloves were advised. In 1997, other forms of facial photoprotection were still used, and included paper-bags, pillow-cases, and topical sunscreens. Some patients resist advice to avoid treatment to face, perhaps because the side effect of a tan is welcome, but most accept it if the rationale is explained. There appeared to be a trend in several centres towards the routine covering of unaffected sites during treatment, rather than advising it only for patients perceived as at high risk of skin cancer.

Use of systemic retinoid-PUVA (Re-PUVA) and retinoid-TL-01 UVB (Re-TL-01) combinations for patients requiring repeated courses, and who tolerate retinoid side effects, may reduce cumulative exposures and radiation dose, and so reduce long-term risks whether or not the retinoids exert a clinically significant anti-neoplastic effect.

Follow-up of "at risk" patients

As the number of patients treated with UVB increases, and PUVA continues to be required for many patients (although the *proportion* who require PUVA is falling), some method of identifying "at risk" patients so that they can be kept under review is essential. In most departments, follow-up remains somewhat haphazard with each individual consultant having different methods, or no method, of following up patients regarded as "at risk". Only two departments visited had a reliable phototherapy unit database system for identifying all those fulfilling selected criteria of "at risk" status, and calling them back for annual total skin examination.

Computer database systems designed to assist follow-up of "at risk" phototherapy patients, the "Metasa" system used in Dundee (Russell et al. 1996), and a database based on Microsoft® "Access" being developed in Glasgow and available free to members of the Scottish Dermatological Society, should help, and are almost essential for departments treating large numbers.

Some economic considerations

Estimation of treatment costs is difficult (Sander et al. 1993). Much of the data required for accurate calculation of costs is not routinely collected, and it is difficult to separate the costs of UVB and PUVA from other costs in a dermatology or physiotherapy phototherapy unit. It is important to consider information on treatment outcomes along with cost per course of treatment (Arikian et al. 1994): a centre with inadequate equipment and relatively untrained staff might have a low cost per individual treatment yet a high cost per effective treatment course.

Patient selection for phototherapy and patterns of use of other, alternative therapies, vary from centre to centre so an attempt to directly compare phototherapy treatment costs between centres is likely to be unhelpful and, if carelessly interpreted, harmful. The administration of phototherapy and PUVA involves medical staff time (including initial assessment and prescription of treatment, assessment of patients with complications during treatment, and follow-up) and secretarial time if general practitioners are to be kept informed and good records, essential for follow-up, are to be kept. Medical physics involvement is also essential to ensure satisfactory dosimetry. These costs have not been included in the calculations below[3] because reliable information on number of hours of medical, secretarial, and medical physics input into each course of treatment could not be readily obtained. An attempt was made to estimate treatment costs in 1996 for three centres with particularly detailed documentation on treatment course outcomes (**Table 2.7**).

It is reassuring to note that these figures are not *markedly* different from previous estimates of treatment costs - PUVA for 1 year at £560 and UVB <u>and</u> tar-baths (not necessary with an optimal TL-01 UVB regimen) at £222 for a 6 week course. (Cork 1993)

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[3] Cost per course of UVB or UVA phototherapy ("**COST**") = **(S + O + L)** ÷ **yearly number of therapy courses**

S= yearly nursing staff salary costs (each phototherapy nurse's salary multiplied by the proportion of working hours devoted to phototherapy or PUVA)

O= "overhead" costs - hospital management's cost per m^{-2} for lighting, heating and cleaning

L= estimated cost per year for replacement lamps + cost for UVB and UVA cubicles (at current prices, and assuming 15 years between replacements)

UVB course cost = COST x (number of UVB courses in year ÷ total number UVB and UVA courses)

PUVA course cost = [COST x (number of UVA courses in year ÷ total number UVB and UVA courses)] + £120 per course to cover oral psoralens and protective spectacles

Cost per effective course (for psoriasis): PUVA course cost or UVB course cost (as appropriate) x (number of courses for psoriasis that year ÷ number of courses for psoriasis in that centre leading to clearance/ MRA)

These absolute figures should be interpreted with caution, particularly considering the costs omitted from the calculations used. However, consideration of the factors leading to the cost differences here may be useful. As could be anticipated, costs in a large teaching hospital unit with a high throughput of phototherapy patients (Centre X) were lower than those for a smaller unit, treating fewer patients (Centre Y). We should, however, keep in mind that these apparently higher costs in a small unit ignore: 1) patient travel expenses and costs resulting from time away from work if patients had to travel further to a larger unit, and 2) the fact that the alternative treatments available to most Centre Y patients would be either inpatient treatment or more toxic (and expensive) systemic therapy rather than travel to a larger unit.

Centre Z showed a particularly high cost per effective course of PUVA. There are many possible explanations: perhaps most important is that few patients were treated with PUVA in this unit and those who were referred for PUVA tended to have especially severe disease for which other therapies, including UVB, had proved disappointing.

Another point for consideration is the markedly higher cost per effective course compared to cost for any UVB course in Centre Y. Although factors such as patient selection are relevant, use of phototherapy in this unit may not have been as effective as in some other units. Improvement in the phototherapy regimen used would involve more resources, for equipment as well as staff education, but it is possible that such resources used now could, in time, free up NHS resources for other uses, and allow more patients to benefit from phototherapy, so avoiding the need for messier and more time-consuming or toxic treatments.

When discussing cost implications it is important to consider cost savings through the effective use of phototherapy and PUVA:

1) Direct savings - avoidance of the costs of alternative inpatient topical treatments and systemic therapies; and

2) Indirect savings - reduction in working hours lost through effective control of handicapping conditions such as psoriasis and atopic dermatitis.

A more comprehensive economic assessment of UVB phototherapy and PUVA than was within the scope of this survey would be of interest.

Table 2.7

	Cost per course		Cost per effective course for psoriasis	
	UVB	PUVA	UVB	PUVA
Centre X.	£53	£173	£60	£203
Centre Y.	£108	£228	£174	£384
Centre Z.	£56	£176	£65	£317

Physiotherapy department phototherapy units

- *21 NHS physiotherapy departments provide phototherapy. In all but 4 of these departments there has been a decline in the number of phototherapy courses administered each year over the past few years.*
- *19 departments have outdated phototherapy equipment.*
- *Although some physiotherapists remain enthusiastic about their role in phototherapy many feel that, because of their other commitments and a decline in referrals for physiotherapy phototherapy, they cannot keep sufficiently up to date with new developments in phototherapy.*
- *Except in geographically remote areas most phototherapy is now administered by phototherapy nurses working in dermatology department-run phototherapy units rather than by physiotherapists.*

There are 21 National Health Service physiotherapy department-run phototherapy units. In all but 4 of these (3 of which worked closely with the local dermatology department) there was a decline in the number of phototherapy courses administered each year. Exact numbers cannot be given because they could only be obtained for a few centres. Physiotherapy phototherapy records tended to be kept in the main hospital notes, or with other physiotherapy records, and so unobtainable for this survey.

One physiotherapy department provided a PUVA, as well as phototherapy, service and another had equipment for PUVA but had not yet started to administer it.

Conditions treated

Conditions treated, in order of frequency according to estimates of numbers treated given by physiotherapists, and those notes which were examined, were:

Psoriasis (particularly guttate psoriasis)

Acne vulgaris

Atopic dermatitis

Polymorphic light eruption

Alopecia areata

Leg ulcers

Pityriasis lichenoides chronica

Physical urticarias (mainly symptomatic dermographism)

Aquagenic pruritus

Some physiotherapists expressed frustration at being asked to treat alopecia areata with UVB (as they perceived the treatment to be ineffective). Others commented on their concern that phototherapy for acne, as customarily administered by many physiotherapists, involves giving starting UVB doses 2 to 3-times the minimal erythemal dose and so causing discomfort for, in many patients, limited benefit.

Equipment

The phototherapy equipment in most physiotherapy departments was outdated (**Figure 2.30**). The Theraktin tunnels in use were fitted with 4 broad-band (TL-12) lamps and 2 infra-red lamps. The Hanau original was a quartz lamp point source that emits a broad spectrum of UVC, UVB and UVA wavelengths. The Kromayer mercury lamp was often used without filters as a UVC "germicidal" source. The Alpine sunlamp was a high pressure mercury vapour arc-lamp.

Only 3 physiotherapy departments had modern stand-up irradiation cubicles (to allow whole body treatment, with short treatment times), and only two of these were fitted with narrow-band (TL-01) UVB lamps.

Phototherapy methodology

The majority of physiotherapists were familiar with minimal erythemal dose determination. Half routinely, and 80% sometimes, used a MED-based UVB starting dose. For psoriasis, 2x or 3x weekly UVB was usual. All the physiotherapy phototherapy units limited routine courses to less than 25 treatments, with treatment stopped on clearance or after a set number of treatments. Follow-up was usually in the referring doctor's clinic, with no physiotherapy department arrangements to ensure long-term follow-up of "high-exposure" patients.

General impressions - physiotherapy phototherapy units

Some physiotherapists remained enthusiastic about their role in phototherapy, but many expressed the opinion that they have so many other duties, which comprise a much greater proportion of their workload, that they cannot keep adequately up to date with developments in phototherapy. In most areas, the exceptions being in places remote from the "local" dermatology unit, most phototherapy is now administered by phototherapy nurses in dermatology unit-run departments, leading to few referrals to the remaining physiotherapy phototherapy units. As phototherapy is increasingly used, often with other treatments prescribed by dermatologists and administered by dermatology nurses, this decline in physiotherapy phototherapy will probably continue. The problem of providing a modern, optimally effective and safe phototherapy service to those who live far from their closest dermatology department awaits a solution. In some regions the solution may be a carefully supervised home phototherapy service run by a dermatology unit.

Figure 2.30 Physiotherapy phototherapy unit equipment

Theraktin tunnel (13 units)

Hanovia Alpine sunlamp (13 units)

Stand-up units (3 units)

2

1

3

6

5

2

1

Two departments have PUVA facilities - currently in use in one

Kromayer lamp (3)

Hanau original (1)

1
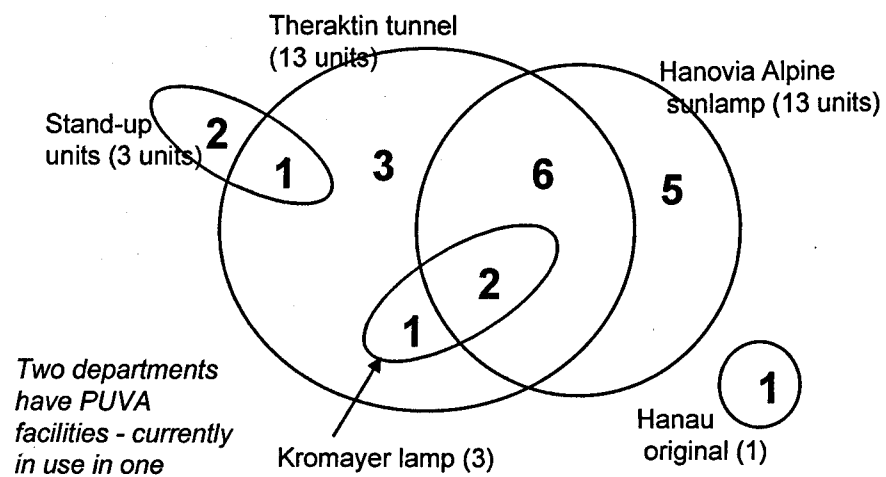
Concluding comment, Chapter 2

Following the 1991 audit, there have been great improvements in the PUVA service in Scotland. In particular, PUVA use is now more selective, aided by the availability in most centres now of UVB phototherapy as a more convenient and safer alternative. Various improvements could still be made: not all centres yet base the UVA starting dose on minimal phototoxic dose assessment, for example. However, the major deficiency in the PUVA service, is the lack of a reliable system in all centres to identify and follow-up patients at risk of skin cancer development as a consequence of therapy.

As regards UVB phototherapy, the 1996/1997 survey has of necessity been largely descriptive. Although, in Chapter 6, recommendations for UVB phototherapy are given, many of these are based on limited evidence, as there remain many aspects of UVB phototherapy methodology that require proper study, with well designed clinical trials. Original research designed to expand the evidence base on which we can make recommendations is contained in the following three chapters of this thesis.

Chapter 3

A new development discussed in Chapter 1 was the introduction of narrow-band (TL-01) UVB phototherapy. One of the findings of the survey phase of the Scottish phototherapy and PUVA audit (described in Chapter 2) was that, since 1991, broad-band UVB lamps have been replaced by TL-01 lamps in almost all dermatology phototherapy units. This chapter consists of a meta-analysis of the published controlled studies comparing this new therapy with broad-band UVB for chronic plaque psoriasis, the most frequent indication for UVB phototherapy.

Summary of meta-analysis of studies comparing narrow-band (TL-01) with broad-band ultraviolet B for psoriasis

Since narrow-band (TL-01 lamp) UVB phototherapy was introduced in 1984, 13 small comparative studies have reported that it is a superior psoriasis treatment to broad-band UVB. It is now widely used, but it has not replaced broad-band UVB everywhere. Should those centres still using broad-band UVB change? To answer this we need to know not just that TL-01 is more effective, but how much more effective it is.

A literature search (electronic database and manual, including search terms in English and German) revealed 20 published (2 as abstract only) clinical studies addressing the relative efficacy of TL-01 compared with broad-band UVB. Fourteen were controlled or quasi-controlled (2 with historical controls) studies. Six open studies were excluded. The controlled studies included 9 with a within-patient, paired design. Five studies were randomised or quasi-randomised (randomised by birth date, or method not described).

The main comparable end-points (observer assessed "better treatment" on pairwise comparison, complete clearance, remission at 1 year) varied. The odds ratio, with 95% confidence interval, for achievement of a better outcome with TL-01 than with broad-band UVB was calculated for each of the 13 studies including sufficient data to allow this. Using a fixed effects model, the combined odds ratio favouring TL-01for all these studies (comprising data from 455 subjects) was 9.1 (95% 4.3 to 19.4). Sensitivity analysis included re-analysis with a random effects model, and separate analyses of selected studies judged to be of better methodological quality (within-patient paired studies and randomised studies) and those just examining an end-point of particular interest (odds of achieving clearance versus not clearing). The findings of all analyses were similar, suggesting that, despite the heterogeneity in study design and comparable end-points, the overall conclusion that TL-01 is significantly more effective than broad-band UVB is robust.

If in a population treated with broad-band UVB we expect a good outcome in 60%, and we conservatively take the lower end of the summary odds ratio (4.3) as reflecting the "true" figure, the number needed to treat to see one extra good outcome is just 5. This magnitude of greater benefit with TL-01 suggests that, unless we believe it is safer (for which there is no evidence), the use of broad-band UVB for psoriasis is no longer appropriate.

A meta-analysis of controlled studies comparing the efficacy of PUVA and TL-01 UVB for psoriasis

Every dermatology department phototherapy unit in Scotland offers narrow-band (TL-01) UVB phototherapy. At the time of visiting the departments for the survey described in the last chapter, one department still also used broad-band UVB. That department had one TL-01 UVB cubicle, and two broad-band UVB cubicles.

Most UVB courses in Scotland are administered using TL-01 lamps. However, broad-band UVB is still used in one dermatology phototherapy unit, and most physiotherapy phototherapy units, in Scotland. In other countries, broad-band UVB remains frequently used, and in some regions is the only form of UVB available. It is therefore important to know whether TL-01 UVB is more effective than broad-band UVB, and if it is to know how much more effective. Is narrow-band UVB sufficiently more effective than broad-band UVB that we should recommend a change of lamps and treatment regimens to the centres where broad-band UVB is still used?

Meta-analysis methodology

Search strategy

Articles comparing narrow-band (TL-01) UVB and broad UVB to treat psoriasis were identified as those previously known to us, those identified in a review of narrow-band UVB (Bilsland et al. 1997), and by search of EMBASE® (Elsevier Science, Amsterdam) and MEDLINE® (National Library of Medicine, Bethesda) using Ovid search software, version 7.8 (Ovid Technologies Inc, 1988). Search terms (subject headings and key-words) included "psoriasis" AND ["phototherapy" OR "ultraviolet radiation" (in

EMBASE®) OR "ultraviolet rays" (in MEDLINE®). To narrow the search, key-word search terms combined with these previous terms included: "narrow-band" OR "TL-01" OR "311nm" OR "311-313nm" OR "312nm" OR "Schmalspektrum". Some publications described more than one separate study.

Study inclusion criteria

All controlled studies comparing TL-01 UVB with broad-band UVB sources to treat psoriasis, and reported in sufficient detail to allow calculation of an odds ratio for an important comparable end-point, were included. Studies concerning TL-01 UVB for psoriasis that were excluded were: 1) open studies, 2) studies comparing different adjuncts to TL-01 phototherapy, and 3) studies designed to compare different ways of administering TL-01 therapy. We chose not to use any arbitrary quality rating scales, because of concern that this could itself be a source of bias (Detsky et al. 1992), and instead documented important features of study design to allow these to be openly taken into account when interpreting the findings.

For this meta-analysis all controlled trials, whether randomised or not, were included. Systematic reviews comparing treatments published by the Cochrane collaboration usually exclude studies that are not identified as randomised controlled trials. This is because most studies that do not use random allocation to decide who gets which treatment are more likely to be affected by treatment allocation bias.

When different study subjects receive each treatment, avoidance of such bias, which can lead to spurious results caused by systematic differences between the subjects who get treatment A and those who receive treatment B, is essential. In the comparison of phototherapy treatment regimens for psoriasis

it is possible to compare two treatments at the same time within the same subjects. With this type of study, the risk of allocation bias influencing study results is less than in studies involving between (rather than within) subject comparisons. Therefore, although in paired, within-subject comparison studies, randomisation can usefully aid observer masking to treatment allocation (and lack of observer masking is a potential source of bias in assessment of treatment effects) it is not as essential as in the more frequent between-subject comparison studies considered by the Cochrane collaboration in their insistence on randomised controlled studies.

Analysis

For each study, the most readily comparable end-point of treatment, assessable on an intention-to-treat basis, was identified. To calculate odds ratios (ORs) and 95% confidence intervals for the paired (within-patient and cross-over) studies, the methods of Morris and Gardner, (Morris & Gardner 1989) with reference to standard tables for the binomial distribution, (Lentner 1982b) were used. Standard formulae were used to calculate these for the unpaired studies (Armitage et al. 1994). To permit odds ratio calculation for studies with no events in a cell of the 2x2 contingency table used for analysis, a small sample correction was made by adding 0.5 to each cell. The data were examined and, in the absence of significant heterogeneity, a fixed effects model odds ratio meta-analysis conducted and forest plot drawn using the macro written by Sharp and Sterne (Sharp & Sterne 1997) for "Stata" statistical software (Intercooled Stata, Release 6.0, College Station, Texas, 1999). Sensitivity analysis was performed by repeating analysis using a random effects model, and by separate analyses examining just those studies in which the comparable end-point was clearance or minimal residual psoriasis *versus* not cleared, and also examining just those judged to be of greatest methodological quality (half-body paired studies, randomised, and masked

studies). To aid interpretation of the clinical importance of odds ratios shown on the forest plot, corresponding numbers needed to treat (NNTs) were indirectly calculated from the odds ratios (Sackett et al. 2000).

Results of broad-band UVB versus TL-01 UVB meta-analysis

Fourteen controlled studies comparing TL-01 and broad-band UVB phototherapy for psoriasis, reported in 10 papers (van Weelden et al. 1984, van Weelden et al. 1988; Green et al. 1988; Larko 1989; Karvonen et al. 1989; Barth et al. 1990; Picot et al. 1992a; Storbeck et al. 1993; Hofmann et al. 1997; Coven et al. 1997; Walters et al. 1999), were identified (**Table 3.1**). All but one of these studies were included. This one (Hofmann et al. 1997) was excluded because of insufficient data provided to calculate an odds ratio for clearance or similar end-point. This was an 11 patient, randomised, within-patient paired comparison of TL-01 and broad-band UVB, both with adjunctive coal tar solution. Although initial clearing (during first 3 weeks) was faster with TL-01 in 2 patients, complete clearing was achieved equally quickly with both treatments, and there was no detectable difference in remission duration.

For two half-body paired studies, reported in an abstract only (van Weelden et al. 1984), odds ratios were based on extrapolated numbers of subjects clearing with TL-01 and with broad-band UVB. These extrapolations were based on assuming that the probability reported as "P<0.05" in favour of TL-01 was in fact P=0.05, so may have under-estimated the true odds ratio in favour of TL-01.

Six reports of TL-01 for psoriasis were excluded because they were not controlled studies (Picot et al. 1992b; Alora et al. 1997; Wishart 1998; de Rie et al. 1998; Gupta et al. 1999; Carrozza et al. 2000). A further eleven controlled studies were identified, but were not comparisons of TL-01 and broad-band

UVB: 5 were studies of adjunctive therapies (George et al. 1993b; Kerscher et al. 1993; Calzavara-Pinton 1998; Brands et al. 1999; Behrens et al. 2000), three compared TL-01 with PUVA (Van Weelden et al. 1990; Green et al. 1992; Tanew et al. 1999; Gordon et al. 1999), and three compared different TL-01 administration regimens (Dawe et al. 1998; Hofer et al. 1998; Wainwright et al. 1998).

Table 3.1 Controlled studies comparing TL-01 with broad-band UVB phototherapy for psoriasis

Study (1st author & year)	Controls	Randomized?	Masking?	Pattern of psoriasis	Adjunctive therapy	Number of subjects		Main comparable end-point
						TL-01	Broad-band	
Van Weelden, 1984	Crossover (historical controls)	No	No	Not stated	Not recorded	8	8	"better treatment" as assessed by observer
Van Weelden, 1984	Within patient paired	Not stated	Not stated	Not stated	Not recorded	9	9	"better treatment" as assessed by observer
Van Weelden, 1988	Within patient paired	Yes (method unclear)	Observer-masked	"Widespread"	Salicylic acid ointment	10	10	"better treatment" as assessed by observer after 10 treatments
Green, 1988	Historical controls	No	No	Chronic plaque and "extensive" (>20% body surface) guttate	Emollients	52	25	Remission at 1 year
Larko, 1989	Within patient paired	No	Not stated	"Extensive" (average 57% body surface)	None	29	29	Patient preference
Karvonen, 1989	Within patient paired	No	Not stated	Chronic plaque	Dithranol	20	20	"better treatment" as assessed by observer
Karvonen, 1989	Contemporary, unpaired	Yes (by birth-date)	Not stated	Chronic plaque	Dithranol	17	23	"good result" after 12 treatments
Picot, 1989a	Contemporary, unpaired	Yes (method unclear)	Double-masked	Chronic plaque and guttate	Salicylic acid ointment	15	15	Patient preference after 20 treatments
Barth, 1990	Within patient paired	No	Not stated	Exanthematic (guttate)	Salicylic acid ointment	22	22	Complete clearance
Storbeck, 1993	Within patient paired	Yes (method unclear)	Observer-masked	Chronic plaque	Salicylic acid/ emollients	10	10	One side better
Storbeck, 1993	Within patient paired	Yes (method unclear)	Observer-masked	Chronic plaque	Dithranol	13	13	One side better
Coven, 1997	Within patient paired	No	No	Chronic plaque	Coal tar (below waist)	22	22	"better treatment" as assessed by observer after 20 treatments
Walters, 1999	Within patient paired	No	Observer-masked	Chronic plaque	Emollients	11	11	Clearance by 18 treatments

The fourteen controlled (13 included in combined analysis, 1 not) studies are summarised in **Table 3.1**. It should be noted that although I have considered the first van Weelden, 1984 study (one of two studies reported in the one abstract) to be controlled, the controls were historical, but were the same patients. The control group used in study by Green et al (Green et al. 1988), in the early stages of investigation of TL-01 for psoriasis, was a population of unmatched patients who previously attended the same unit.

Nine studies were of a within-patient paired (comparing TL-01 to one body-half with broad-band UVB to the other half) design. Such a design lends power to the study, allowing for careful controlling of any potential confounding factors. Lack of randomisation (a potential flaw with 7 of these paired studies) is likely to matter less than in unpaired studies. Some studies looked at several outcomes but some, for example number of treatments to clearance, could not be compared across all studies.

All the studies showed Tl-01 to be more effective than broad-band UVB (**Figure 3.1**), although the 95% confidence interval for all but three included the possibility that there might be no difference or that broad-band UVB might be slightly better. It should be noted that the method of calculating confidence intervals used for paired studies was a conservative method based only on the sample size of discordant pairs (patients better on one side than another). While this is intuitively appropriate for those studies in which the end-point was direct comparison of sides and decision about which was better, it seems less appropriate for the studies with end-point of clearance assessed independently.

Despite the differences in study design and end-points, it is clear that every study points towards TL-01 being more effective, with the summary odds ratio for all studies being 9.1 (95% C.I. 4.3 to 19.4). If in a population treated

Figure 3.1 Odds ratio (and 95% confidence intervals) for all 13 controlled studies. To assist with clinical interpretation of the odds ratios, corresponding numbers needed to treat (NNTs) are shown, based on assuming the patients' expected event rate (PEER) [the number expected to clear if using broad-band UVB] is 60% or 85%.
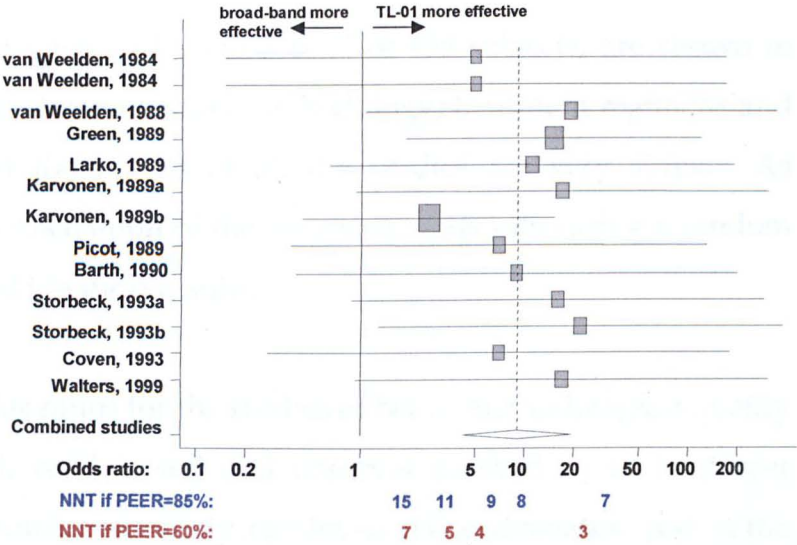
with broad-band UVB, we expect to see a good outcome in 60%, then the lower end of this confidence interval corresponds to a need to treat just 5 patients with TL-01 instead of broad-band UVB to see 1 extra good outcome.

The results of these studies, including a total of 455 subjects, are shown in **Figure 3.1**. Despite variations in study methodology, treatment regimens and outcomes investigated the results of all the studies are very similar. As expected from this, re-calculation of the summary odds ratio using a random effects model produced identical results.

Examination of the odds ratios for the studies of better methodological quality (within-patient paired, randomised and observer masked as to treatment allocation) produced similar summary results, as did examination just of the studies for which odds ratios for the end-point of clearance could be calculated (**Figure 3.2**). The most frequent study end-point on which sufficient data was provided to allow calculation of odds ratios was assessment of treatments after a pre-decided number of exposures (**Table 3.1**), following which patients were offered the better treatment to whole body. The data from these studies does not therefore include numbers of subjects clearing completely, although it is probably reasonable to assume that the better treatment at pre-determined study end-points of 10 (van Weelden et al. 1988), 12 (Karvonen et al. 1989), 18 (Walters et al. 1999), or 20 treatments (Picot et al. 1992b; Coven et al. 1997) is also the treatment that will clear more patients.

The most frequent pattern of psoriasis studied was chronic plaque psoriasis, but the one study that recruited only guttate (exanthematous) pattern psoriasis patients showed a similar advantage in using TL-01 to the others (Barth et al. 1990). The majority of subjects included were of skin phototypes I to III but in one study 10 of 22 subjects were of skin phototypes V or VI (Coven et al. 1997).

Figure 3.2 Odds ratio (and 95% confidence intervals) for all controlled studies, paired half-body studies, all randomized studies, studies with observer masking to treatment allocation, and studies in which comparable outcome was cleared versus not cleared (rather than other end-points in Table 1).
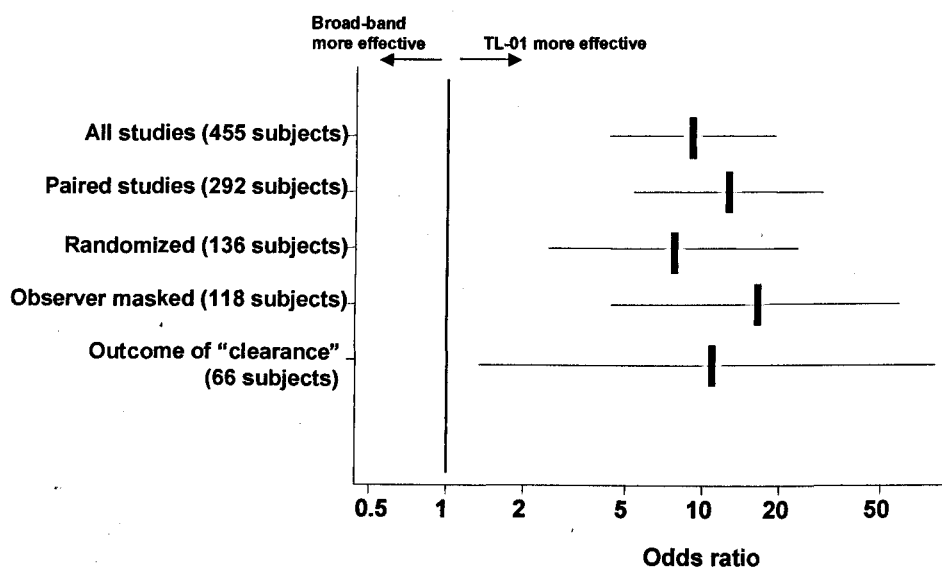
What can we conclude from this?

This review of the published studies comparing Tl-01 UVB with broad-band UVB supports the conclusion, expressed by the authors of all but one relevant controlled trial (Hofmann et al. 1997), that TL-01 UVB is more effective than broad-band UVB. The main value of this quantitative review is that it gives a more precise estimate of the degree of magnitude by which TL-01 is more effective than broad-band lamps. If we look at all the comparable studies together, and conservatively look at the lower end of the odds ratio for a better response to TL-01, we can convert this into a number needed to treat (to see one better outcome through using TL-01 rather than broad-band UVB) of 5 if we assume we can get a good response in 60% of those treated with broad-band UVB. Even if we optimistically assume that 85% will reach clearance (or other favourable response) with broad-band UVB, we need to treat 11 or fewer with TL-01 to get an extra good outcome.

How reliable are the findings of this review? We need to consider the possibility of missed studies (most likely unpublished, but possibly published in non-European languages or in non-indexed journals) that showed important different findings. Also, shortcomings in design could be found in all the studies we examined, and the outcome measures were mixed.

We cannot rule out the possibility of missed unpublished studies, but the community of clinical photo-dermatology researchers is relatively small, and it seems unlikely that we could be unaware of sufficient unpublished studies, with different results from those reviewed, for publication bias to have significantly affected our overall findings. One small, but otherwise well-designed, study did have to be excluded (Hofmann et al. 1997) because it concentrated mainly on examining the end-point of rate of clearing, and insufficient information was published to allow comparable odds ratios to be calculated. This paired study, comparing 5x weekly regimens, with arbitrary

starting doses followed by 20-50% increments, with adjunctive coal tar solution to each side, found no statistically significant differences between the therapies. They may have been treating a group of patients likely to respond particularly well to any form of UVB: 7 of 11 patients had guttate psoriasis (although 5 were described as also having plaques).

Despite imperfections in study design, and in particular the fact that all were small, 146 patients (292 subjects) participated in paired within-patient controlled studies, the results of which are likely to be more reliable than those of the unpaired studies. The fact that we found no differences in direction, nor major differences in magnitude, of effect when comparing results from different study designs is reassuring.

Although different outcomes were compared, they can all be considered as one binary outcome measure: good response *versus* relatively poor response. Relatively few subjects (64) were included in studies in which patients were continued on study treatment until clearance (rather than comparing treatments until a previously chosen end-point short of clearance with both therapies, and then *withdrawing from study*), but the *summary results* (**Figure 3.2**) are similar to those from analysing all included-study patients. It would have been of interest to compare end-points other than a simple better-or-not outcome between studies, but most did not include sufficient data on continuous variables such as treatments or days to clearance.

The findings of this review apply mainly to moderately severe and severe chronic plaque psoriasis, but the one study just involving those with guttate psoriasis showed a similar magnitude of benefit of TL-01 over broad-band UVB. In that study the end-point was <u>complete</u> clearance, rather than clearance or minimal residual activity (trace disease) which are more realistic end-points to examine when treating chronic plaque psoriasis. We found no suggestion that TL-01 is any less advantageous compared to broad-band UVB

in patients of high skin photo-types (SPTs), but the majority of included subjects were of photo-types I to III, so we cannot confidently extrapolate our summary findings to SPT IV to VI patient populations.

Narrow-band (TL-01) UVB is more effective than broad-band UVB for moderately severely and severely affected skin photo-type I to III chronic plaque psoriasis patients. It remains possible that for patients with less severe psoriasis than included in these studies the difference in efficacy is less marked, but there are indications that even for the usually readily treatment-responsive guttate psoriasis (Barth et al. 1990) TL-01 is to be preferred. The magnitude of greater benefit is such that, on efficacy grounds, the use of broad-band UVB for psoriasis is hard to justify.

A concern about any new phototherapy lamps relates to the risk it will cause skin cancers. As mentioned in Chapter 1, psoralen-UVA photochemotherapy carries an increased risk of non-melanoma skin cancer development (Stern et al. 1998), and there is a suggestion that it possibly also increases the risk of later development of melanoma (Stern et al. 1997). The risks associated with UVB lamps (broad-band or narrow-band) have not been so carefully studied, but appear to be significantly lower (Studniberg et al. 1993; Stern et al. 1994; de Gruijl 1996). In the absence of long-term follow-up data for TL-01 UVB, which has only been used for just over 15 years, the relative skin cancer risks associated with this lamp compared to broad-band UVB lamps remain unclear, but the best current evidence suggests the risks are likely to be less with TL-01 (Young 1995).

What is the evidence for use of TL-01 for other dermatoses previously treated with broad-band UVB?

As shown in the list of indications for TL-01 recorded during the Scottish phototherapy audit (**Table 2.7**, Chapter 2), TL-01 phototherapy is used for many indications, including all those previously treated with broad-band UVB. For all these indications other than psoriasis we lack any controlled trial data comparing broad-band and TL-01 lamps.

Controlled trials comparing TL-01 with PUVA for atopic dermatitis and polymorphic light eruption (PLE) (Bilsland et al. 1993; Der-Petrossian et al. 2000) have been published. A previous study showed PUVA to be more effective than broad-band UVB as a prophylactic treatment for PLE (Murphy et al. 1987), and by extrapolation we can conclude that TL-01 is likely to be more effective than broad-band UVB. The controlled trial comparison of TL-01 and PUVA for atopic dermatitis was small, and could not exclude a moderate difference in efficacy of the two treatments. However, if we take the practical problems of PUVA administration and its adverse effects into account, the conclusion is that TL-01 should be used in preference to PUVA for atopic dermatitis. Clinical experience and open studies are supportive of the use of TL-01 phototherapy for many other conditions previously treated with broad-band UVB, for example patch-stage mycosis fungoides (Clark et al. 2000).

As psoriasis is the major indication for phototherapy, accounting for over 80% of broad-band UVB courses administered (**Figure 2.17**, Chapter 2), a change over to TL-01 lamps on the basis of comparative studies for this indication is easy to justify.

For most of the other UVB indications, clear evidence for efficacy of any form of UVB is limited, and, except for pityriasis rosea (Arndt et al. 1983), controlled trial data altogether lacking. Although careful, but uncontrolled, observations of outcomes of broad-band UVB phototherapy for acne vulgaris (Mills et al. 1978) suggested that it was ineffective or, at best, led to a minimal improvement it remains widely used, and it accounted for 1% of UVB courses recorded for the Scottish phototherapy audit (Chapter 2). It is possible, although unproven, that it can be effective if administered with 2 to 3x minimal erythemal dose starting doses intended to cause erythema and desquamation. Such treatment, most readily applied with the more erythemogenic broad-band UVB lamps, is rarely if ever warranted now that more effective treatments are available, so a comparative trial of narrow-band and broad-band UVB for acne would be inappropriate. Acne vulgaris is however one of the many conditions for which we require more evidence on the efficacy of TL-01 UVB compared to other established treatments.

Conclusion to meta-analysis of studies comparing TL-01 with broad-band UVB for psoriasis

Narrow-band (TL-01) UVB is a more effective treatment for psoriasis, at least for chronic plaque psoriasis in skin photo-type I to III patients, than is broad-band UVB. More work is needed to further refine how we use it for psoriasis, and to decide its place in the therapy of the many other conditions for which it is used. Only continued careful follow-up will let us know whether or not it is associated with an increased risk of skin cancer.

Comment

This chapter has described a systematic, quantitative review of previous studies addressing an important question concerning phototherapy methodology. Although assessment of the reviewed studies individually, without an attempt to combine and summarise their findings, would have strongly suggested that TL-01 UVB is more effective than broad-band UVB for psoriasis (the most frequent phototherapy indication) none of these studies individually could give a reasonable idea as to the magnitude of difference in efficacy between these different UVB phototherapy lamps. Also, this review allowed assessment of the effects of including and excluding studies with different designs (and possible flaws), with the finding that our overall conclusions about the treatments' comparative efficacy remained the same when we examined only the studies considered of better methodological quality than the others.

Chapter 4

An important aspect of phototherapy methodology is treatment frequency. This chapter describes a study designed to determine the optimal treatment frequency for TL-01 ultraviolet B phototherapy of chronic plaque psoriasis in a skin phototype I to III population.

Summary of a randomised controlled trial of three times weekly and five times weekly TL-01 UVB phototherapy for chronic plaque psoriasis

We planned to compare the efficacy of three- and five- times weekly narrow-band TL-01 (311-313nm) ultraviolet B (UVB) phototherapy regimens for chronic plaque psoriasis.

A randomised, observer-blinded, half body, within-patient paired study in the phototherapy unit in a university hospital was conducted.

Twenty-one patients with chronic plaque psoriasis (13 men, 8 women; age range 21 to 68; skin phototypes I [2 patients], II [14] and III [5]) entered the study. Sixteen reached clearance or minimal residual activity (MRA) on both sides. Of the other 5; three withdrew because they did not reach clearance or MRA on the 5x weekly side by a maximum of 30 treatments, one when he was satisfied with moderate improvement and one because of repeated failure to attend.

The main outcome measures were number of exposures, cumulative dose and time to achieve psoriasis clearance. Also analysed were change in scaling, erythema and induration scores over the study period for all patients who entered the study, analysed on an intention to treat basis, and the frequency of adverse effects with each regimen.

Those who completed treatment reached clearance or MRA after a median of 35 days with 5x weekly treatment compared to 40 days with 3x weekly treatment (P=0.007), but required a median of 23.5 compared to 17 UVB exposures (P=0.001) and 94 minimal erythemal dose multiples (MEDs) compared to 65 MEDs (P=0.015). Fifteen (out of 16) developed at least one episode of well-demarcated erythema during 5x weekly treatment compared to just 3/16 treated 3x weekly (P<0.001). There was no significant difference between regimens in duration of remission.

In conclusion, for this skin phototype I to III population, the slightly more rapid clearance of psoriasis with 5x weekly phototherapy is not, for the majority of patients, sufficient to justify the extra exposures.

Introduction

In making phototherapy as effective and safe as possible, choice of lamp (as discussed in the previous chapter) is probably the most important factor. But other factors expected to influence efficacy and safety relate to how we use these lamps. An important aspect of UVB phototherapy methodology, and in the administration of any treatment for that matter, is the frequency of treatment.

Frequency of UVB treatment for psoriasis

In Scotland (Chapter 2, page 76), as in the UK as a whole (Dootson et al. 1994), UVB (all sources) is most frequently administered 2x to 7x weekly. We do not, as yet, know the optimum narrow-band (TL-01) ultraviolet B weekly treatment frequency for chronic plaque psoriasis. TL-01 UVB has largely replaced broad-band UVB in Scotland (Chapter 2), and is increasingly used further afield (Bilsland et al. 1997), because of its greater efficacy for psoriasis than broad-band UVB (Chapter 3). When treating psoriasis, our aim is to clear psoriasis with as few unwanted acute effects as possible, and to minimise the risk of late adverse effects (particularly non-melanoma skin cancer) by minimising each patient's cumulative UVB treatments and dose.

Traditionally outpatients attending Ninewells Hospital for phototherapy were treated 3x weekly, and inpatients 5x weekly. Although the question: "How often should we administer UVB?" has exercised dermatologists since at least 1930 (Aitken 1930c), the answer has remained unclear even for conventional broad-band sources. However, a paired comparison study of 9 patients showed no demonstrable advantage in treating chronic plaque psoriasis (with "Sunlamp" irradiation) twice daily compared to once daily (Petrozzi et al. 1981). A retrospective comparison of a 3x weekly with a 5x weekly broad-band (FS72 T12 lamp) UVB regimen showed no significant differences in dose or number of treatments to clearance and that the 3x weekly regimen was better tolerated (Adrian et al. 1981).

That study was a retrospective review, not a controlled study, and factors other than the differences in treatment frequency may have been important. If, on the basis of this limited evidence, we accept that 3x weekly is preferable to 5x weekly broad-band UVB, this is of limited help in deciding how frequently to administer TL-01. The optimum frequency of phototherapy with one ultraviolet source need not be the same as that for another. As the TL-01 lamp has a minimal output of the therapeutically unimportant (Parrish et al. 1981), but erythemogenic (van Weelden et al. 1988) wavelengths we might expect more frequent treatment than would be appropriate with broad-band UVB to be tolerated, and, possibly, to be more effective.

Patients often comment that a fortnight sunbathing on holiday clears their psoriasis, while it may take 4 to 7 weeks of 3x weekly hospital phototherapy to achieve the same result. A recent study which compared Canary Islands heliotherapy with broad-band UVB phototherapy in Finland provided some evidence to support this frequently heard anecdote. It showed heliotherapy to clear psoriasis more rapidly and with a lower cumulative UVB dose than phototherapy (Snellman 1992). One of several possible explanations for this finding is that more frequent therapy was more effective.

We conducted a study designed to 1) test the hypothesis that 5x weekly TL-01 UVB would clear psoriasis more rapidly and with fewer UVB exposures and a lower cumulative dose than 3x weekly treatment, and by doing so to 2) help to answer a question of practical, clinical importance: "How frequently should we administer TL-01 phototherapy for chronic plaque psoriasis?"

Methods

Study design

This was an observer-blinded, randomised paired (within-patient) comparison study. Patients gave their informed consent after an opportunity to discuss the

study implications and reading a patient information leaflet. The Tayside Committee on Medical Research Ethics approved the study. We treated each half-patient (sagittal plane) independently following our standard minimal erythema dose (MED)-based, low percentage dose incremental, (Wainwright et al. 1996) UVB phototherapy regimen **(Table 4.1)**, with only the treatment frequency differing between sides. A random number table-generated treatment allocation list, held by a member of department not involved in recruiting patients to this study, was used to determine which (right or left) side was treated 3x and which side 5x weekly. Patients wore a half-body suit (adapted work overalls) made of material that allowed transmission of no detectable UVB and negligible UVA **(Figure 4.1)**, (as assessed by Hitachi U-3210 double beam reflectance spectrophotometer). If the dose due to be delivered to each side differed, the higher dose side was treated first with the difference between the prescribed doses. The suit was then removed to allow administration of the remaining dose to both sides. At each visit patients were assessed and the psoriasis severity graded by an observer unaware of treatment allocation. The decision to stop treatment was made following our unit's standard protocol. Those patients whose psoriasis cleared completely had their treatment stopped at that point. Those who reached a state of "minimal residual activity" (MRA) of psoriasis, defined as trace disease below knees or on sacrum only, were given a maximum of 4 treatments after this was first recorded.

After discharge all patients were followed-up for a year, or until relapse, at monthly intervals by telephone or visit to our department for assessment. If there was any suggestion of psoriasis recurring on either side, the patient was asked to attend for review. Relapse was defined as either 1) an increase of global score to 50% of that at baseline or 2) a return of psoriasis of sufficient severity for the patient to be unwilling to continue with emollient therapy alone.

Table 4.1   UVB (TL-01) phototherapy regimen

1	Determine MED (minimal erythemal dose) at 24 hours
2	Initial dose: 70% of MED Maximum exposure dose: 2066 mJcm^{-2}
3	Treat each side independently - 3x/week (Monday, Wednesday, Friday) or 5x/week (daily - Monday to Friday), as randomly allocated
4	Increments given at each visit, based on a percentage of previous dose and erythema response: No erythema - 20% increment Mild (grade 1, barely perceptible) erythema - repeat previous dose and reduce to 10% increments Moderate (grade 2, well defined asymptomatic) erythema - postpone 1 treatment, repeat previous dose at next visit and reduce to 10% increments Severe (grade 3, painful, persisting for more than 24 hours) erythema - no treatment, and further treatment at discretion of doctor (no grade 3 erythema occurred during the study)
6	Other unwanted effects: If itch develops - encourage use of emollients If PLE develops - ask doctor to review (and check lupus serology), encourage emollients, and a) if mild adjust regimen as for grade 1 erythema; or b) if moderately severe, treat as for grade 2 erythema
7	Missed appointments: One or two treatments missed - repeat previous dose Three treatments missed - treat with penultimate dose

Figure 4.1   Illustration of patient wearing a half-body suit for a study comparing different phototherapy regimens.

Study setting

The phototherapy and PUVA unit within the dermatology department in Ninewells Hospital, which serves Tayside.

Subjects

We recruited patients with chronic plaque psoriasis from outpatient clinics between November 1995 and June 1996. Patients were excluded if they had a history of skin cancer or solar keratoses or if they were on systemic immunosuppressive therapy. Other study-specific exclusion criteria included: age < 18 years; phototherapy, PUVA or any systemic therapy for psoriasis within the preceding 3 months, guttate psoriasis, known abnormal photosensitivity, and any expressed hesitation about ability to attend daily (except weekends) for treatment.

Irradiation cubicle

Either a Waldmann UV5000 cubicle, fitted with 24 Philips 100W TL-01 lamps, or a Ninewells Medical Physics department-constructed cubicle (**Figure 4.2**), with 50 Philips 100W TL-01 lamps, was used. The same cubicle was used to treat both body-halves, and throughout each patient's treatment course. Irradiance was determined monthly with an International Light IL1400 meter calibrated with a spectroradiometer against a bank of TL-01 lamps, and the UVB exposure time-dosage table was adjusted as necessary. For measurements the meter was clamped at mid-height, 25 cm from the lamps, in the empty cubicle and the mean of 10 readings taken as the output. Irradiances in the Waldmann cabinet ranged from 3.53 to 2.95 mWcm^{-2}, and

Figure 4.2 The phototherapy cubicle constructed by the Medical Physics department at Ninewells Hospital.

those of the Ninewells cabinet from 3.1 to 2.95 mWcm^{-2} during the course of the study.

Minimal erythema dose (MED) determination

This was done on upper back skin following our standard procedure. For skin phototype I and II patients, the doses administered were: 25, 50, 70, 100, 140, 200, 280 and 390 mJcm^{-2}. For skin type III patients, the first two doses in this series were omitted and doses of 550 and 770 mJcm^{-2} added. The MED was taken as the lowest dose to produce just perceptible erythema (**Figure 4.3**).

Treatment regimen

Our low incremental dose treatment regimen is detailed in **Table 4.1**. All male patients wore genital protection, and all patients were offered facial photoprotection (faceshield (Dawe et al. 1996) or topical sunscreen) if facial psoriasis was absent. Adjunctive therapy was restricted to approved emollients known not to significantly reduce UV transmission (Hudson-Peacock et al. 1994) (white soft paraffin/liquid paraffin 50:50 mix, aqueous cream, Diprobase® cream or coconut oil) except for standard topical treatments for scalp, face and flexures. According to our usual practice, treatment was stopped when the psoriasis was deemed clear, or to have been in a state of "minimal residual activity" (MRA) for 4 treatments, whichever occurred first. It is unusual for patients to require more than 30 UVB exposures before reaching clearance/MRA. Below 5% of 2014 psoriasis patients treated with whole-body TL-01 in Ninewells Hospital between 1992 and 1996 required courses in excess of 30 exposures (Scottish phototherapy audit data). We therefore set a maximum limit of 30 exposures for either side.

Assessment

The psoriasis severity of each body-half was assessed at baseline (before the first treatment) and at each subsequent treatment visit by means of a 0 to 4 scale for each of scaling, erythema and induration (SEI) of symmetrical plaques (chosen at baseline) on the upper limbs (arm or forearm), trunk and lower limbs (thigh, leg or buttock). A 0 to 4 ("no" to "very severe" psoriasis) global score was also used. This scoring scheme was based on the standard psoriasis area and severity index (PASI), (Fredricksson et al. 1978) and we had experience of its use in earlier studies. (Collins et al. 1996a; Wainwright et al. 1996)

Statistical methods

The main end-points were time (days), dose and number of treatments to clearance. We also compared psoriasis severity scores at baseline and at the end of treatment. Further, individual patient data, as well as summary data, were examined graphically. The distributions of values, or when appropriate, *differences* in values between sides were examined in graphical form, including quartile-normal plots, and by use of the Shapiro-Francia W′ test to decide if a normal distribution could be assumed. For those variables which could not be assumed to arise from such a distribution we used non-parametric tests, and for normally distributed variables both parametric and non-parametric methods. No differences in interpretation arose from the

Figure 4.3   For this study we took the minimal erythemal dose (MED) as the lowest dose to produce "just perceptible" erythema 24 hours after irradiation. This is the definition used in most European phototherapy units.

different methods of analysis, so for consistency and clarity, only the results of the non-parametric tests are reported. The Wilcoxon matched-pairs signed-ranks test (with a null hypothesis of no difference between the sides) was used for paired data and the Mann-Whitney U test for unpaired data. Confidence intervals (CI) for the differences in medians were calculated using a rank-based method. (Campbell et al. 1989) The proportions of patients developing erythema during treatment were compared by McNemar's exact test for paired proportions. Follow-up data were analysed by the plotting of Kaplan-Meier survival curves. A Cox regression model, taking into account the within-subject "clustering" of data, was used when statistically comparing the follow-up, "survival" (of the patients' psoriasis) data. In general, I have avoided describing results in dichotomous "significant" or "not significant" terms, favouring the reporting of confidence intervals and the actual p-values, but when the term "statistically significant" is used this means that the probability that the null hypothesis of no difference was true was below 0.05. Statistical calculations were performed with "Stata" (with Practical Statistics for Medical Research[1] add-on software to calculate confidence intervals for the medians). (Stata Corporation 1997)

Results

Twenty-one patients, 13 men and 8 women of mean age 43 (range 21 to 68) years, entered the study. They were of sun-reactive skin types I, II and III (**Figure 4.4**). Five patients (4 men and 1 woman) did not reach the end-point of clearance or minimal residual activity (MRA) on both sides: 1 was withdrawn due to failure to attend regularly (intercurrent illness), 1 declined to continue when he was satisfied with a modest improvement on both sides, and 3 did not achieve clearance or MRA. Compliance with treatment was good. Only 5 of

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[1]   Practical Statistics for Medical Research course, Department of Medical Statistics and Evaluation, Royal Postgraduate Medical School, London, 1997.

Figure 4.4 Minimal erythema doses (MEDs) and skin types of study participants.
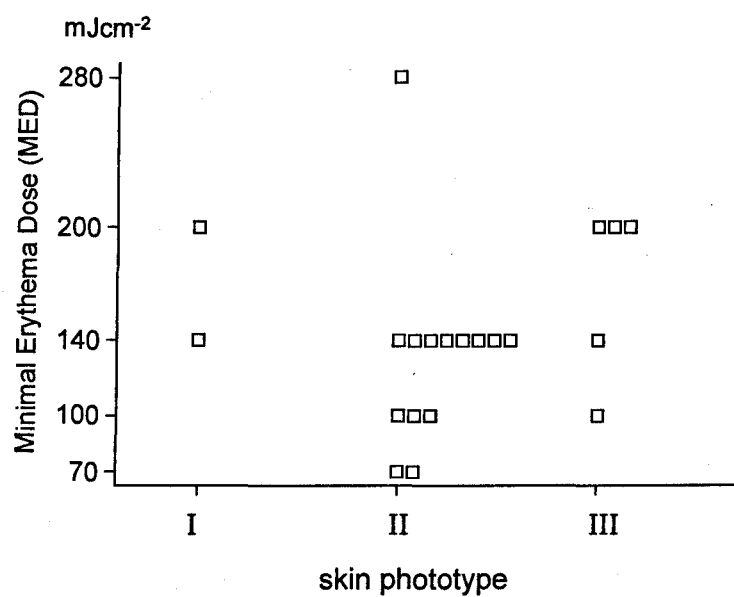
the 16 who completed the study missed any treatments. Of these five, 4 missed only 1 treatment (5x weekly side only - 3 patients; both sides - 1), and 1 missed 4 treatments (5x weekly side only - 1; both sides - 3). Treatments were missed because of intercurrent illness (2), personal reasons (4) and unit closure for public holiday (2).

The median psoriasis severity (SEI) scores of the 16 completing patients at each assessment is shown in **Figure 4.5**, and the baseline and final treatment visit SEI scores for these 16 patients, and (on an intention to treat basis) all 21 entered patients, are described in **Table 4.2**. The median baseline psoriasis severity score (SEI=25) of those who completed the study was not significantly different from that of those who did not complete (SEI=27.5). (P = 0.57; 95% CI for difference in medians -6 to 5).

Psoriasis took longer to clear or reach MRA with 3x weekly than with 5x weekly treatment, clearing in a median of 35 days (range 19-43) with 5x weekly UVB and in a median of 40 days (range 23-63) with 3x weekly

Figure 4.5   Median psoriasis severity (scaling, erythema and induration) score at each assessment.
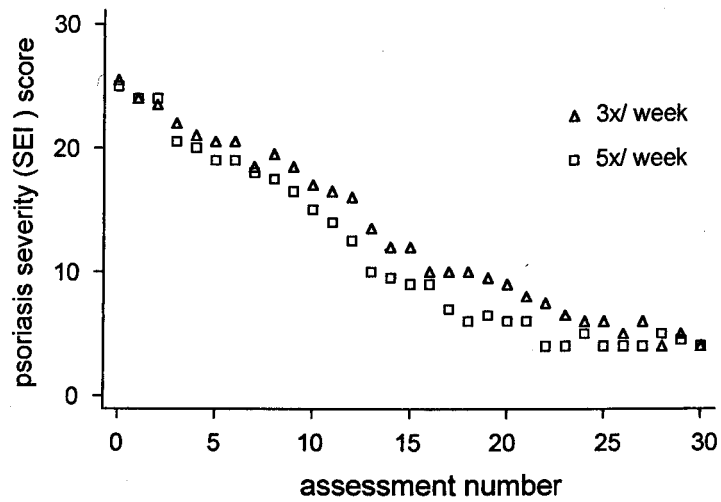
Table 4.2   Median (and range) of psoriasis severity (SEI) scores at begining and end of
treatment

	3x/ week side	5x/ week side	Probability‡	95% C.I.†
Completing patients (n=16)				
Baseline:	25.5 (19-32)	25 (17-31)	P=0.48	-0.5 to 0.5
Final treatment visit:	2 (0-6)	3 (0-6)	P=0.63	-1.5 to 1
All patients (n=21)				
Baseline:	26 (14-34)	25 (14-34)	P=0.22	-1 to 0
Final treatment visit:	4 (0-18)	3 (0-13)	P=0.76	-1.5 to 1.5

‡ Wilcoxon matched-pairs signed-ranks test (null hypothesis of no difference between sides)
† Rank-based confidence interval for *difference* in paired medians

treatment (**Figure 4.6**). (P=0.007, 95% CI for difference in medians 2 to 11). However, this more rapid clearance with the 5x weekly regimen was achieved at the expense of a higher dose of UVB and more treatments. In multiples of each individual's MED, the 5x weekly sides required a median UVB dose of 94 (range 27-164), compared to 64 (range 23-125) MEDs for the 3x weekly sides (**Figure 4.7**). (P = 0.01, 95% CI 5-33). The sides treated 5x weekly received a median of 23.5 compared to 17 treatments for the 3x weekly sides (P=0.001, 95% CI 3.5-8) (**Figure 4.8**).

Inspection of the individual patient data showed only 2 patients with results sufficiently different from the summary results to alter how we would consider treating these individuals in the future. One patient's psoriasis cleared 28 days sooner on the 5x weekly side, with 5 fewer treatments and a lower (by 36 MEDs) cumulative dose. However, his psoriasis relapsed exceptionally quickly - in 6 days on the 5x weekly treated side and 22 days on the 3x weekly side. Another's psoriasis cleared 26 days more quickly on the 5x weekly side, with 1 less treatment (but a slightly higher cumulative dose) compared with her 3x weekly treated side. No features of these two patients that were recorded before starting treatment distinguished them from the other 14 patients.

Acute adverse effects were more troublesome with the 5x weekly compared with the 3x weekly regimen. While no patient suffered a painful (grade 3) erythema, 15/16 on 5x weekly treatment developed at least one episode of well-demarcated (grade 2) erythema as compared with only 3/16 on 3x weekly treatment (P<0.001). Two patients developed polymorphic light eruption (PLE). One patient's episode of PLE affected both sides early during the course and the other's 5x weekly side only was involved after the final treatment.

Figure 4.6 Days to achieve clearance or minimal residual activity (MRA).
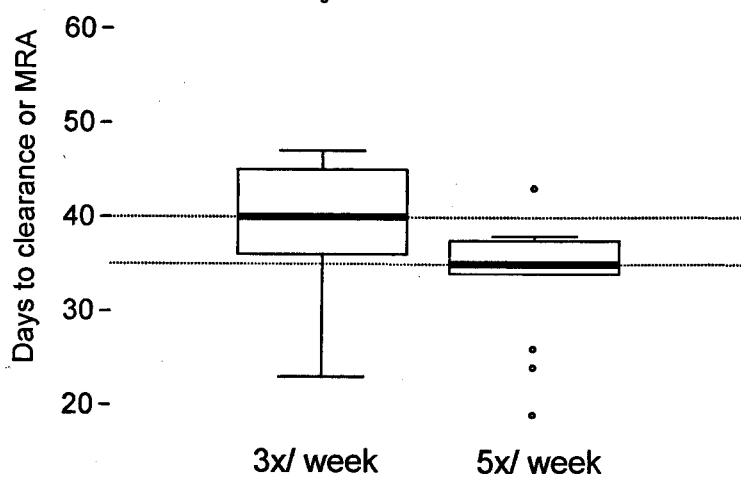
Figure 4.7 Dose in multiples of each individual's minimal erythemal dose (MED). Whilst dose expressed in this way (taking into account each individual's susceptibility to UVB erythema) is not necessarily more reflective of long-term cancer risk than dose expressed as an absolute dose (Jcm^{-2}), expression of the dose like this does have the major advantage of allowing interpretation in other centres with differing dosimetry methods (see Chapter 2, Figure 2.20 for Scottish phototherapy audit data on variation in dosimetry just within Scotland).
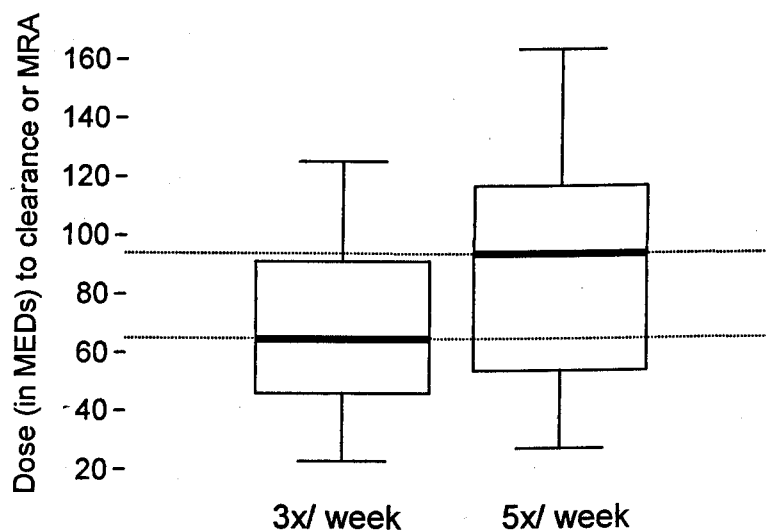
Figure 4.8 Treatments to achieve clearance or minimal residual activity (MRA).
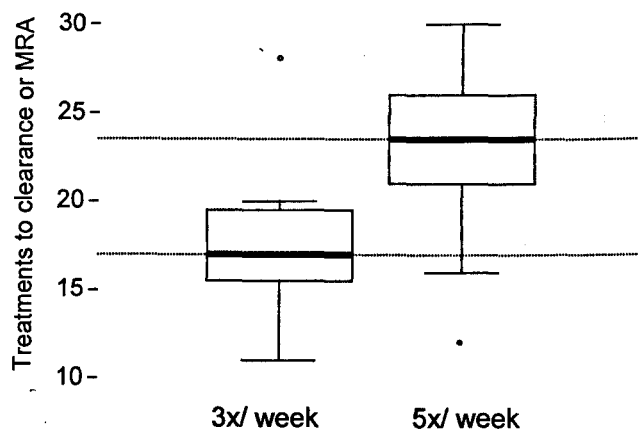
The time to relapse for each side is shown in **Figure 4.9**. There was no significant difference in the probability of relapse between regimens (P=0.1). At relapse, only 3 required therapy other than topical emollients, tar or calcipotriol. Of these three, 1 started PUVA, 1 another course of UVB and the other entered a half-body comparison of PUVA and UVB phototherapy. Two others have since required non-topical therapy - one commencing UVB, and the other PUVA, 6 months after initial relapse.

Discussion

We have shown that for the majority of patients in our population, 3x weekly TL-01 UVB phototherapy is preferable to 5x weekly treatment. Clearance of psoriasis slightly more quickly (by a difference in medians of 5 days) with 5x weekly treatment is not, in our opinion, sufficient to justify the patient inconvenience, the higher frequency of significant erythema provoked during treatment, and the expected greater long-term risk related to the higher cumulative UVB dose and number of exposures required. Consequently, we no longer routinely use 5x weekly treatment for inpatients, as was our previous practice.

Although individual patient response does vary, the absence of factors predictive of a better response to 5x weekly treatment (as occurred in only 2 of our patients) suggests we should base our standard practice on the evidence applicable to the group as a whole. Occasionally, however, for example for a patient anxious to be clear for a specific occasion, it may be reasonable to offer 5x weekly treatment for quicker clearance, despite the increased risk of acute, and presumably, chronic adverse effects.

A within patient paired study allows us to control for all factors other than the single, altered variable under investigation. However, a potential

drawback relates to the possibility of a systemic phototherapy effect - we know that TL-01 UVB produces various alterations in systemic immune function as assessed *in vitro* (Guckian et al. 1995). In practice however, any such effect appears unable to clear psoriasis. In our experience and that of others, (Kienbaum et al. 1996) unexposed flexural psoriasis fails to clear with phototherapy as do, according to an as-yet unpublished study,[1] any plaques covered during treatment. We therefore think it unlikely that any systemic effect of the 5x weekly treatment exerted a clinically important effect in clearing our study patients' 3x weekly-treated sides. Further support for this is given by the fact that the median number of treatments to clearance or MRA for the 3x weekly side was as expected from Dundee data collected during the Scottish phototherapy audit (Chapter 2).

The evidence generated by this study indicates that in our Northern European population of chronic plaque psoriasis patients, a 3x weekly low incremental regimen with an MED-based starting dose is preferable to 5x weekly treatment. Only a few patients will benefit sufficiently from the slightly more rapid psoriasis clearance with 5x weekly therapy to warrant the associated disadvantages. We now only rarely use daily treatment for those requiring inpatient therapy for geographical reasons (no phototherapy unit within reasonable travelling distance): for these occasional patients the disadvantages of an extra week in hospital with 3x weekly treatment may sometimes outweigh the advantages.

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1   Study presented at Scottish Dermatological Society meeting, Edinburgh, 2001 by R.S. Dawe (H. Cameron, R.S. Dawe, S. Yule, I. Man, S.H. Ibbotson and J. Ferguson. Ultraviolet B phototherapy clears psoriasis through local effects).

Figure 4.9　Remission duration following 3x and 5x weekly TL-01 UVB phototherapy for psoriasis.
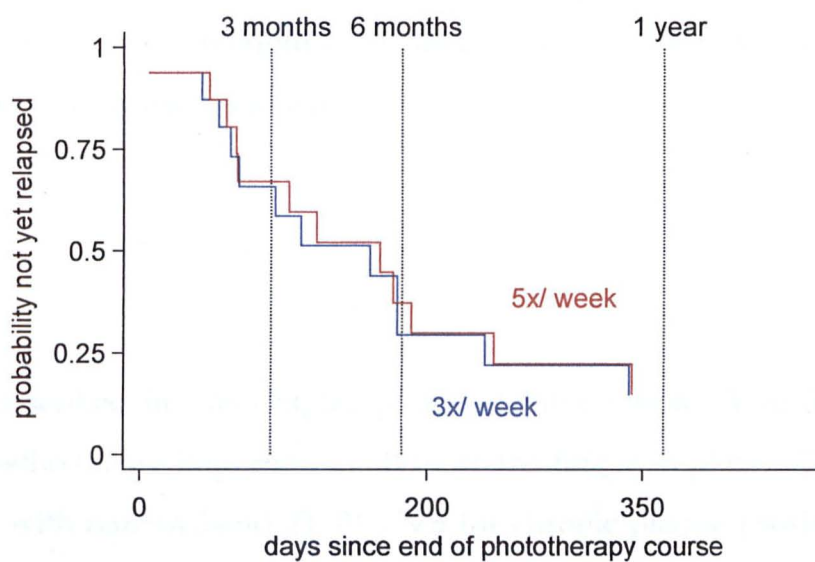
The optimal treatment regimen for populations with many patients of higher skin phototype remains unclear. It seems plausible that treatment in such patients might be less limited by acute erythema, and that more frequent therapy than for our study population might be preferable. A recent publication suggested that 2x weekly TL-01 UVB was in fact preferable to 4x weekly treatment in a Thai population. However, we need to be careful in interpreting this study's findings as it was not a randomised controlled trial, and treatment allocation (by whole-patient, not paired) was decided by patient choice. For now, the optimal treatment frequency for skin phototype IV to VI patients remains unknown.

Comment

The study described in this chapter provided information on an aspect of treatment methodology important to all those treating skin phototype I to III populations with narrow-band TL-01 UVB for chronic plaque psoriasis. The next chapter (Chapter 5) describes a study designed to help answer another question, important to all phototherapy units with (or considering acquiring) TL-01 treatment facilities: For the treatment of chronic plaque psoriasis, should we chose to prescribe psoralen-UVA photochemotherapy, or should we prescribe TL-01 UVB?

Chapter 5

This chapter describes a study designed to assess the comparative efficacy of ultraviolet B (using narrow-band TL-01 lamps) and bath-PUVA for chronic plaque psoriasis. Our findings are analysed in conjunction with those of previous studies addressing the same question (which of PUVA and TL-01 UVB is most effective?), but using different treatment regimens.

A randomised, within-patient, controlled trial comparison of narrow-band ultraviolet B phototherapy and psoralen-ultraviolet A photochemotherapy (PUVA) for chronic plaque psoriasis

The aim of this study was to compare the efficacy of narrow-band (TL-01) ultraviolet B (UVB) phototherapy and trimethoxypsoralen (TMP) bath-PUVA (psoralen-ultraviolet A photochemotherapy) for chronic plaque psoriasis.

A randomised, observer-blinded, intra-individually controlled, paired comparison study was conducted.

Both treatments were administered according to standard, optimised regimens. Treatment was continued until clearance or minimal residual activity (MRA), or a maximum of 30 treatments.

The main outcome measures were treatments and time to clearance/MRA. We also assessed the proportion reaching clearance/MRA, change in psoriasis severity (scaling, erythema and induration), and remission durations with each treatment.

Twenty-eight patients (skin phototypes I to III) with chronic plaque psoriasis participated. Each patient's body halves (sagittal plane) were treated independently, one half with TL-01 UV-B the other with bath-PUVA.

Analysed on an intention to treat basis, 22/28 (75%) reached clearance/MRA with TL-01 compared with 15/28 (54%) with PUVA (95% confidence interval for difference 4% to 37%; P=0.03). Ten patients were withdrawn (4 because of inadequate response of PUVA-treated halves). Of the 18 who completed the study, all reached clearance/MRA with TL-01, but 3 were still not clear by 30 PUVA exposures. TL-01 achieved clearance/MRA a median of 11 (4 to 24.5; P=0.002) days more quickly than PUVA, but required a median of 24.5 compared with 20 exposures (difference 0 to 5; P=0.01). Remission durations did not differ.

In conclusion, when TL-01 and PUVA are both used according to regimens designed to be optimal (on the basis of current knowledge), TL-01 UVB is more efficacious than PUVA for the treatment of chronic plaque psoriasis. This contrasts with earlier work, which indicated PUVA was moderately more effective. This discrepancy may be explained by differences in the treatment regimens compared. On the basis of this study's findings, and a careful review of the earlier work, it can be concluded that TL-01 UVB is the phototherapeutic treatment of choice for chronic plaque psoriasis.

Introduction

Which is the treatment of first choice for moderately severe and severe chronic plaque psoriasis: narrow-band (TL-01) UV-B phototherapy or psoralen- UV-A photochemotherapy (PUVA)? In 1991, guidelines on psoriasis management recommended PUVA as the treatment of choice. (Anon. 1991) Since then, however, as discussed in earlier chapters of this thesis, TL-01 UV-B has become more widely available, replacing the less effective broad-band sources. Should TL-01 UVB also replace PUVA? Important factors encouraging increased prescription of TL-01 UVB, when PUVA might have been prescribed before, include the the absence of psoralen adverse effects, no need for eye protection outwith the treatment cubicle, and the increased skin cancer risks associated with PUVA in the absence of any suggestion (at present) of similar risks with TL-01 UVB. However, relative efficacy is the major consideration. If the two therapies are equally effective, or even if PUVA is a little more effective, most patients and dermatologists would be expected to choose TL-01. If, on the other hand, PUVA is as much more effective than TL-01 UVB as most considered it be compared with broad-band UVB, then (despite its practical disadvantages) PUVA would be the therapy of choice.

Three comparisons of TL-01 UV-B and PUVA as monotherapies (van Weelden et al. 1990; Tanew et al. 1999; Gordon et al. 1999), and one of etretinate+TL-01 and etretinate+PUVA (Green et al. 1992), for chronic plaque psoriasis severe enough to require such treatment have now been published **(Table 5.1)**. Three of these studies showed little difference in treatment efficacy (Van Weelden et al. 1990; Green et al. 1992b; Tanew et al. 1999), and therefore concluded that, for the majority of patients, TL-01 UV-B is to be preferred over PUVA. The fourth of these studies(Gordon et al. 1999) showed PUVA to clear a greater proportion of patients than TL-01 monotherapy (odds ratio favouring PUVA of 3, 95% confidence interval 1.2 to 7.8).

Of the 3 studies comparing TL-01 and PUVA monotherapy, only one used clearance as the main study end-point of interest, (Gordon et al. 1999) the others compared the two treatments after a pre-decided time or number of treatments, and were not designed to provide follow-up data. This one study (Gordon et al. 1999) was designed to compare TL-01 and PUVA when both given twice weekly, as in the first study comparing these therapies (van Weelden et al. 1990). In standard clinical practice in Scotland (audit data in Chapter 2), and the rest of the United Kingdom (Dootson et al. 1994), UVB is most frequently administered 3x weekly whereas PUVA is given 2x weekly. Although 3x weekly TL-01 clears psoriasis almost as quickly, and with fewer treatments, than 5x weekly treatment, as demonstrated by the study described in the previous chapter (Dawe et al. 1998), our experience, and preliminary study data,[1] suggests that 2x weekly treatment may be less effective.

We designed a study to compare TL-01 UV-B and bath-PUVA, with both therapies administered as in everyday practice in a centre with over 10 years' experience of administering both therapies.

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[1] Study presented at Scottish Dermatological Society meeting, Edinburgh, 2001 by H. Cameron (H. Cameron, R.S. Dawe, S. Yule, I. Man, S.H. Ibbotson, J. Ferguson. A comparison of 2x and 3x weekly narrow-band (TL-01) UVB phototherapy in the treatment of chronic plaque psoriasis).

Table 5.1 Previous controlled studies comparing PUVA and TL-01 UVB for psoriasis.

Study	Treatment frequency (per week)		Number of subjects		Study design
	PUVA	TL-01	PUVA	TL-01	
van Weelden, 1990	2x	2x	10	10	Within-patient paired, randomized, observer-masked
Green, 1992	2x	3x	15	15	Unpaired, randomized, not observer-masked; systemic retinoids
Tanew, 1999	3x	3x	25	25	Within-patient paired, non-randomized, not observer-masked
Gordon, 1999	2x	2x	49	51	Unpaired, stratified (matched by plaque size and skin photo-type) randomized, observer-masked

Participants and Methods

Study design

A randomised, observer-masked, within-patient, paired study was designed to compare standard TL-01 UVB and bath-PUVA. The Tayside Committee on Medical Research Ethics approved the study.

As for previous half-body, paired studies (including that described in Chapter 4) patients wore half-body suits (adapted work overalls) made of material which allowed transmission of no UVB and negligible ultraviolet A (0.6% transmission at 365nm, assessed with Hitachi U-3210 double-beam reflectance spectrophotometer).

Assignment

A treatment allocation list, generated from a random number table and held by a departmental secretary not otherwise involved in the study, was used to decide which side (right or left) of each patient was treated with TL-01 and which with PUVA.

Masking

We treated each half-patient (sagittal plane) independently, with the side allocated to TL-01 therapy treated first, followed by bath-water application of the psoralen then ultraviolet A (UVA) irradiation to the other side. At each visit psoriasis severity was graded by an observer unaware of treatment allocation. The decision to stop treatment was made following our unit's standard protocol by the same masked observer. Patients and nurse phototherapists administering treatment were not masked.

Protocol

Participants

Consecutive patients with chronic plaque psoriasis, referred from general dermatology clinics for either PUVA or UVB between September 1996 and May 1999, were invited to participate. Exclusion criteria were: age < 18 years, a history of skin cancer or solar keratoses, or phototherapy, PUVA or systemic therapy for psoriasis within the preceding 3 months.

Treatment regimens

Standard TL-01 UVB and bath-PUVA regimens were used. The TL-01 UVB regimen was the 3x weekly regimen used in the study described in Chapter 4 **(Table 4.1)**. For the bath-PUVA regimen, the psoralen used was 3'4'5' trimethoxypsoralen (TMP) 50mg in 100ml ethanol (Tayside Pharmaceuticals, Dundee, UK). This was mixed in 150 litres 37°C bath-water to make a concentration of 0.33mg/L. The patient soaked in this bath-water for 10 minutes, with immediate UVA exposure thereafter. This treatment was administered twice weekly to the side allocated to PUVA treatment, after the other side had been treated with TL-01 UVB. The UVA starting dose, and incremental regimen, followed the standard regimen described in **Table 5.2**.

All patients without facial psoriasis were offered facial photoprotection with either topical sunscreen or faceshield (Dawe et al. 1996). Male patients wore genital protection. Adjunctive therapy was restricted to emollients known not to significantly impede ultraviolet transmission (Hudson-Peacock et al. 1994), and standard topical treatments for scalp, face and flexures. We set a maximum limit of 30 treatments to either side.

Minimal erythema dose (MED) and minimal phototoxic dose (MPD) determination

This was done on upper back skin following our standard procedures. For MED determination in skin phototype I and II patients, doses administered were: 25, 50, 70, 100, 140, 200, 280 and 390 mJcm^{-2}. For skin type III patients, the first two doses in this series were omitted and doses of 550 and 770 mJcm^{-2} added. The MED was taken as the lowest dose to produce just perceptible erythema at 24 hours. For MPD determination in skin phototype I and II patients, doses of 0.05, 0.07, 0.10, 0.15, 0.22, 0.27, 0.33 and 0.39 Jcm^{-2} were administered, with the first two doses in this series omitted and doses of 0.47 and 0.56 Jcm^{-2} added in for skin type III patients. The MPD was taken as the lowest dose to produce just perceptible erythema at 72 hours.

Irradiation cubicles

For TL-01 UVB, either a Waldmann UV5000 cabinet, fitted with 24 Philips 100W TL-01 lamps, or a Ninewells Medical Physics department-constructed cabinet, with 50 Philips 100W TL-01 lamps, was used. For PUVA, a Dixwell cabinet fitted with 47 Philips R-UVA tubes was used. TL-01 and UVA irradiances were checked monthly.

Reasons for administering psoralen in bath-water

To compare TL-01 monotherapy (not psoralen+TL-01) with psoralen+UVA, the psoralen had to be administered after TL-01 irradiation. The majority of our patients requiring PUVA receive oral psoralens rather than bath-PUVA, which requires extra nursing time (Halpern et al. 2000), but for this study we used our standard bath-PUVA regimen **(Table 5.2)**. This was:

Table 5.2   Bath-PUVA regimen

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1   Determine MPD (minimal phototoxic dose) at
     72 hours

2   Initial dose: 40% of MPD
     Maximum exposure dose: 15 Jcm^{-2}

3   Increments given at each visit, based on a percentage of
     previous dose and erythema response:

     No erythema - 20% increment
     Mild (grade 1, barely perceptible) erythema - repeat
     previous dose and reduce to 10% increments Moderate
     (grade 2, well defined asymptomatic) erythema -
     postpone 1 treatment, repeat previous dose at next visit
     and reduce to 10% increments Severe (grade 3, painful,
     persisting for more than 24 hours) - no treatment, and
     further treatment at discretion of doctor (no grade 3
     erythema occurred during the study)

4   Other unwanted effects:
     If itch develops - encourage use of emollients
     If PLE develops - ask doctor to review (and check lupus
     serology), encourage emollients, and a) if mild adjust
     regimen as for grade 1 erythema; or b) if moderately
     severe, treat as for grade 2 erythema
     PUVA pain – medical review, with management
     (withdrawal of PUVA if necessary) at discretion of doctor

5   Stopping treatment:
     Treatment stopped at clearance or after 4 exposures
     following first documentation of minimal residual
     activity (MRA), whichever comes first.

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1) To make the study less onerous for patients. After one body-half was treated with TL-01 they would bathe in TMP solution, then immediately receive UVA radiation. If we had used our oral PUVA regimen this would have necessitated ingestion of the psoralen after TL-01 exposure and a 2 hour wait before UVA administration.

2) Because bath-PUVA is at least as effective as (Turjanmaa et al. 1985; Lowe et al. 1986), and *possibly* more effective than, oral PUVA (Collins et al. 1990; Calzavara-Pinton et al. 1994c; Cooper et al. 2000), and our aim was to compare optimally effective TL-01 and PUVA regimens.

Assessment

The severity of psoriasis on each body-half was assessed before first treatment and at each subsequent treatment visit. We used a 0 to 4 scale for each of scaling, erythema and induration (SEI) of three symmetrical plaques chosen at baseline on upper limbs (arm or forearm), trunk, and lower limbs (thigh, leg or buttock). A 0 to 4 (no psoriasis to "very severe") global score was also used. This scoring scheme was the same as used when we compared 3x and 5x weekly TL-01 UVB administration (Chapter 5).

Follow-up

All completing patients were followed-up for 1 year, or until relapse, at monthly intervals by telephone and, if there was any suggestion of psoriasis returning on either side, by departmental visit for assessment. Relapse was defined as either 1) an increase in global score to 50% of that at baseline, or 2) a return of psoriasis of sufficient severity that the patient was unwilling to continue with emollient therapy alone.

Literature review and statistical methods

Literature review methods

Articles comparing narrow-band (TL-01) UVB and PUVA to treat psoriasis were identified as those previously known to us, with search of EMBASE® (Elsevier Science, Amsterdam) and MEDLINE® (National Library of Medicine, Bethesda) using Ovid search software, version 7.8 (Ovid Technologies Inc, 1988) to exclude others.

To summarise earlier studies and ours, the most readily comparable end-point of treatment with the two modalities was identified. For studies with sufficient reported data to do this, the proportions of patients clearing with each therapy were compared, using the McNemar exact test (for paired studies) or the two-sample test for independent proportions, with Newcombe's methods to calculate the 95% confidence intervals for differences (Newcombe et al. 2000). Numbers needed to treat were derived (Machin et al. 2000). Odds ratios and exact 95% confidence intervals were also calculated. For the paired, within-patient studies, we used the methods of Morris and Gardner (Morris et al. 1989), with reference to standard tables for the binomial distribution (Lentner 1982). These methods only utilised the paired study data from patients in whom the outcome was different on each side (ignoring the overall sample size), and so produced disproportionately imprecise odds ratio estimates for the paired studies. However the use of odds ratios allowed reasonable comparison of studies where the outcome was a direct comparison of sides (van Weelden et al. 1990; Tanew et al. 1999b), with those with outcome of clearance (clearance/MRA) versus not cleared. The meta-analysis macro of Sharp and Sterne was used to produce a summary diagram (Sharp & Sterne 1997), but because of clinically and statistically significant heterogeneity it was not considered appropriate to quantitatively combine the study results.

Study statistical methods

The study was designed to have a power of 80% to detect a difference of 2 treatments or 7 days to clearance. Assumptions included two-sided alpha = 0.05, and estimates of within-patient standard deviations were based on earlier paired psoriasis treatment studies (that described in the last chapter, and one other (Wainwright et al. 1998)) conducted in the Dundee dermatology department. We calculated that we would require 22 patients and, on the assumption that 80% would complete treatment within the study, recruited twenty-eight.

The main end-points were number of treatments and time (days) to clearance. We also compared psoriasis severity scores at baseline and at end of treatment and, as suggested as a measure of change in disease state over the complete treatment courses (Ashcroft et al. 1999), compared areas under psoriasis severity-time curves. Areas under the curve were calculated by a standard trapezoid method, using user-written add on software to "Stata" package.[2] Not all variables followed a normal distribution so non-parametric tests were used. The Wilcoxon matched-pairs signed-ranks test was used, with confidence intervals for differences in medians calculated using a rank-based method (Campbell et al. 1989). The proportions of patients developing erythema during treatment were compared using McNemar's exact test for paired proportions. Follow-up data were analysed using a Cox proportional hazards model, taking into account the within-subject nature of the data (Cleves 1999). Statistical significance was taken as $p < 0.05$. "Stata" (Intercooled Stata for Windows, release 6; Stata Corp, College Station, Texas) and "CIA" (Bryant 2000), statistical software were used.

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[2]   Package "**auccalc**" from http://www.stata.com/users/dcowart.

Results

Participant flow and follow-up

Twenty-eight patients (11 women; median age 47, range 22 to 71 years-old) of skin phototypes I (6 patients), II (12 patients) and III (10 patients) participated. Recruitment was slow (**Figure 5.1**), with the most frequent reasons for patients declining to participate being 1) inability to take sufficient time off work/home commitments, and 2) previous successful treatment with UVB leading to an unwillingness to take part in a trial involving PUVA. All had plaque psoriasis of greater than one year's duration. Twenty-four had been treated previously with one or more courses of TL-01 UVB or PUVA (11 UVB only), two had previously required systemic retinoids, and one methotrexate. The unusually high proportion (13/28, compared with 75/314 of all psoriasis patients treated in 1996) of participants who had received previous PUVA (only one of whom had not also received TL-01) suggests that those who agreed to participate included a disproportionate number who had responded poorly to, or had short remission following, previous TL-01 UVB.

Ten were withdrawn before study completion due to: inadequate response to treatment (on PUVA-treated body half) in 4 patients, protocol violation (topical steroids required for treatment-induced polymorphic light eruption) in 2, inter-current illness in 1, PUVA itch in 1, pregnancy in 1, and to one patient's repeated failure to attend. The observer masking to treatment allocation was maintained. A concern that differences in pigmentation produced by the two treatments might identify which treatment each side was receiving proved unfounded (for example see **Figure 5.2**).

Figure 5.1   Flow of patients through study.

All referrals for whole-body PUVA or UVB for psoriasis

September 1996 – May 1999

(n=1024)

Randomised

(n=28)

Not randomised (n=996; 855 treated with UVB, 141 with PUVA)

•Declined to participate

•Did not fulfil inclusion criteria (not plaque psoriasis, age, pregnancy, previous skin cancer)

TL-01 UVB (n=28 subjects)

PUVA (n=28)

Withdrawn before completion:

•Inadequate response (on PUVA side) (n=4)

•Protocol violation (required topical steroids) (n=2)

•PUVA itch (n=1)

•Pregnancy (contraindication to PUVA) (n=1)

•Intercurrent illness (n=1)

•Failure to attend (n=1)

Completed to clearance/ minimal residual activity

(n=18)

Completed to clearance/ minimal residual activity (n=15), or

Maximum of 30 exposures (n=3)

Figure 5.2 It was not possible to guess which therapy each side was receiving by the degree or type of pigmentation. It turned out that the right side here was receiving TL-01 (11th treatment visit), and the left side PUVA (8th treatment visit).

Analysis

Analysed on an intention to treat basis, 21/28 (75%) reached clearance/minimal residual activity (MRA) within the study with TL-01 compared with 15/28 (54%) with PUVA, a difference of 21% (95% confidence interval 4% to 37%; P=0.03). The number needed to treat to benefit (NNTB) with TL-01 rather than PUVA to see one extra patient achieving clearance/MRA was 5 (95% confidence interval 25 to 3). This can be compared with the NNTB of 5 (29 to 3) for PUVA instead of TL-01 shown in the study by Gordon and colleagues (Gordon et al. 1999). To assist comparison of our TL-01 versus PUVA study results with the previous studies (in **Table 5.1**) the odds ratios, with conservatively calculated exact 95% confidence intervals, are illustrated in **Figure 5.3**. Also analysed on an intention to treat basis, the median fall in psoriasis severity score was 20 with TL-01 compared with 17.5 with PUVA (95% confidence interval for difference 0 to 6; P=0.036) (**Figure 5.4**). The areas under the psoriasis severity score-time curves were significantly lower with TL-01 than with PUVA (P<0.001).

All 18 patients who completed the study reached clearance/MRA on their TL-01-treated sides, but in 3 the PUVA-treated side was still not clear by the maximum of 30 exposures. TL-01 treatment achieved clearance/MRA a median of 11 (95% confidence interval 6.5 to 25; P=0.001) days more quickly than PUVA (**Figure 5.5a**), but required a median of 24.5 compared with 19 exposures (95% confidence interval for difference 1.5 to 5.5; P=0.01) (**Figure 5.5b**). The high number of TL-01 treatments required (compared with the median of 19 for all whole-body courses for psoriasis administered in our unit **Figure 5.2** It was not possible to guess which therapy each side was receiving by the degree or type of pigmentation. It turned out that the right side here was receiving TL-01 (11th treatment visit), and the left side PUVA (8th treatment visit). -

Figure 5.3
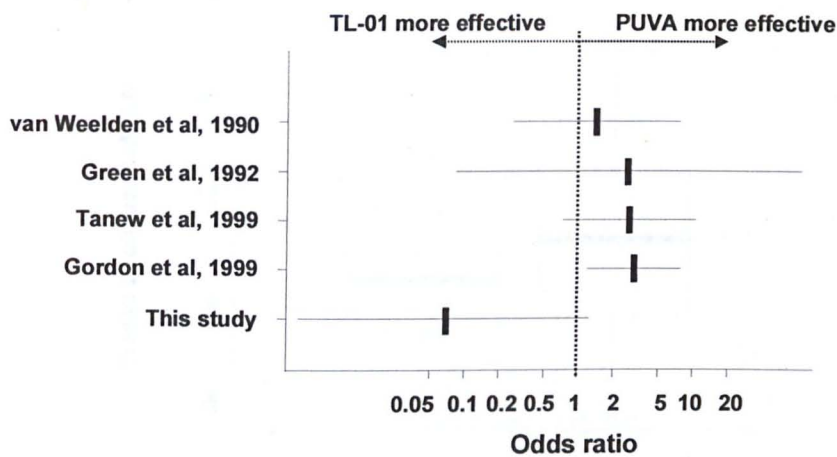
Figure 5.4

SEI scores at start and end of treatment
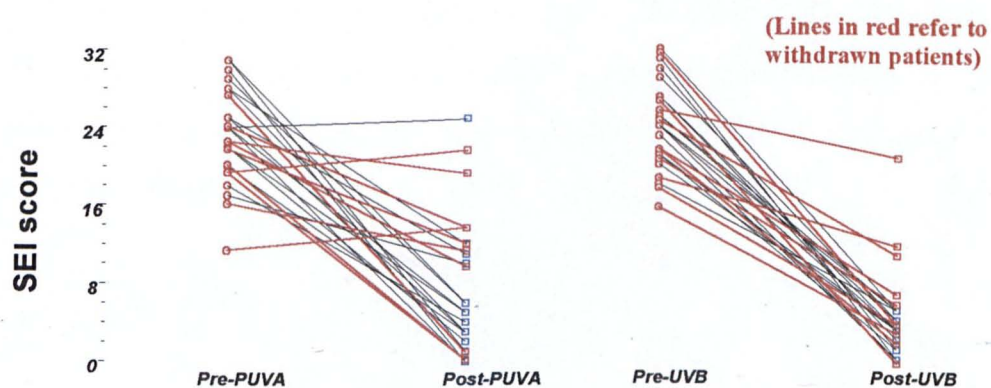
Greater fall in score with TL-01 (P=0.036; intention to treat analysis)

Figure 5.5

(a)
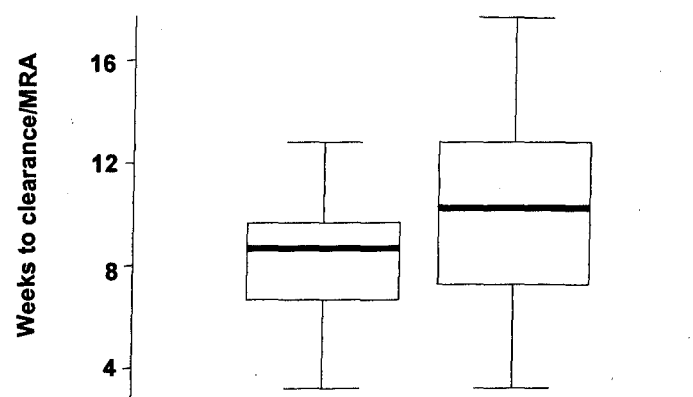
(b)
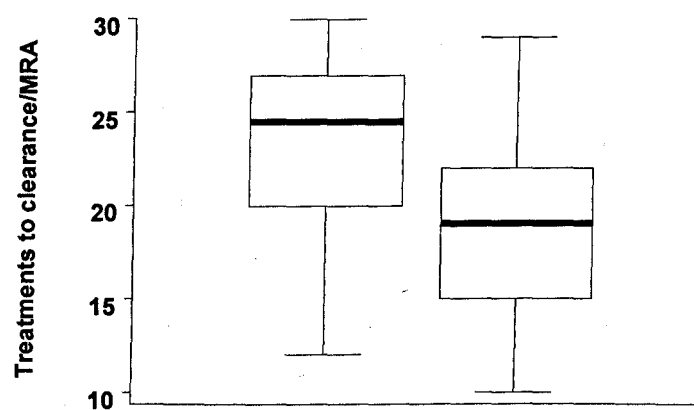
More TL-01 treated sides were affected by grade 1 (asymptomatic, not-well demarcated) erythema episodes (100% of patients) than PUVA (56%) (95% confidence interval for difference 16% to 73%; P=0.008). There were no detectable differences in percentages of patients experiencing grade 2 (well-demarcated, not painful) erythema (33% with TL-01, 11% with PUVA; difference -8 to 52%, P=0.22), or grade 3 (painful) erythema (3 patients [16%] with TL-01, 1 patient with PUVA; difference -9% to 31%, P=0.5). Both patients withdrawn because they required topical steroids for PLE developed this on both sides, although in one it was more severe on the TL-01 treated side. The patient withdrawn because of intense itch on the PUVA treated side was then treated with whole-body UVB, and the PUVA itch resolved over 2 weeks.

After study completion, patients were asked which treatment they would prefer in future: all but 3 expressed a preference for UVB ("more effective" being the most frequent reason volunteered). Two stated they would prefer PUVA ("less time in box, less claustrophobic", "only 2 times a week – easier for work"), and one had no preference.

There was no difference between treatments in remission duration (**Figure 5.6**). The short remission durations shown with both therapies reflect the definition used. Only two required another course of phototherapy at relapse, the rest requiring topical therapy (coal tar solution, calcipotriol, or moderately potent topical steroids) only.

Figure 5.6
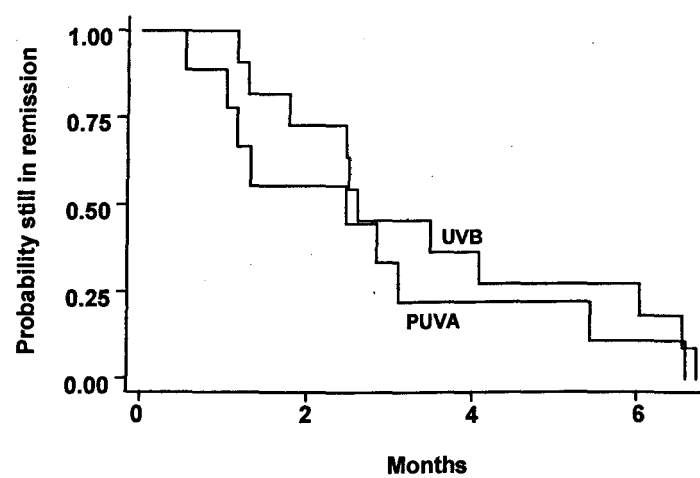
Discussion

This study showed TL-01 UVB to be significantly more efficacious than PUVA in the treatment of chronic plaque psoriasis. Participants in our study may have been atypical of our psoriasis patient population as a whole **(Figure 5.1)**. However, it might have been anticipated that selection bias would have tended to skew our findings in favour of PUVA rather than TL-01 UVB. Patients who took part were more likely to have been treated with PUVA before, and appeared to have more treatment-resistant psoriasis, than non-participants. Those who had previously responded well to UVB, and had therefore never before required PUVA, were less likely to participate in this study.

Our findings contrast with previous studies which favoured PUVA. Presumably the main reasons for these apparently conflicting outcomes relate to the different treatment regimens. Two studies compared TL-01 administered just twice weekly with conventional twice weekly PUVA (van Weelden et al. 1990; Gordon et al. 1999). However we have recently found that 2x weekly administration of TL-01 may be suboptimal (preliminary study results[3]).

The study by Green *et al* (Green et al. 1992), included in **Figure 5.3**, was a comparison of retinoid+TL-01 *versus* retinoid+PUVA, and so not directly comparable with the other studies comparing TL-01 and PUVA as monotherapies. Also, this study did not involve intra-individual controls, and the broad confidence interval (shown in **Figure 5.3**) included the possibility that the retinoid+TL-01 combination might in fact be more effective than retinoid+PUVA.

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[3]   Study presented at Scottish Dermatological Society meeting, Edinburgh, 2001.

Tanew and colleagues administered both TL-01 and PUVA thrice weekly. A difference between their regimens and ours is that they aimed to compare equi-erythemogenic treatment courses, and excluded 4 patients from analysis because of more erythema episodes on the TL-01 sides. The regimens we compared were more typical of current usage. We found that TL-01, (Wainwright et al. 1998), produced significantly more mild erythema episodes administered according to our standard low-incremental regimen than PUVA. The greater relative efficacy of our TL-01 regimen may be related to this.

Another difference between our regimens and those of the previous studies was our choice of the bath-water TMP psoralen. In the absence of a study directly comparing TMP bath-PUVA with oral 8-MOP PUVA, we cannot exclude the possibility that our PUVA therapy was suboptimal. However this seems unlikely, especially as evidence exists to suggest that bath-PUVA is more effective than oral PUVA (Collins et al. 1990; Calzavara-Pinton et al. 1994c; Cooper et al. 2000).

We found that TL-01 UVB was more likely to clear psoriasis than PUVA. Amongst those who achieved clearance or minimal residual activity with both therapies, UVB worked more quickly but more treatments were required than with PUVA.

Although our TL-01 regimen did result in significantly more subjects experiencing mild, asymptomatic erythema episodes than PUVA, there was no detectable difference in the frequency of more severe erythema grades. As only two patients experienced polymorphic light eruption as an adverse effect, this study does not allow comment on its relative induction. Although no patient preferred PUVA because of the difference in erythema frequency, one stated a preference for future PUVA based on the short treatment times

specific to TMP bath-PUVA, and one who preferred PUVA related this to the convenience of attending only twice weekly.

We found no difference in remission durations between the therapies. The short remissions following both therapies could be attributed to the definition used, but may also relate to the severity of psoriasis studied. Although our definition of relapse was crude, and our remission data cannot readily be compared with those from other studies using different definitions, the ability to reliably compare remission durations was a strength of the within-patient comparison design.

Neither this nor the previous controlled comparisons of TL-01 with PUVA for psoriasis could help answer the important questions about relative risk of future skin cancer development. As discussed elsewhere in this thesis, we know that PUVA is associated with a significantly increased risk of skin carcinomas (Stern et al. 1998), particularly squamous carcinomas, and may contribute to a small increased melanoma risk in those who have received multiple treatments (Stern et al. 1997). The risks associated with UVB have not been so carefully studied, but appear to be significantly lower (Studniberg et al. 1993; Stern et al. 1994; de Gruijl 1996). In the absence of long-term follow-up data for TL-01 UV-B, which has only been used for just over 15 years, the relative skin cancer risks associated with this lamp compared with broad-band UV-B lamps remain unclear, but the best current evidence suggests the risks are likely to be less with TL-01 (Young 1995).

To summarise, TL-01 UVB administered according to our standard regimen is more effective than PUVA for the treatment of chronic plaque psoriasis. Although more likely to produce asymptomatic erythema, it is preferred by most patients and, unlike PUVA, is not known to be associated with a significant increased risk of skin cancer. While there are some individual patients who, for particular psoriasis exacerbations appear to do better with

PUVA, we now only consider PUVA if TL-01 has failed or has provided a disappointingly short remission. While other work has shown PUVA to be more effective, even that which showed the strongest PUVA preference suggested it was necessary to treat 5 patients (95% confidence interval 29 to 3) with PUVA to see one extra patient cleared compared with the use of TL-01 (Gordon et al. 1999).

Practical problems with PUVA include the frequent gastro-intestinal adverse effects and eye protection requirements with oral psoralens, or the inconvenience and time involved in bathing in psoralen solution, and its greater cost compared with UVB. In view of these disadavantages, and the well-recognised skin cancer risks, PUVA would have to be much more effective than TL-01 to be considered as the treatment of first choice. The accumulated evidence from our study and the earlier work suggests that TL-01 is the phototherapeutic treatment of choice for chronic plaque psoriasis.

Comment

This chapter describes a study, and the interpretation of its findings in conjunction with previous studies, designed to help determine which therapy (PUVA or TL-01 UVB) we should recommend as the first-line phototherapy for patients presenting with chronic plaque psoriasis. Chapter 6 describes the process of producing recommendations based, whenever possible, on the findings of such original clinical research and systematic reviews of the literature.

Chapter 6

This chapter contains of a list of recommendations on the use of UVB phototherapy and photochemotherapy. These were incorporated in the report on the Scottish phototherapy audit (Chapter 2), circulated to all participating departments, and since discussed at a meeting of the Scottish PUVA and UVB users' group.

The selection of topics for these recommendations was based on the findings of the Scottish phototherapy audit. The quality of the available evidence for each recommendation was graded according to the system used by the Scottish Intercollegiate Guidelines Network (SIGN).The ongoing process of updating, improving, and disseminating these recommendations is discussed.

Audit, clinical research, and the development of evidence-based recommendations

The Scottish phototherapy and PUVA audit

The Scottish phototherapy and photochemotherapy audit survey of 1996/1997 (described in detail in Chapter 2) was intended to 1) determine whether or not the recommendations of the 1991 audit survey had been implemented, 2) to find out how we are using UVB phototherapy, as well as PUVA, and, following this, to 3) form a basis for making appropriate recommendations to assist efforts to continue to improve the phototherapy service available to patients with skin disease throughout Scotland.

The findings of the 1996/1997 survey demonstrated that most of the recommendations made after the 1991 audit had been implemented. An important exception was the recommendation that all centres should have a reliable system to allow recall and monitoring of patients judged to be at a high risk of late adverse effects, principally skin cancer, because of their exposure to PUVA and UVB treatment.

A major change in phototherapy practice in Scotland occurred over the five years after the first audit: the marked increase in the availability of, and use of, ultraviolet B phototherapy, mainly utilising the new narrow-band (311-313nm) UVB lamps. The major reason for differences in how TL-01 UVB was used between centres was the absence of clear evidence on which to base decisions regarding important aspects of treatment methodology, such as frequency of treatment.

Audit as a guide to necessary clinical research

A survey of how a therapy is used cannot, itself, provide information on which to base specific recommendations. These must, when possible, be based on data from controlled studies (such as those described in Chapters 4 and 5), designed to provide information that can reasonably be extrapolated to the population to be treated. What a survey, conducted as part of an audit, can, and did (Chapter 2), provide are data on what aspects of treatment could be improved. For example, the audit showed some centres to require significantly more TL-01 UVB exposures to clear psoriasis than others. Differences in patient selection for treatment may have played a part in this, but it is likely that differences in the efficacy of treatment prescribed were important, and that research designed to guide us as to the optimal treatment regimen for the majority of patients will suggest possible explanations for the differences. For example, it was found that patients with psoriasis treated twice weekly appeared to require more UVB treatments than those treated thrice weekly. Research was needed (and is now ongoing, following the study comparing 3x and 5x weekly TL-01 UVB described in Chapter 4) to determine which of these two treatment frequencies is best. *If* it turns out that the 3x weekly regimen is more effective this finding would help explain the audit observation, and a change, encouraged by the dissemination of recommendations, to routine use of the more effective regimen would be expected to benefit patients who might previously have received sub-optimal therapy.

The development of recommendations for phototherapy practice in Scotland.

Literature searches were conducted using EMBASE® (Elsevier Science, Amsterdam) and MEDLINE® (National Library of Medicine, Bethesda) electronic databases using Ovid search software, version 7.8 (Ovid

Technologies Inc, 1988), and review of references of relevant reports. Appropriate literature was also identified in the bibliographies of standard textbooks and review articles (Abel 1992; Morison 1994; Honigsmann et al. 1996). As recommended by CRAG (Clinical resource and Audit Group 1993), evidence for recommendations was graded according to the scheme of the United States Agency for Health Care Policy and Research **(Table 6.1)** (USDHHS 1992).

Table 6.1

Evidence Levels

Ia.   from meta-analysis of randomised controlled trials

Ib.   from at least 1 randomised controlled trial

IIa.   from at least 1 well-designed controlled study without randomisation

IIb.   from at least 1 other type of well-designed "quasi-experimental" study

III.   from well-designed non-experimental descriptive studies, such as
       comparative studies and case control studies

IV.   from expert committee reports or opinions and/ or   clinical
       experience of respected authorities

Recommendation Grades

A (Ia,Ib)   Requires at least 1 randomised controlled trial as part of the
             body of literature of overall good quality and consistency
             addressing the specific recommendation

B (IIa,   Requires well-conducted clinical studies but no
IIb, III)   randomised clinical trials on the topic of
             recommendation

C (IV)   Requires evidence from expert committee reports or opinions
             and/ or clinical experience of respected authorities. Indicates
             absence of directly applicable studies of good quality.

It should be borne in mind that a "poor" recommendation grade does not imply that the recommendation is not important: what it tells us is that there is a lack of directly applicable published evidence, and so in most cases it is, itself, a recommendation that more research is needed.

It will be noted that some of these recommendations are ideals to aim for, and not likely to be achieved soon, while others are already being implemented.

Treatment indications   *Recommendation grade*

Narrow-band (TL-01) UVB is indicated for:

- Psoriasis   (moderately severe and severe chronic plaque)   (A)
                  (guttate)   (A)
  Meta-analysis in Chapter 3, (Farber et al. 1985; Green et al. 1988; van Weelden et al. 1988b; Larkö 1989; Karvonen et al. 1989; Storbeck et al. 1991, 1993; Kligman 1991; Picot et al. 1992a)
- Atopic dermatitis   (B)
  (George et al. 1993; Collins et al. 1995; Hudson-Peacock et al. 1996)
- Polymorphic light eruption   (A)
  (Bilsland et al. 1993)
- Actinic prurigo   (B)
  (Collins et al. 1995)
- Erythropoietic protoporphyria   (B)
  (Collins et al. 1995)
- Chronic idiopathic urticaria,   (C)

and many other conditions for which the evidence is anecdotal. For some rare conditions, eg. subcorneal pustular dermatosis (Cameron

et al. 1997; Orton et al. 1997), firm evidence of efficacy is unlikely to become available soon - but for others (such as the chronic urticarias, ichthyosis vulgaris, lichen planus, acne vulgaris) evidence is needed as a matter of urgency in order to ensure that we are neither wasting resources, and needlessly exposing patients to potential harm, if TL-01 UVB is ineffective, nor (in centres where these are not accepted indications for TL-01) depriving patients of effective therapy, and perhaps exposing them to greater risks associated with alternative treatments.

In the absence of contraindications, PUVA may be considered for the above conditions if TL-01 UVB fails to produce adequate improvement. In the case of psoriasis, if UVB-induced remission is short it may be worth trying PUVA. These recommendations concentrate on UVB: British Photodermatology Group guidelines provide a referenced review of PUVA indications (British Photodermatology Group 1993).

Staffing

Usually, dermatology nurses will provide phototherapy. In view of (C) the level of responsibility expected of most phototherapy nurses they should be fully-trained, with at least 2 years experience since first on UKCC register. Phototherapy nurses should have sufficient experience of work in a dermatology ward and outpatient unit to be familiar with often-treated conditions, with supporting patients with these dermatoses and with the use of adjunctive treatments (eg scalp psoriasis treatments and bandaging for atopic dermatitis). There have to be sufficient nurses trained in phototherapy to allow for holiday cover, and training of other nurses in the unit.

Equipment

Separate UVA and UVB cubicles are preferable to combined units (C) because:

1) treatment times can be kept shorter (for patient convenience and to allow more patients to be treated) if cubicles are fitted with only one lamp type; and

2) separate units minimise the risk of the potentially serious effects of accidental administration of UVB when UVA irradiation is intended.

For TL-01 administration all cubicles in current use appear reasonable. The cubicle design (breadth, reflectors) is important, as well as number of lamps, in determining output - outputs of, for example, the widely used Waldmann 1000 units allow reasonably short treatment times if used for TL-01 monotherapy. If obtainable larger units may, however, be better for 1) higher outputs, and even shorter treatment times; 2) a greater distance between patient and lamps reduces the risk of erythema episodes due to changes in patient's position in the cubicle during the treatment course and 3) possibly less heat in cubicle, depending also upon other design factors.

For MPD and MED-testing, there are advantages in having (C) irradiation apparatus separate from the treatment cubicles. This must be accurately metered to ensure equivalence of doses administered by this apparatus and by the treatment cubicles.

Separate apparatus saves time and the inconvenience involved in MED/ MPD-testing in the treatment cubicles; and (given adequate staffing) allows patients to be treated at the same time as pre-treatment MEDs and MPDs are determined.

In PUVA units, a bath should be available to allow administration of bath-PUVA when indicated – such as for a patient with a gastrointestinal malabsorption problem, making oral psoralen administration unreliable, or for a claustrophobic patient who would benefit from the short treatment times if topical TMP is used.

(C)

Methodology - UVB

Dosimetry

TL-01 UVB metering should be standardised throughout Scotland. This could be done, following similar principles as those of the Scottish PUVA dosimetry guidelines.

(B)

This would: 1) allow meaningful discussion of doses used in regimens throughout the country; 2) allow patients to be safely transferred from one centre to another during a treatment course; 3) make records of cumulative UVB doses more meaningful; and 4) would, for those centres not yet able to MED-test all patients, reduce the risk of either under-treating or over-treating with the exchange of starting dose and incremental dose protocols between centres.

Starting dose

This should be based on determination of the individual patient's MED rather than based on sun-reactive skin type (Rampen et al. 1988). Most centres use 70% of MED for psoriasis.

(B)

An MED-based starting dose has advantages of:

1) SAFETY - there is no risk of unexpected burns through a starting dose excessively high for the individual. Skin phototype (based on history of reactions to sunlight) does not predict erythemal-responsiveness (Rampen et al. 1988). MED-determination picks up those few patients with an unrecognised photodermatosis such as

solar urticaria or photosensitivity dermatitis/ actinic reticuloid syndrome, who could suffer serious consequences if exposed to whole-body UVB irradiation. It also ensures that the effects of any photosensitising drugs are taken into account in deciding starting dose.

2) Treatment efficacy - a study directly comparing an MED-based UVB regimen with an arbitrary/ skin phototype-based regimen has not been done. However, it seems reasonable to suppose that if an MED is not determined, starting dose will have to be set excessively low for the majority, to save serious burning in a minority of patients. An excessively low starting dose might still be sufficient to lead to photo-adaptive changes, impairing efficacy of subsequent doses even when the therapeutic dose threshold is passed. Even if this does not happen, a low starting dose means extra exposures (causing patient inconvenience, possibly increased risk of chronic adverse effects and waste of resources) before a therapeutic dose is reached.

Doses for MED testing (B)

Should be a geometric, rather than arithmetic, series (Diffey et al. 1991; British Photodermatology Group 1992).

MED readings

Both the MED-test irradiation procedure and reading of the MED (C) must be done by experienced, trained staff (whether nursing, medical, physiotherapist or medical physicist).

(B)

Although there is no evidence that either tungsten-lamp or fluorescent lamp lighting (of equal illuminance) leads to variation in MED determined (Diffey et al. 1992), adequate illumination is essential.

Treatment frequency   (A)

For psoriasis, TL-01 UVB should be administered 3x rather than 5x weekly (Chapter 4, Dawe et al. 1998), except in exceptional circumstances. Whether 2x weekly treatment is as effective is, as yet, unknown although an ongoing trial is expected to answer this. The optimum treatment frequency for atopic dermatitis, PLE and other conditions is unknown. Most now treat these other conditions following the same regimen as is used for psoriasis.

Dose increments   (A)

For psoriasis a low incremental regimen (20% reducing to 10% increments) is preferable to a high incremental dose regimen (40% reducing to 20% increments) (Wainwright et al. 1996).

Adjunctive therapy   (B)

Emollients which act as sunscreens should be avoided (Lebwohl et al. 1995). For psoriasis treatment, there appears to be no benefit, in terms of more rapid clearance, in pre-treatment with an emollient (coconut oil) although this can improve patient comfort (George et al. 1993b).

For atopic dermatitis the usual advice is that emollient use must continue. As long as the emollient chosen is not a sunscreen and contains no potentially photoactive ingredients (for example, plant extracts or fragrances) it can be applied prior to treatment - ideally at the same time prior to each treatment.

The necessary studies have not been done to decide whether or not calcipotriol, dithranol, tar or corticosteroid preparations will improve the efficacy of an otherwise optimal TL-01 phototherapy regimen.

Systemic retinoids (etretinate, acitretin, isotretinoin) may be used in conjunction with TL-01 UVB - particularly for high exposure patients. Etretinate-TL-01 reduces the dose required to reach clearance by one-third (Green et al. 1993). In this randomised study, however, relapse rate at 6 months with Re-TL-01 was 67% compared to only 50% with TL-01 monotherapy or Re-PUVA therapy.

(A)

Stopping treatment

In order to minimise cumulative exposures and dose (and so reduce the risk of chronic adverse effects), maintenance therapy should not be used for psoriasis unless the alternatives are more toxic.

(C)

Maintenance therapy with broad-band UVB slightly prolongs duration of remission of psoriasis (Stern et al. 1986), but at the expense of significantly more exposures (and patient inconvenience). For most patients, maintenance therapy with TL-01 does not hold sufficient advantages (if any) to outweigh the clear disadvantages (patient inconvenience, extra exposures and cost). As with broad-band UVB it is customary, in most centres, to stop at complete clearance or an arbitrary 4 to 6 exposures after minimal residual activity is reached. The rationale is that after near-clearance there may still be residual subclinical psoriasis, and that a few extra treatments may prolong remission. There are, as yet, no objective data to confirm or refute this.

(C)

For uncomplicated psoriasis a written unit discharge policy for nurses/ physiotherapists administering therapy can prevent unecessary treatments after clearance, prior to medical review. For "desensitisation" of the photodermatoses 15 treatments are usually used. Patients with other conditions will often require medical review to decide when to stop a course of phototherapy.

(C)

Methodology - PUVA

For a more comprehensive list of recommendations regarding this treatment, see the British Photodermatology Group Guidelines for PUVA (British Photodermatology Group 1993).

Pre-treatment tests

Some may chose to carry out other procedures, but the following should always be checked:

- LFTs if there is a history to suggest possible liver disease ... (C)

- Baseline ANF <u>and</u> anti-Ro antibodies before a first treatment course in those with a suspected photodermatosis. ... (C)

- History to exclude likely pregnancy; and advice to avoid pregnancy during PUVA ... (C)

- Patients own eye-protection should be tested by one of the methods recommended by the British Photodermatology Group OR only tested and approved eye-protection should be advised ... (C)

Psoralens

A range of psoralens should be available for systemic and topical administration. ... (C)

Starting dose

(A)

This should be based on MPD-assessment for safety, to ensure adequate psoralen in skin at time of irradiation, to take into account any other photosensitising drugs (or drugs that might alter psoralen metabolism) and for increased efficacy in psoriasis treatment - a reduction in cumulative exposures to clearance (Collins et al. 1996b).

Treatment frequency

Twice weekly PUVA is appropriate for a Scottish population of (B)
psoriasis patients (Green et al. 1993). For psoriasis patients living far
from a PUVA centre, once-weekly treatment can be used (Cox (B)
1995). The optimal frequency for other conditions has not yet been
determined - many use 3x weekly treatment for PLE prophylaxis.

Dose increments

As the dose-response curve for PUVA erythema is flatter than that (B)
for TL-01 UVB erythema (Cox et al. 1989), higher incremental
regimens than for TL-01 should be appropriate. No study
comparing different PUVA incremental regimens has been
conducted, but most use a 40% reducing to 20%, or similar,
regimen.

"Aggressive" regimens with maximal suberythemogenic doses (B)
cause more frequent "burning" episodes (Carabott et al. 1989;
Green et al. 1993). A widely used regimen involves 40% increments,
reducing to 20% depending on erythema response. The optimum
regimen remains undetermined.

Adjunctive therapy

There is some evidence (randomised controlled trial) for calcipotriol (A)
(Speight et al. 1994), although how effective the PUVA regimen it is
used with is crucial: adjunctive treatment is most likely to help if
the primary treatment is inadequate.

Systemic retinoids reduce the UVA dose to clearance (Green et al. (B)
1992), and should be offered to patients regarded as at significantly
increased risk of skin cancer as long as there are no
contraindications.

Methotrexate and cyclosporin should NOT be used as adjunctive therapy (Fitzsimmons et al. 1983; Bos et al. 1989; van de Kerkhof et al. 1997). This applies also to UVB phototherapy. It is probable that other immunosuppressives (eg. azathioprine, hydroxyurea) in combination with PUVA or phototherapy will also increase the skin cancer risk.

(B)

Stopping treatment

Maintenance therapy should not be used routinely, but reserved for exceptional patients, usually with mycosis fungoides rather than psoriasis, for whom the risks are likely to be outweighed by the benefits.

Follow-up of "at-risk" patients - UVB and PUVA

A system should be established to allow recall of all patients identified as at increased risk of adverse effects. Ideally, this system should be flexible enough to allow for changes in the definitions of an "at-risk" patient as we gain more knowledge of the long-term effects of TL-01 UVB. For most centres a computerised database system would be appropriate.

One current, cautious, definition of "at risk" (used in Dundee) includes patients:

- who have received more than 150 PUVA exposures

(B)

- who have received more than 150 UVB exposures (the risk associated with this is probably far less than with 150 PUVA exposures but following up all these patients will help in generating epidemiological data concerning the long-term risks of TL-01 phototherapy.

(C)

- who have had previous non-melanoma skin cancer, melanoma, Bowen's disease or solar keratoses.

- who have, separately, received methotrexate or cyclosporin.

In areas where patients may receive UVB or PUVA in more than one centre, follow-up of at-risk patients, and choice of appropriate therapy, would be aided by the adoption of a patient-held cumulative exposure record. The information from such a record could be added to an individual unit's records on completion of each course of therapy there.

(C)

At-risk patients should have a yearly review by a dermatologist. Patients regarded as at increased risk should be alerted to this and told to seek advice about any possible skin cancers or pre-cancerous lesion. These patients' general practitioners should also be informed that their patients may be at increased risk of skin cancer development. In most departments, this follow-up is best organised through the phototherapy unit by the consultant responsible for the phototherapy/ PUVA service.

(C)

Equity of access to phototherapy

Ultraviolet B phototherapy, administered by trained staff using modern equipment, should be available to all for whom this is regarded as the treatment of choice.

(C)

In some areas, more resources to reduce waiting lists for present facilities would fulfil this recommendation. In the more geographically remote regions this aim may never be fully achieved, but suggestions for consideration are:

- The development of a home phototherapy service (Cameron et al. 2000c) (with equipment and patient training provided by the

(B)

"local" dermatology department, which is responsible for monitoring and follow-up) can help some, well-motivated patients.

- In some areas, the best approach may be the development of an existing physiotherapy phototherapy service. This would require modernisation of the service, with provision of equipment allowing whole-body treatment with the most effective and safest available equipment. This approach is only appropriate in areas with a physiotherapist interested in phototherapy, who regards it as an important part of his or her practice. The involvement of the local dermatology department, and medical physics department assistance with dosimetry, should be encouraged.

Some areas for future clinical research

As is clear from the above list of recommendations, many had to be based on very limited evidence. A few areas of required research are listed below.

Necessary research: phototherapy and PUVA indications

- Is TL-01 phototherapy effective for *chronic idiopathic urticaria, acne vulgaris, pityriasis lichenoides chronica, granuloma anulare, lichen planus, mycosis fungoides* and the many other conditions for which there is only open study and anecdotal evidence of efficacy?
- Can we predict which atopic dermatitis patients will respond best?
- What is the phototherapeutic action spectrum for all the conditions treated, excepting psoriasis (the only condition for which this information is available)? Would other UV lamps be more effective than TL-01 lamps for any of these indications?
- How effective is PUVA in comparison to methotrexate, acitretin or cyclosporin for palmo-plantar pustulosis?

Necessary research: phototherapy and PUVA methodology

- What is the appropriate incremental regimen for atopic dermatitis? Most use the same regimen as for psoriasis but this may not be optimal for atopic dermatitis - some dermatologists in Scotland have an impression that lower increments, or even keeping at a constant low dose throughout the course, might be more appropriate.

- Is 2x weekly TL-01 phototherapy for psoriasis as effective as 3x weekly therapy?

- In many centres adjunctive topical treatments are still used when psoriasis is treated with TL-01; but their value is uncertain. Does calcipotriol ointment, coal tar or dithranol in conjunction with TL-01 phototherapy lead to improved clearing/ lower dose/ fewer exposures to clearance?

- For localised treatment for hand and foot conditions are topically applied psoralens as effective as oral psoralens? If "no", can our topical treatment regimens be modified to make them more effective?

Necessary research: phototherapy and skin cancer

What is the risk of skin cancer development with UVB phototherapy? Hopefully, we will eventually have the necessary data to answer this question for the TL-01 source because (as with PUVA, but unlike the situation with broad-band UVB) the patient treatment records have been kept by most centres since its introduction.

Development and dissemination of recommendations

The recommendation in this chapter have been discussed at a meeting of the Scottish PUVA and phototherapy users' group, and an abbreviated overview presented at a meeting of the Scottish Dermatological society. Also, they were included in the report on the Scottish phototherapy audit circulated to all participating centres. Each centre was given their individual centre identification number, used on graphs in the audit report, so they could see how some aspects of their practice compared with that in other centres. For example, the consultant responsible for the service in centre 11 **(Figure 2.15)** could note that they used more treatments per course for psoriasis than others. The interpretation of this would be most appropriately made locally, but if it was decided that the reason was likely due to sub-optimal therapy, rather than selection of patients with relatively unresponsive psoriasis for this treatment, then this would be expected to encourage improvements in treatment methodology, such as introducing MPD testing to determine starting UVA dose.

Some recommendations, such as the need to develop efficient follow-up systems for patients at risk of skin cancer as a result of treatment, might be best implemented by national action, with development of a computerised database of all patients given PUVA or UVB, and recording of, at a minimum, cumulative exposures for each therapy. For this to work well, it will be necessary for every department to agree on certain aspects of the treatment process, and would be assisted by some standardisation in how these treatments are used, for example by the introduction of a standard UVB/PUVA referral form to be used by everyone. The development of national (Scotland-wide) clinical standards for phototherapy, with guidelines, based on good evidence, followed by all centres could be used to help everyone in implementing agreed recommendations. For those aspects of treatment methodology for which we lack any directly applicable, good

quality, evidence from clinical research, it should be recognised that local variations in practice are to be expected, and may even be beneficial. Standardisation of aspects of practice for which we lack good evidence could be counter-productive as it might reduce the impetus to carry out the necessary research.

A centralised computer database follow-up system for phototherapy and PUVA patients, to which all centres could be linked, would not only assist with the local follow-up of at risk patients, but would make future audit of the service much easier. For example, data on between-centre differences in numbers of treatments per course for psoriasis could, with the agreement of everyone concerned, be collected automatically.

Chapter 7

This chapter starts with a short discussion of the history of the use of knowledge derived from quantitative observation and clinical experiment in guiding medical practice, related to the history of phototherapy described in Chapter 1, the Scottish phototherapy audit, and clinical research to help establish the most appropriate phototherapy regimens now.

This is followed by a discussion of what the Scottish phototherapy audit has achieved so far, and what still needs to be done to implement its recommendations, and to aid future efforts to establish how our use of phototherapy is changing.

This discussion includes comment on the use of quantitative reviews (meta-analyses) to help answer questions about the magnitude of the difference in efficacy between treatments (broad-band versus narrow-band UVB, narrow-band UVB versus PUVA). The results of the two clinical studies included in this thesis (in Chapters 4 and 5) are re-visited, with comment on how we should use the findings of such studies to guide standard treatment regimens. Possible problems in extrapolating these findings to different patient populations are mentioned, as is the need for further clinical experimentation to answer other questions about what are the most appropriate treatment regimens.

Finally, this chapter includes further discussion concerning methods of developing and implementing recommendations, based on knowledge of what we are doing (survey phase of the audit), and experimentally derived evidence to guide us as to what we should be doing.

Bringing together the components of this thesis

The preceding chapters describe the development of dermatological phototherapy in Scotland, recent research aimed at answering important questions about how we should use these treatments, and the role of clinical audit in establishing how we are using them. A theme of this thesis, connecting the strands of original clinical research, careful quantitative review of previously published clinical studies, and audit is that these together form a basis on which we can base treatment recommendations.

Medical arithmetic and experimentation (evidence-based medicine)

Such attempts to base medical practice on experimentally derived evidence, and knowledge of current practice derived from quantitative observation, are not new. In the eighteenth century, many publications, largely by Scottish trained authors, exemplified the increasing interest in practice based on "medical arithmetic and experimentation" (recently re-named "evidence-based medicine"), rather than practice based largely on dogma derived from the current pathophysiological theories (Tröhler 2000).

However, not everyone then, or more recently, has approved of attempts to develop guidelines based on evidence from observation and experiment. For example, Robertson, a naval surgeon, gained his MD from Aberdeen University for his quantitative comparisons of treatments for fevers. These studies showed Peruvian bark to be more effective than the blood-letting favoured by the traditionalists, who based their practice purely on the current pathophysiological theories. Robertson had to defend his "Observations on the jail, hospital or ship fever" (Robertson 1783) against those who pronounced medical statistics "dry and insipid reading or altogether useless in the practice of physic". Another 18th century clinical statistician was

prevented from re-entering the army medical service because he was regarded as a "Jacobin, leveller, republican and democrat ..." (Millar 1798).

Presumably those who now oppose evidence-based medicine do so, at least in part, as a result of similar fears: they worry that proponents of evidence-based medicine threaten "to subvert the traditional order of things" (Tröhler 2000). Perhaps some are concerned that the current increasing emphasis on evidence-based medicine might harm, through competition for funding (and other resources, including interested clinicians), our rapidly expanding knowledge about the pathophysiological mechanisms of disease. Of course all aspects of medical research are important, whether carried out at population, individual, cellular, or molecular level. But for the readily forseeable future it is likely that the findings of clinical research, such as that described in Chapters 5 and 6, will continue to provide the evidence most immediately helpful in guiding treatment decisions.

The Scottish phototherapy and PUVA audit: achievements to date

The Scottish phototherapy and PUVA audit (Chapter 2) has contributed to knowledge of how we are using phototherapy and PUVA. It is likely that the improvements in the PUVA service described in Chapter 2 relate, at least in part, to the 1991 survey and subsequent recommendations.

It is now clear that how UVB phototherapy is used varies significantly from centre to centre. For example, regarding phototherapy indications, chronic ordinary (idiopathic) urticaria is an important indication nation-wide, with 1.5% of courses prescribed for this, yet several departments have never treated urticaria with UVB. Such differences in when phototherapy is used, and the differences in how it is used (in the treatment regimens), are not surprising when there is no, or limited, published data on which to base

practice, and emphasises the need for more research. To return to the example of UVB for chronic urticaria, are those who attend centres where UVB is not prescribed for this indication disadvantaged by not receiving a useful treatment (and possibly by exposure to the adverse effects of other therapies), or are those centres that do use UVB for urticaria simply wasting resources, and needlessly exposing patients to an increased risk of developing skin cancers in future? We do not know. Some other unanswered questions, which I regard as particularly important, are included at the end of the last chapter.

Assessing the evidence: the role of meta-analysis

The meta-analysis described in Chapter 3 illustrates the potential of such "research on the research literature" in helping to clarify the answer to a question already fairly extensively studied. On the basis of this meta-analysis, it is clear that narrow-band TL-01 lamps are preferable to broad-band UVB lamps for the treatment of plaque psoriasis in populations of predominantly Northern European extraction and skin phototypes I to III. Despite imperfections in study methodology (when looking back with the benefit of hindsight) I would regard a new large randomised, controlled trial to compare TL-01 with broad-band UVB lamps for psoriasis in this sort of population as unnecessary, a waste of resources, as the question has already been answered. However, lessons from the deficiencies of the previous studies will hopefully guide any future study comparing these two UVB modalities. The results of such a study in a predominantly high skin phototype population would be of interest, and of particular importance in resource-poor countries.

Clinical studies: interpretation and extrapolation of results

The clinical studies described in Chapters 4 and 5 illustrate attempts at answering questions identified as important during the audit. The study comparing 3x with 5x weekly TL-01 UVB phototherapy (Chapter 4) clearly showed that, for the majority of patients in our population, 3x weekly treatment is preferable.

This study also, however, illustrates the importance of allowing flexibility in the implementation of recommendations based on controlled studies. While we can reasonably extrapolate our study results to other skin phototype I to III skin phototype patients of northern European origin who have chronic plaque psoriasis, this study has not determined the optimal treatment frequency for those in other populations, with different types of psoriasis. Recommendations based on the findings of this study can only be used very cautiously, in the absence of any good more directly applicable evidence, to guide those treating different patient populations. Also, in our study there were two patients whose responses to the treatments compared suggested that these particular individuals would be most appropriately treated 5x weekly. Although 3x weekly treatment can be advised as the standard treatment frequency in populations of patients like our study participants, there will always be individual patient exceptions. It is important that we do not bind ourselves so strictly by guidelines that we cannot continue to take the experiences and preferences of individual patients into account when choosing therapy. Guidelines are to guide, not dictate, clinical practice.

The chapter on a study comparing PUVA with TL-01 UVB illustrates some of the factors we must consider when extrapolating from findings in a study population to all the patients we will be treating in future. As illustrated in **Figure 5.1**, the proportion of those who are considered for a study who are eligible for entry, and who agree to participate, can be small. This

information, on the proportion of the potential study population who actually take part, is often still not included in published study reports, but will often be small, especially if the study is time consuming or complicated for participants.

As it turned out in this study, TL-01 UVB was more effective than PUVA. We would have expected selection bias to favour PUVA. Most participants had previously received treatment with phototherapy or PUVA. Those who did well with the simpler treatment (TL-01 UVB) were less inclined to take part in time consuming study than those who had not responded well. As we would have expected selection bias to favour PUVA it is possible that TL-01, as administered in this study, is even more superior to PUVA than the study showed. We can reasonably extrapolate our study findings to our wider potential patient population. Of course the caution mentioned above regarding the need for flexibility in treating individuals, a few of whom will fare better with PUVA, applies.

What about populations attending other units: one study (Gordon et al. 1999) did produce conflicting results, and strongly favoured PUVA for efficacy in clearing psoriasis. This may in part have reflected differences in the patients considered suitable for PUVA or UVB, but differences in treatment methodology are probably the explanation. The use of meta-analysis tools, particularly a forest plot (**Figure 5.3**) to graphically compare the different studies' results, were helpful in judging how different the results really were. Re-analysis of the published data of the earlier studies illustrated the value of presenting results in terms of clinically relevant measures of effect, particularly the concept of number needed to treat (NNT). The Gordon et al. (1999) study showed an odds ratio of 3 favouring PUVA. Only after "translating" this figure into a NNT of 5, that is five patients would need to be treated with PUVA to see one clearing who would not have cleared with UVB, is it easy to apply this study finding to clinical practice.

Developing and implementing recommendations

One of the benefits of producing evidence based recommendations is that it highlights the major areas where appropriate evidence is lacking. However, even in the absence of strong evidence, guidelines agreed upon by a group of interested people (ideally including not only dermatologists, but nurse and physiotherapist phototherapists, and patients) would prove useful to the many phototherapists who currently want advice as to whether or not what they are doing is still appropriate. Hopefully, Scotland-wide clinical standards for phototherapy can incorporate such guidelines. It is important that they are produced and agreed upon by representatives of everyone concerned, and that it is clear that they are *guide*lines, and not designed to restrict variations in clinical practice where we currently lack good evidence, nor to discourage flexibility in the application of evidence from study population data to individuals.

Chapter 8

This concluding chapter summarises the current state of phototherapy in Scotland. It incorporates comment on the most important next steps to improve the Scottish phototherapy service, including further research required to guide how we use PUVA, UVB, and new developments in phototherapy such as UVAI.

Now, exactly a hundred years after it first became available in Scotland, phototherapy using artificial ultraviolet sources retains an important, and expanding, place amongst the treatments available for many inflammatory skin diseases. It is likely to remain important. Knowledge about the mechanisms involved in the inflammation of conditions such as psoriasis is increasing, and may lead to new therapies targeting important components of the disease process. But, for the readily foreseeable future, we will continue to rely on rather non-specific anti-inflammatory and immunosuppressive therapies. Although topical anti-inflammatories, particularly corticosteroids, work for many conditions, they are not suitable for all, and are not always sufficiently effective. Other treatment is then required and phototherapy and PUVA do, through their predominantly local actions on the skin, achieve a degree of selectivity, reducing the risk of adverse effects, not obtainable with the currently available systemic immunosuppressive agents.

Major advances in phototherapy have included the development of more effective lamps for the treatment of psoriasis. Fortunately these narrow-band (TL-01) lamps are also proving effective in other conditions. Psoralen-UVA photochemotherapy (PUVA) retains its primary place in the treatment of certain conditions, such as plaque stage mycosis fungoides, but for psoriasis, polymorphic light eruption prophylaxis, and for atopic dermatitis TL-01 UVB has usurped its place as the standard phototherapy. Regardless of its disadvantages, in particular the concern about side effects, and it not being significantly more effective in whole study populations, PUVA does remain important for those particular individuals for whom it is more effective.

Lessons have been learnt from the past failure to properly document broad-band UVB treatments, or to follow-up patients. Such careful follow-up of patients treated in the initial large PUVA studies showed that there were real risks of skin cancer development as a late adverse effect. Since the introduction of TL-01 UVB, every department in Scotland has kept treatment

records, and it is hoped that a system to ensure the follow-up of all UVB and PUVA patients will be set up in every unit. If agreement amongst departments, and funding support, can be obtained a centralised computer database system could have the added advantage of greatly reducing the work involved in future audits of the phototherapy service.

Much clinical research is still required to clarify when we should use UVB, and when PUVA, and to determine the optimal treatment regimens for every responsive disease. Recommendations based on good quality research data should assist with the dissemination of the findings, and guide the development of standard phototherapy regimens, while not discouraging appropriate adaptation of how these treatments are used in individual departments, and for individual patients.

New developments in the phototherapy of skin diseases continue to emerge, and clinical experimentation, and audit of outcomes, will tell us what place such potential advances as UVAI (340 to 400nm UVA) should have in our therapeutic armamentarium.

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Appendix: relevant publications

The following pages consist of publications based on the studies included in this thesis, and other publications to which I have significantly contributed, and which pertain directly to the topics of this thesis.

AS ORIGINAL

Narrow-band (TL-01) ultraviolet B phototherapy for chronic plaque psoriasis: three times or five times weekly treatment?

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Summary   Three and five times weekly narrow-band TL-01 (311–313 nm) ultraviolet (UV) B phototherapy regimens for chronic plaque psoriasis were compared in a randomized, observer-blinded, half-body, within-patient paired study. Twenty-one patients [13 men, eight women, age range 21–68 years, skin phototypes I (two patients), II (14) and III (five)] entered the study. Sixteen reached clearance or minimal residual activity (MRA) on both sides. Of the other five, three withdrew because they did not reach clearance or MRA on the 5× weekly side by a maximum of 30 treatments, one when he was satisfied with moderate improvement and one because of repeated failure to attend. Those who completed treatment reached clearance or MRA after a median of 35 days with 5× weekly treatment compared with 40 days with 3× weekly treatment ($P = 0.007$), but required a median of 23·5 compared with 17 UVB exposures ($P = 0.001$) and 94 minimal erythema dose multiples (MEDs) compared with 64 MEDs ($P = 0.01$). Fifteen (of 16) developed at least one episode of well-demarcated erythema during 5× weekly treatment compared with just three of 16 treated 3× weekly ($P < 0.001$). There was no significant difference between regimens in duration of remission. For this skin phototype I–III population, the more rapid clearance of psoriasis with 5× weekly phototherapy is not, for the majority of patients, sufficient to justify the extra exposures and higher UVB dose. We no longer use 5× weekly phototherapy for psoriasis.

We do not, as yet, know the optimum narrow-band (TL-01) ultraviolet (UV) B weekly treatment frequency for chronic plaque psoriasis. UVB phototherapy using TL-01 lamps is in widespread use due to its greater efficacy[1–6] and, possibly, safety[1,7–11] compared with broad-band UVB sources. Our aim when administering this treatment is to clear psoriasis with as few unwanted acute effects as possible, and to minimize the risk of late adverse effects (particularly non-melanoma skin cancer) by minimizing each patient's cumulative UVB treatments and dose.

Traditionally, as in many centres, we have treated our out-patients 3× weekly and in-patients 5× weekly. The treatment frequency in published studies involving TL-01 UVB for psoriasis ranges from 2× to 5× a week. Current TL-01 treatment frequencies in routine use in Scottish treatment centres are 2, 3 and 5× per week (unpublished observation, R.S.Dawe, Scottish PUVA and phototherapy audit data). In the U.K., as a whole, UVB (all sources) is administered 2× to 7× weekly.[12]

Although the question: 'How often should we administer UVB?' has exercised dermatologists since at least 1930,[13] the answer has remained unclear even for conventional broad-band sources. However, a paired comparison study of nine patients showed no demonstrable advantage in treating chronic plaque psoriasis twice daily compared with once daily.[14] A retrospective comparison of a 3× weekly with a 5× weekly broadband (FS72 T12 lamp) UVB regimen showed no significant differences in dose or number of treatments to clearance and that the 3× weekly regimen was better tolerated.[15] Even if we accept (bearing in mind the retrospective design of this study, and the likely differences other than treatment frequency between the two groups compared) that 3× weekly is preferable to 5× weekly broad-band UVB, this is of limited help in deciding how frequently to administer TL-01. The optimum frequency of phototherapy with one UV source need not be the same as that for another. As the TL-01 lamp has a minimal output of therapeutically unimportant,[16] but erythemogenic[1] and carcinogenic[17] shorter UVB and UVC wavelengths it is possible that more frequent treatment than with broad-band UVB would be beneficial.

Patients often comment that a fortnight sunbathing on holiday clears their psoriasis, while it may take 4–

7 weeks of 3 × weekly hospital phototherapy to achieve the same result. A recent study which compared Canary Islands heliotherapy with broad-band UVB phototherapy in Finland provided some supporting evidence— showing heliotherapy to clear psoriasis more rapidly and with a lower cumulative UVB dose than phototherapy.[18] One of several possible explanations for this finding is that more frequent therapy was more effective.

We conducted a study designed to (i) test the hypothesis that 5 × weekly TL-01 UVB would clear psoriasis more rapidly and with fewer UVB exposures and a lower cumulative dose than 3 × weekly treatment, and (ii) help to answer a question of practical clinical importance: 'How frequently should we administer TL-01 phototherapy for chronic plaque psoriasis?'

Materials and methods

Study design

This was an observer-blinded, randomized, paired (within-patient) comparison study. Patients gave their informed consent after an opportunity to discuss the study implications and reading a patient information leaflet. The Tayside Committee on Medical Research Ethics approved the study. We treated each half-patient (sagittal plane) independently, following our standard minimal erythema dose (MED)-based, low percentage dose incremental,[19] UVB phototherapy regimen (Table 1), with only the treatment frequency differing between sides. A treatment allocation list generated from a random number table was used to determine which (right or left) side was treated 3 × and which side 5 × weekly. Patients wore a half-body suit (adapted work overalls) made of material which allowed transmission of no detectable UVB and negligible UVA (as assessed by Hitachi U-3210 double beam reflectance spectrophotometer). If the dose due to be delivered to each side differed, the higher dose side was treated first with the difference between the prescribed doses. The suit was then removed to allow administration of the remaining dose to both sides. At each visit patients were assessed and the psoriasis severity graded by an observer unaware of treatment allocation. The decision to stop treatment was made following our unit's standard protocol.

After discharge all patients were followed up for a year, or until relapse, at monthly intervals by telephone or visit to our department for assessment. If there was any suggestion of psoriasis recurring on either side, the patient was asked to attend for review. Relapse was defined as either an increase of global score to 50% of that at baseline or a return of psoriasis of sufficient severity for the patient to be unwilling to continue with emollient therapy alone.

The study was carried out in the Phototherapy and PUVA unit of the Dermatology Department, Ninewells Hospital, which serves the Tayside area.

Subjects

We recruited patients with chronic plaque psoriasis from out-patient clinics between November 1995 and June 1996. Patients were excluded if they had a history of skin cancer or solar keratoses or if they were on systemic immunosuppressive therapy. Other study-specific exclusion criteria included: age < 18 years; phototherapy, PUVA or any systemic therapy for psoriasis within the preceding 3 months; guttate psoriasis; known abnormal photosensitivity and any expressed hesitation about ability to attend daily (except weekends) for treatment.

Irradiation cubicle

Either a Waldmann UV5000 cubicle, fitted with 24 Philips 100 W TL-01 lamps, or a cubicle constructed by the Ninewells Medical Physics Department, with 50 Philips 100 W TL-01 lamps, was used. The same cubicle was used to treat both body halves and throughout each patient's treatment course. Irradiance was determined monthly with an International Light IL1400 meter calibrated with a spectroradiometer against a bank of TL-01 lamps, and the UVB exposure time–dosage table was adjusted as necessary. For measurements the meter was clamped at mid-height, 25 cm from the lamps, in the empty cubicle and the mean of 10 readings taken as the output. Irradiances in the Waldmann cabinet ranged from 3·53 to 2·95 mW/cm^2, and those in the Ninewells cabinet from 3·1 to 2·95 mW/cm^2 during the course of the study.

Minimal erythema dose determination

This was done on upper back skin following our standard procedure. For skin phototype I and II patients, the doses administered were: 25, 50, 70, 100, 140, 200, 280 and 390 mJ/cm^2. For skin type III patients, the first two doses in this series were omitted and doses of 550 and 770 mJ/cm^2 added. The MED was taken as the lowest dose to produce just perceptible erythema.

Table 1. UVB (TL-01) phototherapy regimen

1	Determine minimal erythema dose (MED) at 24 h
2	Initial dose: 70% of MED
	Maximum exposure dose: 2066 mJ/cm^2
3	Treat each side independently: 3× per week (Monday, Wednesday, Friday) or 5× per week (daily, Monday to Friday) as randomly allocated
4	Increments given at each visit, based on a percentage of previous dose and erythema response:
	No erythema: 20% increment
	Mild (grade 1, barely perceptible) erythema—repeat previous dose and reduce to 10% increments
	Moderate (grade 2, well defined asymptomatic) erythema—postpone one treatment, repeat previous dose at next visit and reduce to 10% increments
	Severe (grade 3, painful, persisting for more than 24 h) no treatment, and further treatment at discretion of doctor (no grade 3 erythema occurred during the study)
6	Other unwanted effects:
	If itch develops—encourage use of emollients
	If polymorphic light eruption develops—ask doctor to review (and check lupus serology), encourage emollients, and (a) if mild adjust regimen as for grade 1 erythema; or (b) if moderately severe, treat as for grade 2 erythema
7	Missed appointments:
	One or two treatments missed—repeat previous dose
	Three treatments missed—treat with penultimate dose

Treatment regimen

Our low incremental dose treatment regimen[19] is detailed in Table 1. All male patients wore genital protection, and all patients were offered facial photoprotection. Faceshield[20] (Ultra Violet Products Ltd, Cambridge, U.K.) or topical sunscreen, if facial psoriasis was absent. Adjunctive therapy was restricted to approved emollients (white soft paraffin/liquid paraffin 50:50 mix, aqueous cream, Diprobase cream or coconut oil) except for standard topical treatments for scalp, face and flexures. According to our usual practice, treatment was stopped when the psoriasis was deemed clear, or to have been in a state of 'minimal residual activity' (MRA) for four treatments, whichever occurred first. We set a maximum limit of 30 exposures for either side.

Assessment

The psoriasis severity of each body half was assessed at baseline (before the first treatment) and at each subsequent treatment visit by means of a 0–4 scale for each of scaling, erythema and induration (SEI) of symmetrical plaques (chosen at baseline) on the upper limbs (arm or forearm), trunk and lower limbs (thigh, leg or buttock). A 0–4 ('no' to 'very severe' psoriasis) global score was also used. This scoring scheme was based on the standard psoriasis area and severity index;[21] we had had experience of its use in earlier studies.[19,22]

Statistical methods

The main end-points were time (days), dose and number of treatments to clearance. We also compared psoriasis severity scores at baseline and at the end of treatment. Further, individual patient data, as well as summary data, were examined graphically. The distribution of values, or, when appropriate, differences in values, between sides was examined in graphical form, including quartile-normal plots, and by use of the Shapiro–Francia W' test to decide if a normal distribution could be assumed. For those variables which could not be assumed to arise from such a distribution we used non-parametric tests, and for normally distributed variables both parametric and non-parametric methods. No differences in interpretation arose from the different methods of analysis, so for consistency and clarity, we report only the results of the non-parametric tests. The Wilcoxon matched-pairs signed-ranks test (with a null hypothesis of no difference between the sides) was used for paired data and the Mann–Whitney U-test for unpaired data. Confidence intervals (CI) for the differences in medians were calculated using a rank-based method.[23] The proportions of patients developing erythema during treatment were compared by McNemar's exact test for paired proportions. Follow-up data were analysed by the plotting of Kaplan–Meier survival curves, compared by the logrank test.[24] Statistical calculations were performed with 'Stata' (with Practical Statistics for Medical Research add-on software to calculate CI for the medians, Department of Medical Statistics

and Evaluation, Royal Postgraduate Medical School, London, 1997).[25]

Results

Twenty-one patients, 13 men and eight women of mean age 43 years (SD 13·6, range 21–68), entered the study. They were of sun-reactive skin types I, II and III (Fig. 1). Five patients (four men and one woman) did not reach the end-point of clearance or MRA on both sides: one was withdrawn due to failure to attend regularly (intercurrent illness), one declined to continue when he was satisfied with a modest improvement on both sides, and three did not achieve clearance or MRA on both sides by the maximum of 30 exposures (to the 5× weekly side). Compliance with treatment was good. Only five of the 16 who completed the study missed any treatments. Of these five, four missed only one treatment (5× weekly side only—three patients; both sides—one), and one missed four treatments (5× weekly side only—one; both sides—three). Treatments were also missed because of intercurrent illness (two), personal reasons (four) and unit closure for public holiday (two).

The median psoriasis severity (SEI) scores of the 16 completing patients at each assessment are shown in Figure 2; and the baseline and final treatment visit SEI scores for these 16 patients, and (on an intention-to-treat basis) all 21 entered patients, are described in Table 2. The median baseline psoriasis severity score (SEI = 25) of those who completed the study was not significantly different from that of those who did not

complete (SEI = 27·5). (*P* = 0·57; 95% CI for difference in medians − 6 to 5).

Psoriasis took longer to clear or reach MRA with 3× weekly than with 5× weekly treatment, clearing in a median of 35 days (range 19–43) with 5× weekly UVB and in a median of 40 days (range 23–63) with 3× weekly treatment (Fig. 3a). (*P* = 0.007, 95% CI for difference in medians 2–11). However, this more rapid clearance with the 5× weekly regimen was achieved at the expense of a higher dose of UVB and more treatments. In multiples of each individual's MED, the 5× weekly sides required a median UVB dose of 94 (range 27–164), compared with 64 (range 23–125) MEDs for the 3× weekly sides (Fig. 3b). (*P* = 0·010, 95% CI 5–33). The sides treated 5× weekly received a median of 23·5 compared with 17 treatments for the 3× weekly sides (*P* = 0·001, 95% CI 3·5–8) (Fig. 3c).

Inspection of the individual patient data showed only two patients with results sufficiently different from the summary results to alter how we would consider treating these individuals in the future. One patient's psoriasis cleared 28 days sooner on the 5× weekly side, with five fewer treatments and a lower (by 36 MEDs) cumulative dose. However, his psoriasis relapsed exceptionally quickly—in 6 days on the 5× weekly treated side and 22 days on the 3× weekly side. Another patient's psoriasis cleared 26 days more quickly on the 5× weekly side, with one less treatment (but a slightly higher cumulative dose) compared with her 3× weekly treated side. No features of these two patients before starting treatment distinguished them from the other 14 patients.

Acute adverse effects were more troublesome with the 5× weekly compared with the 3× weekly regimen.

Figure 1. Minimal erythema doses (MEDs) and skin phototypes (ST) for the 21 patients who entered the study. The five patients who did not complete the study were all of ST-II; four with MED of 140 and one of 100 mJ/cm².
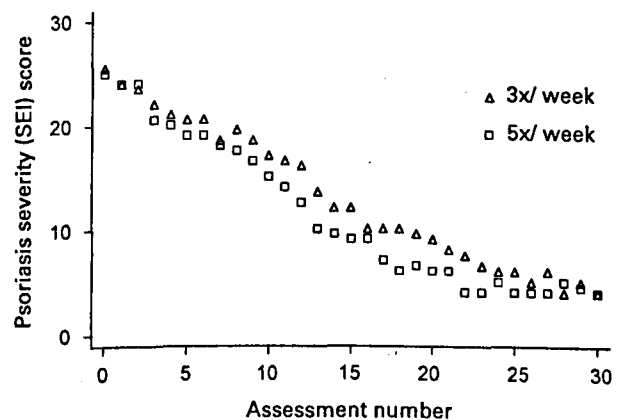

Figure 2. Median psoriasis severity (Scaling, Erythema and Induration—SEI) scores for 3× weekly and 5× weekly treated sides at each assessment for completing patients (*n* = 16). The graph of induration scores alone (on file) is similar.

Table 2. Median (and range) of psoriasis severity (SEI) scores at beginning and end of treatment

	3 × per week side	5 × per week side	Probability[b]	95% CI[a]
Completing patients ($n = 16$)				
Baseline	25·5 (19–32)	25 (17–31)	$P = 0.48$	−0·5 to 0·5
Final treatment visit	2 (0–6)	3 (0–6)	$P = 0.63$	−1·5 to 1
All patients ($n = 21$)				
Baseline	26 (14–34)	25 (14–34)	$P = 0.22$	−1 to 0
Final treatment visit	4 (0–18)	3 (0–13)	$P = 0.76$	−1·5 to 1·5

[a]Rank-based confidence interval for *difference* in paired medians.
[b]Wilcoxon matched-pairs signed-ranks test (null hypothesis of no difference between sides).

While no patient suffered a painful (grade 3) erythema; 15 of 16 on 5 × weekly treatment developed at least one episode of well-demarcated (grade 2) erythema as compared with only three of 16 on 3 × weekly treatment ($P < 0.001$). Two patients developed polymorphic light eruption (PLE). One patient's episode of PLE affected both sides early during the course and the other's 5 × weekly side only was involved after the final treatment.

The time to relapse for each side is shown in Figure 4. There was no difference in the probability of relapse between regimens ($P = 0.73$). At relapse, only three required therapy other than topical emollients, tar or calcipotriol. Of these three, one started PUVA, one another course of UVB and the third entered a half-body comparison of PUVA and UVB phototherapy. Two others have since required non-topical therapy: one commencing UVB, and the other PUVA, 6 months after initial relapse.

Discussion

We have shown that for the majority of patients in our population, 3 × weekly TL-01 UVB phototherapy is preferable to 5 × weekly treatment. Clearance of psoriasis slightly more quickly (by a difference in medians of 5 days) with 5 × weekly treatment is not, in our opinion, sufficient to justify the patient inconvenience, the higher frequency of significant erythema provoked during treatment, and the expected greater long-term risk related to the higher cumulative UVB dose and number of exposures required. Consequently, we no longer routinely use 5 × weekly treatment for in-patients, as was our previous practice.

Although individual patient response does vary, the absence of factors predictive of a better response to 5 × weekly treatment (as occurred in only two of our patients) suggests we should base our treatment decisions on the evidence applicable to the group as a whole. Occasionally,

however, for example for a patient anxious to be clear for a specific occasion, it may be reasonable to offer 5 × weekly treatment for faster clearance, despite the increased risk of acute and, presumably, chronic adverse effects.

A within-patient paired study allows us to control for all factors other than the single, altered variable under investigation. However, a potential drawback relates to the possibility of a systemic phototherapy effect—we know that TL-01 UVB produces various alterations in systemic immune function as assessed *in vitro*.[26] In practice, however, any such effect appears unable to clear psoriasis. In our experience and that of others,[27] unexposed flexural psoriasis fails to clear with phototherapy as do, according to ongoing study, any plaques covered during treatment (data on file). We therefore think it unlikely that any systemic effect of the 5 × weekly treatment exerted a clinically important effect in clearing our study patients' 3 × weekly treated sides. Further support for this is given by the fact that the median number of treatments to clearance or MRA for the 3 × weekly side was as expected.

Our findings should be of value to other phototherapy units treating a similar patient population. Now, over 10 years after the introduction of the TL-01 source, its advantages over broad-band UVB sources for chronic plaque psoriasis are becoming steadily more clear. We also have open study evidence of its efficacy in atopic dermatitis,[28–30] and controlled study evidence of its value in PLE,[31] although more information is required to assess its value, and method of use, in the many other TL-01-responsive conditions. A priority, however, remains the generation of further objective information on its effective and safe use in psoriasis and atopic dermatitis. The evidence generated by this study indicates that in our northern European population of chronic plaque psoriasis patients, a 3 × weekly low incremental regimen with an MED-based starting dose is preferable to 5 × weekly treatment.

Figure 4. Duration of remission—the percentage of patients whose psoriasis has not yet relapsed at each time point is plotted in red for the 5 × weekly regimen and blue for the 3 × weekly regimen.
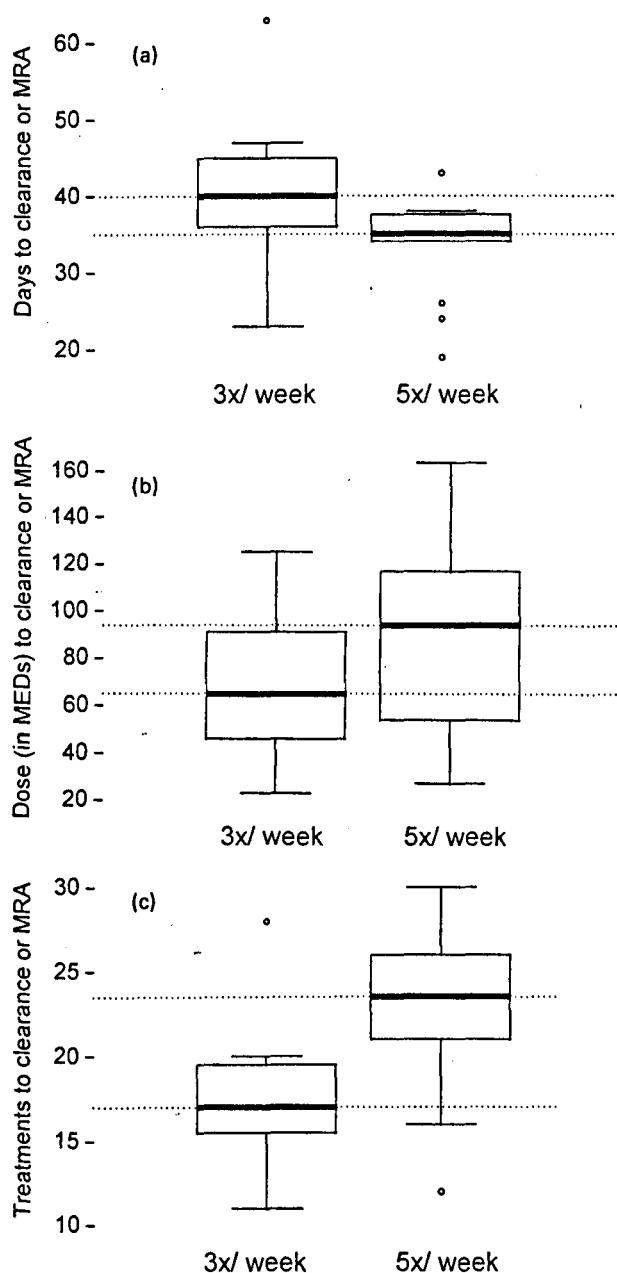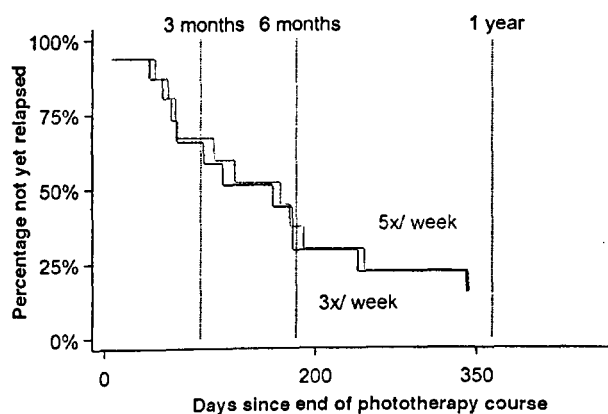
Figure 3 (a). Days to clearance or minimal residual activity (MRA). The thick central lines represent the medians for each treatment frequency, and the boxes enclose the interquartile ranges (IQRs). The whiskers enclose adjacent values (to 1½× the IQR) and a '᎔' is used to represent individual outlying values. (b) Dose [in multiples of each individual's minimal erythema dose (MED)] to clearance or MRA. (c) Number of treatments to clearance or MRA.

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Service outcome was evaluated at these centres by means of a two sided questionnaire completed by 30 consecutive new patients with atopic eczema during their initial consultation and again 6 weeks later (Phase 3).

98% of the centres responded to the Phase 1 questionnaire. The validation visits revealed only minor discrepancies between reported and observed facilities. Over 90% of the centres had facilities for measuring height and weight in children, 98% had access to patch testing and 91% had access to a photochemotherapy unit. Although 91% had trained nursing staff available in outpatients only 76.5% of these had time to demonstrate treatments. 97% of centres had access to inpatient paediatric facilities but only 58.5% of these had access to nurses with any dermatological experience. 89% had a rapid access appointment system for patients who deteriorate and 77.5% of these were patient initiated although the average waiting time was greater than 3 days in 33% of cases. 96% had access to a dietician with the waiting list being under 8 weeks in 81% of cases. Only 62.5% of the centres had access to counselling services and the waiting list for this was more than 8 weeks in 39% cases. 80% of centres provided information leaflets for all new patients but only 50% of the centres sent out new appointment letters requesting the patient to bring along their current and previous eczema treatment.

These Phase 1 results highlight some possible shortfalls in the service that we provide for patients with atopic eczema and form the basis for discussion of future audit standards.

THE SCOTTISH PHOTOTHERAPY AUDIT: THE NEED FOR EVIDENCE BASED GUIDELINES?

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Ultraviolet B phototherapy (UVB) and photochemotherapy (PUVA) are widely used. An audit of PUVA use in Scotland in 1991 (W. Perkins) led to a range of recommendations to improve PUVA use. Since then more information on the skin cancer risks of PUVA has emerged. This has coincided with the increasing use of the narrow-band TL-01 UVB lamps which are more effective at clearing psoriasis than broad-band UVB lamps.

The aims of this audit were 1) To assess the current use of both UVB phototherapy and PUVA throughout Scotland and to make appropriate recomendations, and 2) To find out if the recommendations of the 1991 PUVA audit have been implemented.

Information was collected from all 19 dermatology department phototherapy/PUVA units and 19 separate physiotherapy department phototherapy units. Information was obtained by questionnaire, visits to departments and notes review. Recommendations for good practice were based on observations made and graded according to the quality of evidence.

Ultraviolet B (using TL-01 lamps in 19 departments) is increasingly used for a wide variety of conditions. PUVA use has declined since 1994. The recommendations of the 1991 PUVA audit have been successfully implemented with the exception, so far, of developing in all centres a reliable system for follow-up of patients regarded as at increased risk of skin cancer. UVB and PUVA methodology is generally appropriate and based on accepted standards. There is, however, significant variation between centres in outcome measures, such as number of treatments required to clear psoriasis, reflecting differences in aspects of treatment methodology.

UVB phototherapy and PUVA are widely available and used appropriately. However, a number of evidence-based guidelines designed to improve the current service can be made.

THE NATURAL HISTORY OF THE PHOTOSENSITIVITY DERMATITIS AND ACTINIC RETICULOID SYNDROME

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The natural history of the photosensitivity dermatitis and actinic reticuloid (PD/AR) syndrome (syn. chronic actinic dermatitis) has not previously been clearly defined. Knowledge of the course of this condition is important to: 1) advise patients on their prognosis; and 2) for possible clues to pathogenesis.

We conducted an historical cohort study, following up 178 patients diagnosed between 1972 and 1995, for 1 to 24 (median 4) years. All patients were re-assessed clinically and by monochromator phototesting and, in 54 patients, by repeat patch testing to previously identified contact allergens. The probability of clinical improvement and of defined "complete resolution" during follow-up was assessed by plotting Kaplan-Meier survival curves.

The majority showed clinical improvement, however complete resolution of abnormal photosensitivity, defined as 1) no longer clinically photosensitive and 2) phototesting results within normal population limits, occurred in only 23 (13%). Taking into account the variation in follow-up duration, resolution of abnormal photosensitivity can be expected in 7% after 5 years, 22% after 10 years and 50% after 16 years of follow-up. Only one of 54 patients in whom repeat patch testing was performed lost all previously identified contact allergens; and loss of 1 or more contact allergen was not associated with resolution of abnormal photosensitivity ($p=0.81$; logrank test).

The abnormal photosensitivity, but not the contact allergic dermatitis, component of the PD/AR syndrome spontaneously resolves in some patients.

ENVIRONMENTAL FACTORS AND MELANOMA: HORMONES, SUNBURNS AND SUNBEDS.

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Although studies on familial melanoma support the role of genetic factors in melanoma, sun exposure is important in the aetiology of this tumour. Exposure to natural and artificial ultraviolet radiation as well as hormonal factors have been investigated in many case-control studies of melanoma but results have been conflicting. The results reported here are part of a case-control study of melanoma in the UK including 426 cases and 411 controls. As well as undergoing a skin examination, the subjects were interviewed concerning sun exposure, sunbeds and reproductive factors.

A past history of one or more severe sunburns was associated with a relative risk (RR) for melanoma of 1.2 (0.9-1.6) when adjusted for age and sex. More than 10 severe sunburns yielded a RR of 1.8 (0.9-3.7). However, when adjusted for skin type the RR was 1.0. Sunburn at an early age, outdoor occupation and residence in hot countries were not associated with an increased risk of melanoma. Use of sunbeds for 100 hours or more gave a RR of 1.2(0.9-1.9) when adjusted for age, sex and skin type. There were 278 female cases and 254 female controls. Use of the contraceptive pill was not a risk factor: RR of 1.0 (0.9-1.0). No

Main Plenary Session: Summaries of Papers

A systematic review of antistreptococcal interventions for guttate and chronic plaque psoriasis

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The Cochrane Collaboration was developed in 1992 to provide systematic, up-to-date reviews of randomized controlled trials of health care interventions and to disseminate this information to health care workers, providers and consumers. Many accepted treatments for skin conditions have never been formally evaluated or compared with alternatives and much of dermatological practice is based on tradition rather than evidence. The Cochrane Skin Group, formed in 1997, consists of an international network of individuals committed to producing and updating reviews of trials relating to skin conditions. A further role of the group is to identify priorities for research. We present the results of a review of anti-streptococcal interventions in the treatment of guttate and chronic plaque psoriasis and discuss its implications.

Guttate psoriasis is closely associated with preceding streptococcal sore throat or tonsillitis. Some claim that chronic plaque psoriasis may also be exacerbated by streptococcal infection. In view of this, many dermatologists recommend antibiotic therapy for flares of guttate psoriasis in particular and some advocate tonsillectomy for those with severe psoriasis associated with recurrent tonsillitis. The objective of this review was to assess the evidence for effectiveness of antistreptococcal interventions in the management of acute guttate and chronic plaque psoriasis. An extensive search of electronic databases (including Medline, Embase and The Cochrane Controlled Trials Register) and other sources identified only one randomized study which met the inclusion criteria. 20 psoriasis patients, predominantly of guttate type and with evidence of β-haemolytic streptococcal colonization, were randomized to receive 1 of 2 oral antibiotic schedules in which either rifampicin or placebo was added to the final 5 days of a 14-day course of phenoxymethylpenicillin or erythromycin. No patient in either arm of the study improved during the observation period. No controlled studies of tonsillectomy were identified.

Although both antibiotics and tonsillectomy have frequently been advocated for patients with recurrent guttate psoriasis or chronic plaque psoriasis, there is, to date, no good evidence that either intervention is beneficial. There is clearly a requirement for further research in this area. The following studies would help to determine whether antistreptococcal interventions should be recommended in patients with guttate and chronic plaque psoriasis.

1. Treatment: Antistreptococcal antibiotic vs. placebo in acute guttate psoriasis.

2. Prophylaxis: Antibiotics vs. placebo for symptoms of sore throat in patients following resolution of an episode of guttate psoriasis.

3. Long-term prophylaxis: Antibiotics vs. placebo in patients with chronic plaque psoriasis with evidence of recurrent streptococcal sore throat.

4. Tonsillectomy vs. no tonsillectomy: for patients with severe recurrent guttate or chronic plaque psoriasis with evidence of recurrent streptococcal sore throat.

A comparison of TL-01 UVB phototherapy and bath-PUVA for chronic plaque psoriasis

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We designed a study to help answer the question: is there any difference in efficacy between 3× weekly narrow-band (TL-01) UVB phototherapy and 2× weekly TMP bath-PUVA for chronic plaque psoriasis? This was an observer-masked, within-patient (half-body) paired study.

Twenty-eight patients (11 women; median age 47, range 22–71 years old) participated. Ten were withdrawn before study completion due to: inadequate response to treatment (on PUVA-treated body half) [4 patients], protocol violation (topical steroids for polymorphic light eruption) [2], inter-current illness [1], pregnancy [1], severe PUVA itch [1], repeated failure to attend [1]. The median reduction in scaling, erythema and induration (SEI) score for all 28 patients, analysed on an intention-to-treat basis, was 20·5 with UVB and 18 with PUVA [95% C.I. for difference 0·6; $P = 0·04$].

All 18 who completed the study reached clearance or minimal residual activity (MRA) with UVB, but in 3 the PUVA-treated side was still not clear by a maximum of 30 exposures. UVB treatment achieved clearance a median of 11 [95% C.I. 4·5–24·5] days more quickly than PUVA, but required a median of 24·5 compared to 20 exposures [95% C.I. for difference 0–5]. UVB produced more asymptomatic, well-demarcated erythema episodes (32% of all patients) than PUVA (14%) [95% C.I. for difference 036%]. Kaplan–Meier survival analysis showed no significant difference between modalities in time to relapse ($P = 0·34$).

Overall, administered according to our standard protocols, TL-01 UVB is at least as effective as bath-PUVA.

Psychological distress affects the efficacy of PUVA in patients with psoriasis

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Furthermore, the vasculitic skin lesion had appeared in both patients, several weeks after administration of these agents.

We believe that the time relationship to the operation (21 and 7 days, respectively) and the concurrent pericardial involvement, may both be implicated in its occurrence, probably through immune complex formation and deposition. Immune complexes have been demonstrated in patients with the post-pericardiotomy syndrome, possibly associated with antiheart antibodies.[3] We suggest an immunologically mediated reaction may be induced either by the cardioplegic agents used during the operation or by a delayed reaction to blood cell units given during the CABG.

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Urticarial vasculitis

Sir, I write to provide follow-up information on a patient reported recently.[1] In 1995 this patient developed a chronic lower leg ulcer which failed to respond to combined high-dose azathioprine and prednisone. A liver biopsy was performed showing periportal inflammation and a repeat cryoglobulin determination was positive. Urticaria, the initial cutaneous problem, has not recurred since immunosuppressive therapy was reinitiated nor after discontinuing this. At present, no immunosuppressants are being administered, and alpha interferon is being given for treatment of hepatitis C. It would appear that this patient had urticarial vasculitis evolving into the more typical cryoglobulinaemia-associated vasculitis as a manifestation of chronic hepatitis C infection.

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Borrowing from museums and industry: two photoprotective devices

Sir, In photodermatology, as in other medical disciplines, technological developments often lead to improvements in patient care. We wish to share experience of the use of two devices, one originally designed to protect museum exhibits and the other biotechnology industry workers.

Our attention was drawn to the UVC-803 Face Shield (Fig. 1), available from Ultra Violet Products Ltd, Science Park, Milton Road, Cambridge, by Abel's text.[1] It is designed to protect those working with transilluminators in biotechnology and forensic science, but is also useful to both patients and staff in a PUVA and phototherapy unit. It prevents UVC, UVB and UVA transmission (Fig. 2).

Many patients attending for phototherapy or PUVA do not require face treatment. Facial photo-protection in the irradiation cubicle reduces the frequency and severity of early unwanted effects including erythema, pigmentation and reactivation of cold-sores. It should also reduce the risk of late complications such as malignancy. Staff involved in metering tasks also require adequate protection as does the parent or staff member supervising treatment of a young child.

Prior to this new clear, light-weight face shield we used either a welder's helmet or topical sunscreen. The helmet was heavy and uncomfortable so most patients preferred the sunscreen despite difficulties in ensuring it covered exactly the same area of skin at each visit and the length of time required to remove it after treatment.

All our patients who require facial photo-protection prefer the new face shield to helmet or sunscreen. It is now also in routine use by staff during maintenance and metering tasks.

Another device that colleagues might find useful is Museum 200 Film, manufactured by Sun Guard, Florida, U.S.A. and obtainable in the U.K. from Bonwyke Window Films. Bonwyke
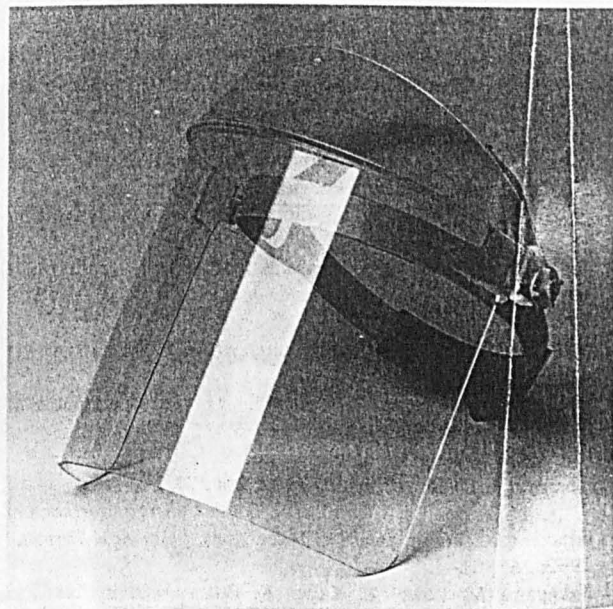

Figure 1. UVC-803 face shield.

House, 41–43 Redlands Lane, Farnham, Hampshire. This clear, lightweight film, initially produced to protect museum exhibits from ultraviolet radiation, is of value to patients with severe photosensitivity to UVB and UVA wavelengths. The sticky-backed film is almost undetectable when applied with care to house, hospital or windowglass in cars. When fitted to car windows it will not interfere with vision or the winding down of side windows and allows increased freedom of activity for many patients. The film prevents transmission of nearly all UVR wavelengths (Fig. 3) and after 1 year of south-facing window sunlight exposure (data on file) the transmission spectrum is unchanged. It is of particular value in the management of severely affected patients with the idiopathic photodermatoses in which UVB and UVA wavelengths are important (photosensitivity dermatitis/actinic reticuloid syndrome, actinic prurigo, solar urticaria) and the photogenodermatosis–xeroderma pigmentosum.

Both these devices, originally developed for quite different purposes, have proven helpful in patient care.

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Reference

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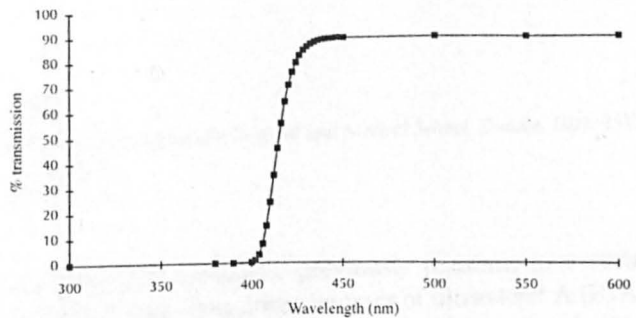
Figure 2. Effect of 803 face shield on transmission.
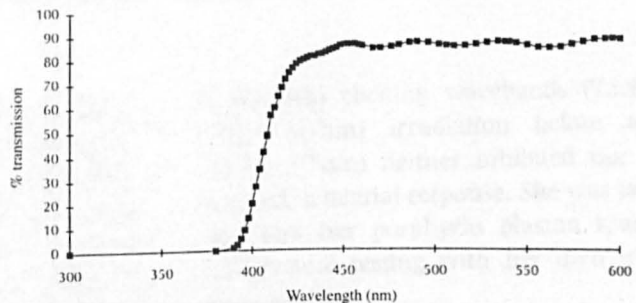
Figure 3. Effect of Museum 200 film on transmission.

Historical vignette

Medical history from the Journal

Ordinary Meeting of the Dermatological Society of London held on 13 February 1895.

Dr Colcott Fox showed a girl of 11 years with an unusual ringed Eruption of the fingers. On the flexor aspect of the left ring-finger was a ring of eruption extending from the proximal phalanx to the distal phalanx and half way up the sides of the finger. This oval ring was characterized by a smooth, rounded, projecting border, white in colour, doughy in consistence, quite an eighth of an inch wide, and about one-sixteenth of an inch in height. The enclosed area was normal, or perhaps a little reddened. There were no subjective symptoms, except that the border was slightly tender on pressure. On the little finger of the right hand was a similar ring but rather smaller and broken up in places

into rounded nodules. The affection was cutaneous, and seemed to involve all the layers of the skin. The mother stated that the rings each began in a nodule before Christmas and gradually extended peripherally .... The exhibitor said that he was at a loss to make a diagnosis. The indolent spread of the rings ..., the depth to which the skin was involved, and the absence of vesication and desquamation, seemed to put 'ringworm' out of court.[1]

Reference

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A nice description of granuloma annulare.

Julian Verbov, Editor

Prolonged benefit following ultraviolet A phototherapy for solar urticaria

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Summary   Two patients with severe idiopathic solar urticaria, previously resistant to a variety of therapies including plasma exchange, benefited from springtime courses of ultraviolet A (UVA) monotherapy. Sites which are normally exposed to sunlight were treated, in a cabinet fitted with Philips R-UVA lamps (emitting UVA and visible wavelengths, with peak at 350 nm), twice daily for 2–3 weeks. One patient has been treated in this way for 3, and the other for 2, consecutive years. Repeat monochromator phototesting 3 months after their latest courses of UVA showed a persistent reduction in severity of abnormal photosensitivity. Both patients describe a sustained improvement in their condition lasting over 6 months after treatment.

Idiopathic solar urticaria is an uncommon condition that presents with immediate erythema and wealing on exposure to ultraviolet (UV) and/or visible wavelengths. The diagnosis is confirmed by provocation testing with appropriate wavebands and exclusion of known causes of solar urticaria—drugs or cutaneous porphyrias.[1] It can be severely handicapping and the response to treatment is variable. Spontaneous resolution is unusual.[2,3] Sunlight avoidance measures alone, including sunscreen use, are rarely sufficient. Antihistamines provide adequate relief for some.[4-6] Although doxepin may occasionally be helpful,[7] as may antimalarial drugs,[8-10] our experience with these has been disappointing.

Phototherapy with various sources (broad-band UVB,[11] narrow-band TL-01 UVB,[12] UVA[13-17] and visible light[13,18]) helps some patients, as does photochemotherapy.[19-21] Plasma exchange, used for a few severely affected patients,[22] has for the majority proved disappointing despite reports of persistent remission in three cases.[23-25]

We describe the successful use of UVA phototherapy, followed by prolonged improvement in two cases.

Case reports

Patient 1

A 36-year-old woman was diagnosed as having idiopathic solar urticaria in 1991. Monochromator phototesting[26] confirmed the diagnosis, and showed UVB, UVA and visible (305 ± 5 to 430 ± 30 nm half-maximum

bandwidth) eliciting wavebands (Table 1). Red light (650 ± 30 nm) irradiation before and after UVA (365 ± 30 nm) neither inhibited nor augmented the induced urticarial response. She was taking no medication and her porphyrin plasma scan was negative. Intradermal testing with her own irradiated plasma was negative.

Sunlight avoidance measures, including appropriate sunscreens, various antihistamines and a trial of hydroxychloroquine were of minimal benefit. The severity of her photosensitivity with UVB precluded TL-01 phototherapy. A trial of plasmapheresis was of no benefit. She was unable to walk the 800 m to work even in the early morning, to shop during daylight hours and to go outside with her children. Monochromator phototesting in May 1994 confirmed the continuing severity of her condition. Her UVB (TL-01) minimal urticarial dose (MUD) was below 6 mJ/cm². Her UVA (R-UVA lamp) MUD after oral 8-methoxypsoralen (8-MOP) was 0·3 cm² (erythema and flare with 0·1 J/cm²), whereas with R-UVA lamp irradiation alone her MUD was not as low, at 2 J/cm² (erythema and flare with 0·5 J/cm²). This phenomenon of a photosensitizing drug lowering the threshold for induction of one of the idiopathic photodermatoses remains unexplained, although we have noted it occasionally in polymorphic light eruption as well as solar urticaria. These results meant that neither TL-01 phototherapy nor PUVA would be practicable treatments, and a course of UVA phototherapy was given following the protocol in Table 2.

Table 1. Minimal urticarial doses in mJ/cm² (patient 1)

	November 1991 presentation	April 1996 before 3rd UVA course	April 1996 immediately after UVA course	August 1996 3 months after 3rd UVA course
Medication	Nil	Nil	Loratidine 10 mg/day	Nil
Waveband (nm)				
Testing on upper back				
305 ± 5	<1·8	>33	NT	>47
335 ± 30	<100	560	NT	>4700
365 ± 30	<100	12,000	NT	>10,000
400 ± 30	560	22,000	NT	>47,000
430 ± 30	5600	>82,000	NT	>82,000
460 ± 30	>82,000			
Testing on volar forearm				
335 ± 30		1000	4700	>4700
Testing on buttocks				
335 ± 30		NT	NT	3300

>, no urticaria demonstrated with doses up to that stated.
NT, not tested.

She has now had 3 yearly courses of UVA phototherapy. For the first we treated only face, neck and dorsal hands. During her last course (1996) she was treated wearing a T-shirt and shorts. Apart from one episode of urticaria affecting popliteal fossae, treatment has been uncomplicated.

After each course of phototherapy she reported that the benefit lasted until the next spring. In 1995 her only summertime episodes of solar urticaria affected her soles when she attempted sunbathing, and palms when putting out washing. Last year (1996), after her third UVA course, she stopped antihistamine therapy and did not take special precautions, yet had only one episode of solar urticaria affecting untreated buttock skin through clothing. After each course of UVA she aimed to expose herself to sunlight for up to half an hour daily. This was not always possible, yet she did not develop solar urticaria on re-exposure after a few days without outdoor sunlight.

The improvement she describes has been paralleled by a steady rise in the doses required to provoke urticaria. This year, phototesting on unexposed back skin was much improved even before UVA phototherapy compared with previous years' results, and was normal 3 months after the course of UVA. Only a high dose of 335 ± 30 nm waveband irradiation could provoke urticaria on buttock skin.

Table 2. UVA phototherapy regimen for solar urticaria

Treatment given in Dixwell stand-up cubicle with 48 × 100 W and 12 × 40 W Philips R-UVA lamps (peak emission at 350 nm).
Irradiance = 18·8 mW/cm²

1. Determination of minimal urticarial dose (MUD) and immediate minimal erythema dose (MED)
2. First exposure—70% of MUD or immediate MED reading (whichever is lower)
3. Subsequent exposures—initially increase dose once daily, with increment based on a percentage of previous dose and on immediate erythema or urticarial responses. If no problems after first 10 exposures give increment with each dose.
a. If no immediate erythema or urticaria—40% increment given
b. If just perceptible immediate erythema—same dose given
c. If well demarcated or symptomatic immediate erythema, or mild urticaria (no systemic symptoms)—same dose; then 20% increments.
   Treat twice a day, 5 days a week for 18–26 exposures. Treat only habitually exposed sites. Keep patient in the phototherapy unit for 1 h observation after each exposure and ensure exposures always separated by a minimum of 6 h.
4. Maximum dose administered = 15·6 J/cm².

Patient 2

A 60-year-old man presented in 1984 following abrupt onset of his complaint. Solar urticaria, with UVA and visible (335 ± 30 to 600 ± 30 nm) eliciting wavebands, was confirmed by monochromator phototesting. His plasma porphyrin scan was normal. Intradermal testing with irradiated autologous plasma and serum was positive.

Antihistamines produced some improvement, as did 8-MOP PUVA and TL-01 UVB phototherapy. Both allowed an increase in tolerable sunlight exposure from 5 min to a more acceptable 1 h, with up to 4 months sustained subjective improvement. However, he remained significantly handicapped. Plasmapheresis produced a marked, but short-lived, improvement.

We used UVA phototherapy because of the significant benefit that patient 1 gained from this the year before. The same treatment protocol was followed (Table 2). He has now had two spring courses of UVA (in 1995 and 1996). The only complication has been asymptomatic immediate erythema affecting skin of trunk (including that covered by a white T-shirt) midway through his last course. As with patient 1 advice was given that he should cautiously, but deliberately, seek sunlight exposure (15 minutes daily, to be gradually increased) after the treatment course.

He has since been able to stay outdoors for as long as 2–3 h at a time: longer than ever before since onset of solar urticaria 12 years ago. The only episodes of sunlight provoked urticaria have been on palms and volar wrists: sites relatively shaded during treatment. Although improvement in his life quality following UVA has not been as dramatic as for patient 1, partly because of his being restricted by other medical problems, he has found UVA phototherapy to be of greater benefit than any of the previous treatments tried.

Phototesting on his back (not exposed to UVA during treatment) and his volar forearm (a treated site) was conducted before, immediately after, and 3 months after his last course of phototherapy (Table 3). Urticaria could no longer be induced on either site immediately after phototherapy (testing with 430 ± 30 nm waveband) and 3 months later could only be elicited on his back with doses two to 10 times higher (depending upon waveband) than before, and could still not be provoked on the forearm.

Discussion

These two patients with exceptionally severe idiopathic solar urticaria have both benefited greatly from phototherapy using a source emitting predominantly UVA (with peak at 350 nm) as well as visible wavelengths. The degree of improvement, especially in patient 1, and the long-lasting benefit after treatment raises the possibility of spontaneous resolution. However, as spontaneous resolution in this condition is unusual,[2,3] we suspect the improvement is treatment-related.

The mechanism of action of UVA phototherapy in solar urticaria is unclear. The patients described by

Table 3. Minimal urticarial doses in mJ/cm^2 (patient 2)

	May 1996 before 2nd UVA course	May 1996 immediately after 2nd UVA course	August 1996 3 months after 2nd UVA course
Medication (daily dose)	Ranitidine 300 mg Cetirizine 20 mg	Ranitidine 300 mg Cetirizine 20 mg	Ranitidine 300 mg —
Waveband (nm)			
Testing on upper back			
305 ± 5	>39	NT	NT
335 ± 30	>3900	NT	NT
365 ± 30	>12,000	NT	NT
400 ± 30	>47,000	NT	NT
430 ± 30	4700	>10,000	47,000
460 ± 30	2200	NT	15,000
500 ± 30	8200	NT	18,000
600 ± 30	>82,000	NT	>10,000
Testing on volar forearm			
430 ± 30	3300	>10,000	>10,000

>, no urticaria demonstrated with doses up to that stated.
NT, not tested.

Ramsay.[13] who were treated with sources matching their photosensitivity action spectrum, lost their induced tolerance within 72 h of missing a treatment. Other reports, describing patients whose improvement following UVA phototherapy was sustained over the summer months, suggested that careful, deliberate sunlight exposure after treatment was important in maintaining the benefit.[15,16] Only one patient, treated with a predominantly UVA source and a UVB/UVA source, is described as having achieved almost complete remission following phototherapy.[14]

A difficulty in determining the mechanisms of action of treatment in idiopathic solar urticaria is that this is likely to be a heterogeneous group of conditions, at least if patients are classified according to response to intradermal injection of their own, or others', plasma, serum or tissue fluid,[27] or by wavelength dependency.[28,29] Solar urticaria may, in some patients, be due to a true, IgE-mediated, allergy to a mast cell-binding photoallergen.[30]

Various hypotheses have been put forward to explain tolerance induction by exposure to the inducing stimulus, a phenomenon also recognized in other physical urticarias. In solar urticaria the tolerance induced by UVA irradiation is capable of providing protection against other eliciting wavelengths.[15,16] Tolerance induction seems not to be due to depletion of mast cell histamine, and Keahey et al. regard depletion of a circulating serum factor as unlikely, given that in their three patients untreated shadowed sites did not show increased tolerance.[16] They postulated an increase in mast cell degranulation threshold produced directly by UV irradiation. However, repeated injection of in vitro irradiated autologous plasma or serum can also induce tolerance.[31] It has been suggested that during the state of tolerance IgE binding sites on mast cells may be occupied by a photoallergen and, until new IgE is formed, IgE mediated release of urticogenic substances from mast cells is blocked.[30,31] Pigmentation and epidermal thickening induced by UVA may also be important, although such induced photoprotection would be expected to be more effective at blocking UVB/UVA transmission than visible wavelengths.[15]

Any explanation for the effect of UVA in these two patients has to explain the prolonged duration of improvement, lasting for up to a year, and the apparent steady improvement each year. It must also explain why sites shielded from UVA during treatment (although admittedly exposed to visible light through clothing) also show a demonstrable improvement. If we accept the immunological hypothesis for solar urticaria

pathogenesis, perhaps one of the mechanisms is a true immunological desensitization phenomenon, with phototherapy leading to the production of a blocking antibody or other factor.

Whatever the mechanism of action, UVA phototherapy, delivered according to the protocol described here, has proved remarkably effective in these two patients. We now consider its early use for new patients presenting with idiopathic solar urticaria.

Acknowledgments

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(TL-01) UVB phototherapy. she was commenced on a second course using the same regimen but without the sulpha-methoxypyridazine. She again responded well. with complete clearance of the eruption (Figs 1 and 2). Unfortunately, 2 months after completion, the condition began to relapse.

The position of SCPD as a distinct entity, separate from the spectrum of pustular psoriasis. is still hotly debated. In over 15 years, our patient has never developed any features to suggest a diagnosis of psoriasis. Most cases of SCPD respond to treatment with dapsone or sulpha drugs, although this is not invariable.[2] Indeed, many other treatments have been advocated including antibiotics. oestrogens. immunoglobulins and corticosteroids. None has proven to be the uniform therapeutic choice. Less toxic treatments would be an advantage for this benign. chronic. but troublesome dermatosis.

Our patient highlights the difficulty of maintaining a satisfactory therapeutic response and that this may require the long-term use of potentially toxic drugs. In our patient, a satisfactory response was achieved with PUVA, albeit only for a short time. There are only four reports of SCPD responding to PUVA.[1,3-5] In addition to improving with PUVA. our patient has twice achieved a satisfactory clinical response with narrowband (TL-01) UVB phototherapy.

Park et al. describe a 12-year-old boy with SCPD who achieved a therapeutic response, maintained for 8 months, after a course of broadband UVB treatment. We suggest that narrowband UVB phototherapy deserves further evaluation in the treatment of patients with SCPD who fail to improve with dapsone or other sulpha drugs.

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Subcorneal pustular dermatosis (Sneddon–Wilkinson disease) treated with narrowband (TL-01) UVB phototherapy

SIR, A 76-year-old woman presented with a 2-week history of a symmetrical polyarthropathy of the metacarpophalangeal joints. She had rings of pustules, some with hypopyon, symmetrically affecting the axillary skin. the medial thighs and beneath the breasts. Histopathology of a pustule showed a subcorneal blister containing a few neutrophils with scattered acute and chronic inflammatory cells in the dermis. There was no acantholysis and direct immunofluorescence was negative. Microscopy of pus showed no organisms and culture was negative. Blood tests revealed an acute phase response with a raised plasma viscosity and a polyclonal increase in immunoglobulins, especially IgA and IgG. Her latex rheumatoid factor test was positive. with raised IgA and IgM antibodies on ELISA.

A diagnosis of subcorneal pustular dermatosis (Sneddon–Wilkinson disease) was made and dapsone, 50 mg daily. commenced. A few days later, she developed palpable purpura on the legs and buttocks. which resolved within a few days of stopping the dapsone. Minocycline, 200 mg daily, and topical steroids were started, and the eruption and synovitis resolved within 8 weeks. Apart from the raised IgA rheumatoid factor. her blood indices returned to normal.

Seven months after presentation, she suffered a severe recurrence of her skin disease, but not of her arthritis, despite being on minocycline. Her eruption cleared after 1 week of oral prednisolone, 20 mg/day. but recurred if the prednisolone
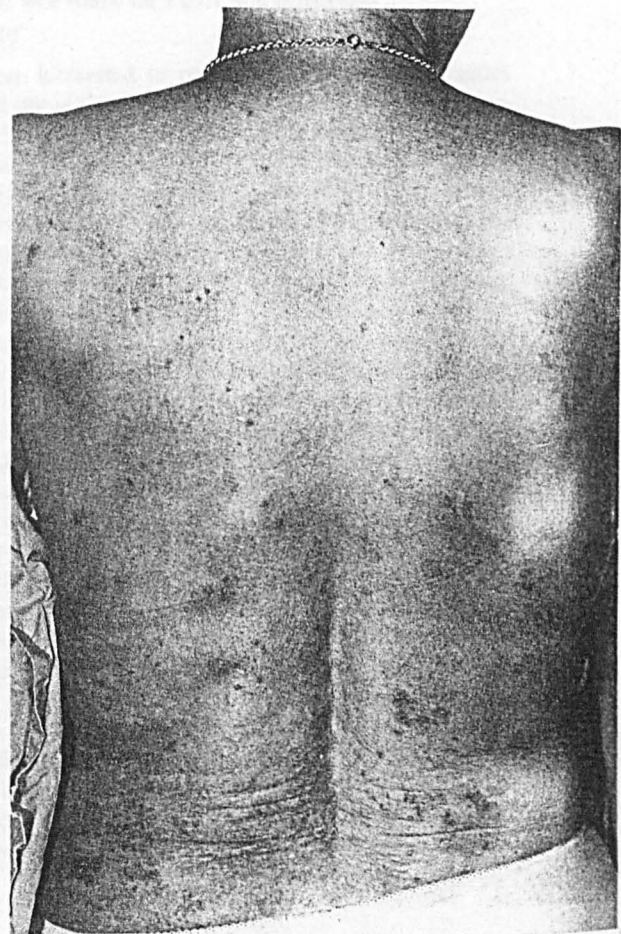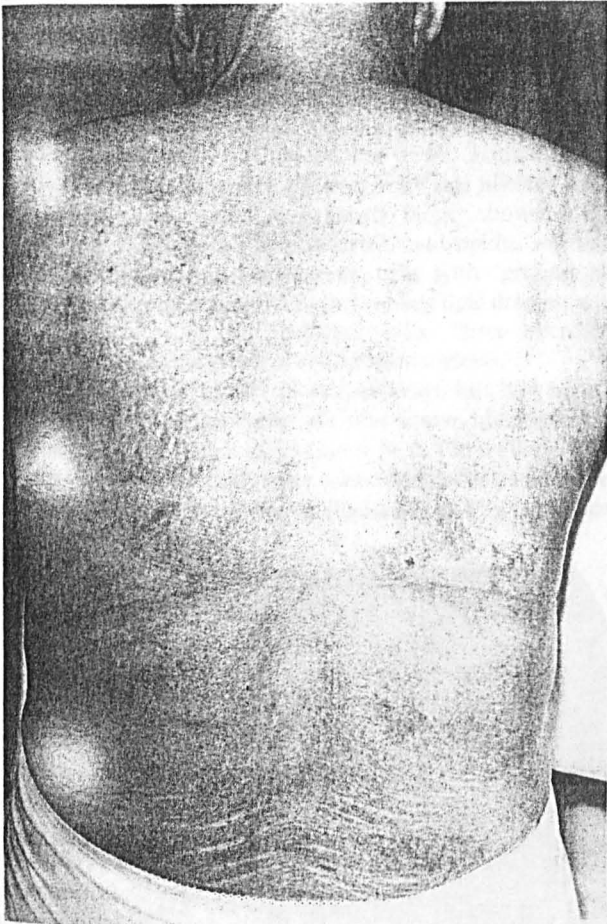

Figure 1. Before phototherapy.

Figure 2. After 31 UVB exposures.

dosage was reduced below 10 mg daily. Sulphasalazine, 1 g daily, was of no benefit.

Narrowband (TL-01) ultraviolet (UV) B phototherapy was introduced using a minimal erythemal dose-based, thrice weekly, incremental regimen. This appeared to be successful (Figs 1 and 2). By the end of the course of 31 exposures (total UVB dose 27.981 mJ/cm^2), her condition was much improved, despite some residual pustules on the axillae, lateral aspects of the thighs and back. Prednisolone was stopped without an exacerbation of her condition which, for 5 months after completing the course of phototherapy, was controlled on only minocycline, 100 mg/day.

Subcorneal pustular dermatosis[1] is a rare condition of unknown aetiology, occasionally associated with an arthropathy.[2] Treatments reported as beneficial include dapsone,[1] corticosteroids,[2] topical PUVA,[3] systemic retinoids[3] and broadband UVB phototherapy.[4] Orton et al. (Orton DI, Wakelin S, George SA, pers. commun.) reported the use of TL-01 UVB phototherapy in a resistant case with clearance following 53 treatments. The mechanism of action of broad- or narrowband UVB in subcorneal pustular dermatosis remains unknown. However, effects on the skin immune system including an

inhibitory influence on neutrophil chemotactic factors, such as leukotriene B$_4$, may be important.[5,6]

Subcorneal pustular dermatosis has a variable course and it is possible that in our patient spontaneous improvement coincided with phototherapy. Nevertheless, we think that UVB phototherapy is worth trying in cases where control is difficult.

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A disposable face mask for PUVA and ultraviolet phototherapy

SIR, We were interested to read that Dawe and colleagues recommend use of the UVC-803 faceshield by patients undergoing PUVA and ultraviolet (UV) B phototherapy.[1] We used this faceshield for a number of years in our unit but were frustrated by the need to clean the headband between patients, especially in the light of any risk of cross-infection, and the yellowing and scratching of the visor which occurs over time. We recognize the need, during PUVA and UVB phototherapy, to shield the face if it is not involved with psoriasis, as it receives frequent exposure to sunlight and is the most common site for non-melanoma skin cancers. A further reason for protecting the face is to prevent tanning which some psoriasis sufferers find distressing to explain away, particularly during the winter months (R.Jobling, pers. commun.). In addition to faceshields, protection can be achieved with sunscreens, which are messy and time consuming to apply, or an opaque material (e.g. a towel) over the face, which is claustrophobic.

As we felt none of these options was ideal, we designed, in conjunction with the Centre for Industrial Design at the University of Northumbria, the disposable face mask in shown in Fig. 1. This protects the face and ears, but is easily cut and shaped to allow treatment of hairline or isolated psoriatic plaques on face. It is visibly clear but blocks all UVA, UVB and UVC radiation (i.e. all wavelengths below 400 nm). Each mask is specific to a patient throughout their course of treatment and is then thrown away. It is assembled with a single movement in seconds and folds flat between treatment sessions for

PUVA for diffuse cutaneous reticulohistiocytosis

SIR, A 65-year-old man gave up swimming, embarrassed by an itchy rash affecting his trunk. On presentation 3 months later, he had a symmetrical eruption of multiple, firm, pink-brown papules and small nodules on the trunk, arms and thighs (Fig. 1a,b). His forearms and legs were less affected and his face and hands spared. A diagnostic biopsy showed a mixed infiltrate of histiocytes, lymphocytes, neutrophils, eosinophils and a few multinucleated giant cells with 'ground glass' cytoplasm. A fat stain (SR19) showed fine lipid droplets within the cytoplasm of the histiocytic cells. These microscopic findings were suggestive of reticulohistiocytosis.

He had a past history of osteoarthritis, but had no active inflammatory arthropathy. He was under investigation for breathlessness, which was found to be due to a dilated cardiomyopathy of uncertain cause. Clinical assessment and investigation did not reveal any malignancy, and no evidence of extracutaneous reticulohistiocytosis was found. In particular, a magnetic resonance imaging scan of the heart and myocardial biopsy did not show multicentric reticulohistiocytosis to be the cause of his heart failure.

Potent topical steroids provided limited relief from itch, but did not alter the appearance of his eruption. After his condition had persisted for 17 months, confined to his skin, we started an empirical course of 8-methoxypsoralen-ultraviolet A photochemotherapy (PUVA). He was treated twice a week, with 20% increments following a starting dose of 70% of his minimal phototoxic dose. As his face was unaffected it was protected from UVA irradiation with a face-shield. After eight exposures, itch was reduced and the eruption was beginning to fade. By his 14th exposure he was asymptomatic and his skin was clear. One year after stopping PUVA his eruption has not recurred.

Spontaneous resolution, known to occur in multicentric reticulohistiocytosis,[1,2] cannot be excluded. However, the long unchanging course of his condition prior to PUVA, and rapid improvement during treatment, suggest that PUVA was responsible for clearance. Classification of the non-Langerhans cell histiocytoses remains complex.[3] Some regard diffuse cutaneous reticulohistiocytosis and multicentric reticulohistiocytosis as conditions within a spectrum of disease.[4,5] Our diagnosis of diffuse cutaneous reticulohistiocytosis, rather than multicentric reticulohistiocytosis in this patient depended on the exclusion of extracutaneous involvement.

Reported treatments for diffuse cutaneous and multicentric reticulohistiocytosis include surgery for an underlying malignancy,[6] systemic immunosuppressive therapy and cytotoxics.[2,7–10] For those with crippling arthritis, or other severe systemic involvement, such treatment is justified. Although malignant melanoma is one of the malignancies associated with multicentric reticulohistiocytosis,[11,12] there is no evidence that patients with non-malignancy associated reticulohistiocytosis are at increased risk of melanoma if exposed to PUVA. For a patient like ours, with disease restricted to the skin and no evidence of associated malignancy, a trial of PUVA therapy may be preferable to more toxic systemic therapy.

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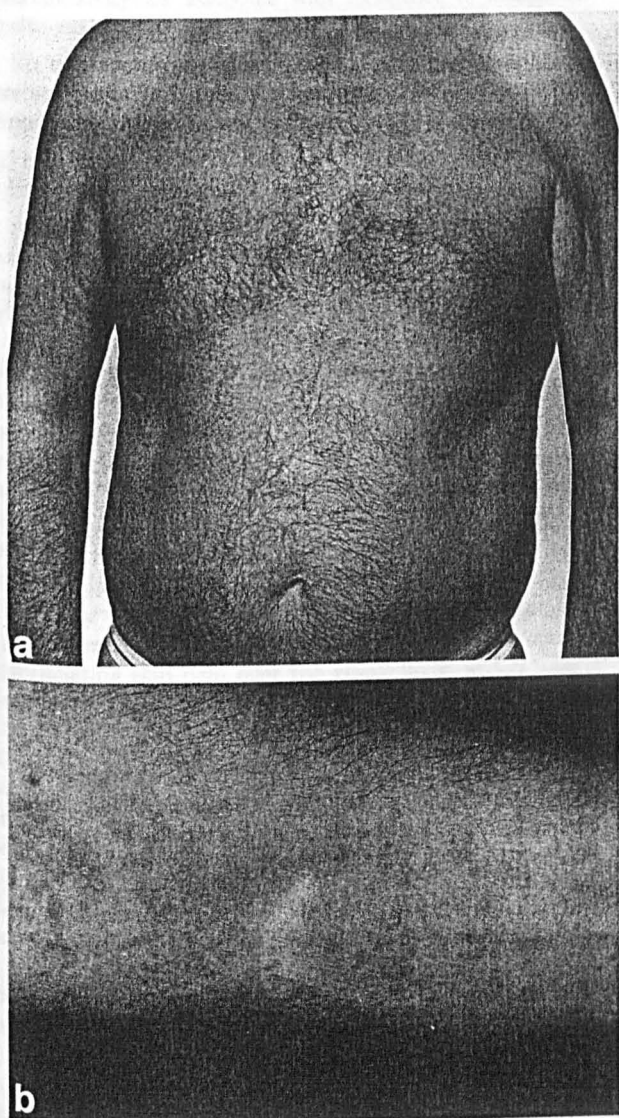
Figure 1. The patient, (a) before PUVA, and (b) close-up of left forearm.

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Severe skin pain after combined ultraviolet B and ultraviolet A phototherapy for atopic dermatitis

SIR, It has been reported that eight (4%) of 210 patients[1] and 17 (5%) of 335 patients[2] who received oral 8-methoxypsor-alen photochemotherapy (PUVA) developed abnormal skin pain. Here we report a patient who had similar skin pain just after phototherapy with combined ultraviolet (UV) A and UVB[3] for atopic dermatitis.

A 28-year-old man, with a 5-year history of adult-type atopic dermatitis, initially underwent topical PUVA therapy for 3 months with a successful outcome. He had no abnormal sensation on his skin or other side-effects. However, 10 months after the last topical PUVA session, the atopic skin lesions had worsened. He therefore received combined UVA/UVB photo-therapy using a UVA/UVB combination unit at our university hospital. The initial UVB dose (40 mJ/cm^2) was just below the patient's minimal erythema dose, established by phototesting. The UVA dose was started at 3 J/cm^2. Several hours after the first phototherapy session, the patient complained of unexpec-ted excruciating skin pain over the whole body, which later became localized to the back, and disturbed his sleep at night. Although the abnormal symptoms persisted for 1 week, he tried one more phototherapy session with a lower dose of UVB (30 mJ/cm^2) to confirm this peculiar phenomenon, but this again resulted in severe burning or pricking skin pain over the whole body. He was not given systemic or topical phototoxic agents during the phototherapy. Erythrocyte, faecal and urinary porphyrin levels were not raised. Systemic adminis-tration of analgesics, including indomethacin or mefenamic acid and antihistamines, had no significant effect on the discomfort. Although previously reported patients with hyper-algesia related to PUVA therapy occasionally showed associ-ated neurological or emotional disturbance,[4] our patient showed no such abnormalities. In our patient, the excruciat-ing pain occurred after combined UVA/UVB phototherapy, and not after PUVA therapy, suggesting that simple irradiation of

UVB and/or UVA is able to be a causal factor of skin pain. Although the aetiology is unknown, UVB-mediated inflam-matory substances or neurotransmitters, such as bradykinin, serotonin or substance P, might be responsible for the skin pain because our patient showed a quick response, in contrast to PUVA-treated patients. This aspect has not been reported previously.

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Systemic plasmacytosis with deposition of interleukin (IL)-6 and elevated expression of IL-6 mRNA in the skin lesions

SIR, Systemic plasmacytosis was first described by Watanabe et al.[1] in 1986. The disease is characterized by infiltration of mature plasma cells in more than two organs, and polyclonal hyperimmunoglobulinaemia. Multiple brownish eruptions, microscopically characterized by prominent hyperplasia of mature plasma cells, are found. This disease had been thought to be seen only in Japanese, in whom 54 similar cases have been reported.[2] However, a similar case with a peculiar skin eruption was recently reported from Spain.[3] As for the pathogenesis of plasma cell hyperplasia, a close relationship with interleukin (IL) 6 has been suggested,[4] but it still remains unknown why plasma cell hyperplasia is observed in the dermis of systemic plasmacytosis.

A 45-year-old Japanese woman had had asymptomatic brownish eruptions on the trunk for 7 years. They were scattered, well-demarcated hard papules and nodules (Fig. 1) which had generally spread and increased in size. She was transferred to our hospital on 2 May 1996 for evaluation of the eruptions. Superficial lymph nodes in the neck, axillary and inguinal regions were palpable. Laboratory findings were as follows: haemoglobin 6·5 g/dL (normal, N: 12–15·5), platelets 514×10^9/L (N: 150–450×10^9), erythrocyte sedimentation rate 156 mm in the first hour (N: <15), serum total protein 9·2 g/dL (N: 6·3–7·9), γ-globulin level 54·4% (N: 9·6–20·0), and polyclonal hypergammaglobulinaemia with IgG 6289 mg/dL (N: 770–1700), IgA 513 mg/dL (N: 90–450) and IgM 443 mg/dL (N: 60–250). C-reactive protein (CRP) was 17·1 mg/dL (N: <0·1). Urinalysis was normal. A bone marrow aspirate showed a hypocellular marrow with a slightly increased number of plasma cells (6%). Pathological examination of involved skin revealed dense perivascular infiltrates composed mainly of plasma cells beneath a normal epidermis. These plasma cells

Narrowband ultraviolet B (TL-01) phototherapy for psoriasis: which incremental regimen?

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Summary   Narrowband (311–313 nm) ultraviolet B phototherapy with the Philips TL-01 lamp is used increasingly in the treatment of psoriasis with little information available on the optimum irradiation regimen. We compared a high and a low incremental dose regimen in 20 patients with symmetrical chronic plaque psoriasis using a randomized half body study and thrice weekly exposures. Paired trunk, leg and arm plaques of psoriasis were scored blind prior to and at each treatment for scaling, erythema and induration. Patients were treated to clearance or minimal residual activity and followed up until relapse. The low increment regimen achieved a 10% reduction in the median cumulative dose to clearance (16,401 vs. 18,246 mJ/cm^2) with one extra treatment in 50% of the patients. However, the duration of treatment (median 53·5 days) was identical for both regimens except for one patient because there were 50% fewer episodes of erythema requiring postponement of treatment with the low increment regimen. We now favour the low increment regimen for phototherapy in our psoriasis population.

The Philips TL-01 lamp with its output primarily at 311 nm is now widely used in the U.K. and Europe as a light source for phototherapy in dermatology. The emission spectrum of the lamp lies almost entirely within the therapeutic action spectrum for psoriasis phototherapy[1,2] and several studies have favoured the lamp over the traditional broadband ultraviolet (UV) B sources in the treatment of psoriasis.[3–8] The extensive use of photochemotherapy (PUVA) is now clearly associated with an increased risk of non-melanoma skin cancer,[9,10] and other studies, albeit few in number at present, have not shown any marked benefit of PUVA over TL-01 phototherapy.[11,12] Additionally, UVB phototherapy can be used in pregnancy, in children, and does not require concomitant medication or eye protection after treatment.

Such factors have promoted the use of the TL-01 lamp, but as yet there is little published on the optimum irradiation regimen to be employed with this source to achieve complete psoriasis clearance with the minimum number of exposures, the minimum cumulative UV dose and with as few acute and chronic side-effects as possible. The variables in a phototherapy regimen include the starting dose, the exposure frequency and the dose increments. A pilot study in our department, looking at the last of these variables, had suggested that a lower dose regimen than that commonly used for broadband

UVB phototherapy might be effective in clearing psoriasis.[13] We decided, therefore, to carry out a full study comparing a high and a low incremental dose regimen in the treatment of chronic plaque psoriasis.

Subjects and methods

Subjects

Twenty patients with moderate to severe, symmetrical chronic plaque psoriasis affecting the trunk and limbs were recruited from out-patient clinics between November 1994 and October 1995. Each patient was provided with study information and after full discussion, written consent was obtained. The study was approved by the Ethical Committee.

Exclusion criteria

These were: age < 18 years, systemic or phototherapy/ PUVA for psoriasis in the preceding 3 months, a history of skin cancer, ongoing systemic immunosuppressive therapy or topical treatment for psoriasis, apart from emollients and treatment of the scalp or photoprotected areas.

Study design

A half body, single blind method was employed where

Table 1. Narrowband ultraviolet B (TL-01) irradiation regimens

1	Determine MED prior to phototherapy
2	Treat each body half independently × 3/week (Mon., Wed., Fri.)
3	Initial dose to both sides: 70% MED
4	Increments given at each exposure according to erythema response at 48 h and allocated regimen
	High increment regimen. Erythema response at 48 h:
	None—40% incremental increase.
	Grade 1 (mild)—barely perceptible erythema—repeat previous dose and reduce to 20% increments thereafter, further reduce to 10% increments when necessary.
	Grade 2 (moderate)—well defined, asymptomatic erythema—postpone one treatment, repeat previous dose at next visit, with 20% increments thereafter, further reducing to 10% increments when necessary.
	Grade 3/4 (severe)—symptomatic erythema and/or bullae. Postpone therapy until recovery then penultimate dose with 10% increments thereafter.
	Low increment regimen. Erythema response at 48 h:
	None—20% incremental increase.
	Grade 1 (mild)—barely perceptible erythema—repeat previous dose and reduce to 10% increments.
	Grade 2 (moderate)—well defined, asymptomatic erythema—postpone one treatment, repeat previous dose at next visit and reduce to 10% increments.
	Grade 3/4 (severe)—symptomatic erythema and/or bullae lasting more than 24 h. Postpone therapy until recovery then penultimate dose with 5% increments thereafter.
5	Maximum exposure dose: 2066 mJ/cm^2
	Maximum number of treatments: 35
	Missed treatments: 1 or 2 treatments—repeat previous dose
	3 treatments—treat with penultimate dose
	> 3 treatments—doctor will review dose required.

MED, Minimal erythema dose.

for each patient, one body half was randomly allocated to a high increment dose regimen while the other half was treated with a low increment dose regimen. Both regimens were based on a minimal erythema dose (MED) determined prior to treatment. Where there was a difference in dose between the sides, the difference was administered first, protecting the lower dose side with a half body suit (100% Microguard Overall; Orvec International, Hull, U.K.) folded in on itself, through which no UV transmission was detectable using a Hitachi U-3210 double beam reflectance spectrophotometer (Nissei Sangyo Co., Finchampstead, Berks, U.K.). The suit was then removed and both sides treated together with the remaining dose. UVB protective goggles or faceshield,[14] and, in males, genital protection, were worn throughout phototherapy unless psoriasis affected these areas and required treatment. Concomitant topical treatment was allowed if required, in the form of barrier cream (sun protection factor 25) to the face, moderately potent topical steroid to shadow sites and coal tar based preparations for the scalp. The use of emollients throughout the study was encouraged but these were not applied in the 4 h prior to exposure as this would interfere with the assessment of scaling. Patients were assessed at each visit and after completing phototherapy were followed up with further review appointments or monthly telephone calls until their

psoriasis relapsed. During this period, patients were encouraged to use emollients but specific antipsoriasis treatments were excluded. Relapse was taken as the point when the patient demanded further active treatment.

Treatment regimens

These are summarized in Table 1. The starting dose for both sides of the body corresponded to 70% of the MED and thereafter incremental doses were determined according to the erythema response. The maximum exposure dose for both regimens was 2066 mJ/cm^2. Each side of the body was treated independently until clearance or minimal residual activity (MRA) was achieved, subject to a maximum of 35 exposures on each side. A three times weekly exposure regimen was chosen in keeping with our current practice.

Minimal erythema dose determination

This was done by our standard method of irradiating a template of eight 1×1 cm squares on the upper back with a range of doses from a TL-01 UVB source placed 20 cm from the patient. The doses administered are: 25, 50, 70, 100, 140, 200, 280, 390, 550 and 770 mJ/cm^2 (the lower eight doses are used for skin types 1 and 2 and the upper eight doses for skin types 3 and 4). The

Table 2. Median number of days in treatment, exposures and cumulative doses to clearance/minimal residual activity

	High increment regimen	Low increment regimen	P-value	95% CI for difference in medians
Days	53·5	53·5	0·32	0
IQR	45–60	45–60		
Range	35–97	35–97		
Exposures	20·5	21	<0·005	0·5–1·0
IQR	17–23	17–24		
Range	13–31	14–32		
Cumulative dose (mJ/cm²)	18,246	16401	<0·005	1107·5–3347
IQR	11,642–22.170	8573–19,452		
Range	6848–30,529	4630–30,242		
Cumulative dose (MEDs)	133·2	117·1	<0·005	

IQR, interquartile range; MED, minimal erythema dose; CI, confidence intervals.

erythemal response is evaluated at 24 h postexposure and the MED is taken as the dose producing perceptible, but defined, erythema at the test site.

Irradiation cubicle

Treatments were carried out in a cubicle (constructed by the Medical Physics Department at Ninewells Hospital) containing 50 Philips 100 W TL-01 fluorescent lamps. The irradiance in the cubicle was measured monthly according to a standardized protocol using an International Light (IL-1400) meter (Able Instruments, Reading, U.K.) calibrated using a spectroradiometer. During the study it varied from 3·2 to 2·8 mW/cm² and the exposure times were adjusted accordingly to achieve the required doses.

Assessments

For all patients, the psoriasis on each body half was scored independently prior to therapy and thereafter at each treatment by a blinded observer. It was graded for scaling (S), erythema (E) and induration (I) at three symmetrical plaque sites on each body half, chosen from the trunk and the upper and lower limbs. Each parameter was scored on a 0–4 scale and an overall psoriasis severity (SEI) score calculated for each body half by summing the scores for each of the three chosen plaques. The scheme was based on the widely used psoriasis area and severity index system. A global (0–4) score representing the overall psoriasis severity was also recorded.

Erythema following phototherapy was graded and any consequent adjustments to the phototherapy regimen made as summarized in Table 1. The number of

exposures, the cumulative dose and the number of days in treatment were recorded for each patient on each body half along with any adverse effects. The date at which each body half cleared was recorded and the patient followed up to collect relapse of psoriasis data for each body half.

Statistical methods

The paired data for each body half consisting of exposures, cumulative doses, psoriasis scores, days in treatment and remission were in general not normally distributed and therefore the Wilcoxon Signed Rank Test was used. Relapse data were analysed using Kaplan–Meier survival plots.

Results

Twenty patients, 11 men and nine women with chronic plaque psoriasis, aged 20–79 years (median 31; interquartile range 27–41·5), were recruited to the study over an 11-month period. Skin types 1 ($n = 3$), 2 ($n = 11$) and 3 ($n = 6$) reflected our local population and their MEDs ranged from 70 to 550 mJ/cm². Two patients deemed themselves adequately clear of psoriasis and withdrew from the study before the defined endpoint of clearance or MRA.

For the 18 patients who completed the study, the median cumulative dose to clearance was lower on the low increment side than the high increment side (16,401 vs. 18,246 mJ/cm²; $P < 0·005$), but the median number of treatments required was marginally higher (21·0 vs. 20·5; $P < 0·005$). In eight patients the same number of treatments was required on each side, in nine one extra and in one three extra treatments were
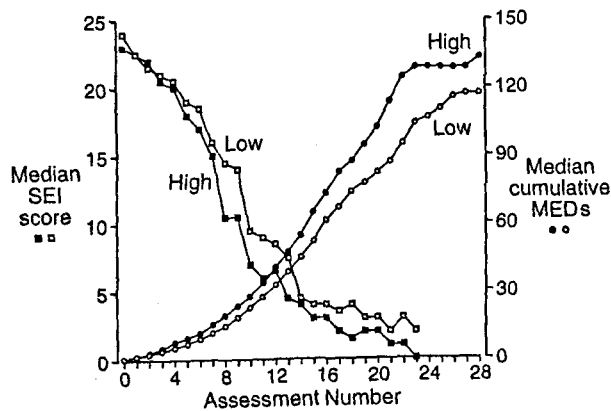
Figure 1. Median psoriasis scores (SEI: scalings, erythema, induration) and cumulative doses in minimal erythema dose (MED), at each treatment.

Figure 3. Relapse data—the probability of psoriasis not having relapsed is plotted against follow-up time.

needed on the low increment side. However, the median duration of treatment (53·5 days) was identical under both regimens for all patients except one, in whom the low increment side took 7 days longer to achieve clearance (Table 2). The rate of decline in the median psoriasis scores (SEI) with treatment was similar under both regimens and is shown in conjunction with the increasing cumulative doses on each side (Fig. 1).

Acute side-effects were limited to erythema and there were almost twice as many erythema episodes (grades 1 and 2) on the high increment side as on the low increment side. Although there were no episodes of painful erythema (grade 3) under either regimen, 12 episodes of grade 2 erythema occurred in 11 patients on the high increment side compared with just four such episodes in four patients on the low side (Fig. 2). More specifically, both skin type 1 and one of five skin ty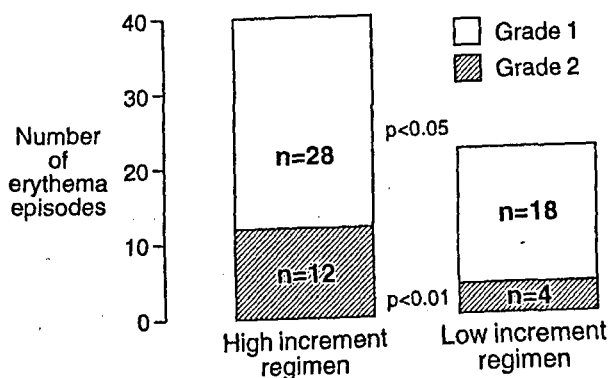pe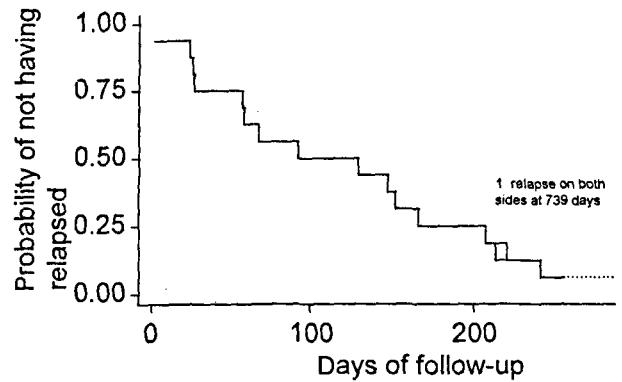 3 patients experienced grade 2 erythema under both regimens; eight of 11 skin type 2 patients experienced grade 2 erythema on the high increment side with only one of 11 having such erythema on the low increment side.

The remission times ranged from 2 to 739 days (median 129 days) with no significant difference between the sides (Fig. 3). In one patient, the remission on the high increment side was 7 days longer, that side having cleared 7 days sooner.

Discussion

The study showed that the low increment regimen was effective in clearing psoriasis and did so with a 10% reduction in the median cumulative dose. No additional treatments were required in 44% of patients and just one extra in 50% of patients. In spite of this slight increase in the average number of treatments, the number of days in treatment was the same in 94% of patients. The reason for this apparent discrepancy and one of clear relevance to patients, is that under the low increment regimen there were fewer postponements of treatment on account of grade 2 erythema. With the high increment regimen there were three times as many such episodes. The time taken for the psoriasis to relapse was the same under both regimens in all but one patient, as illustrated by the almost coincident lines in Figure 3; 50% of patients had not relapsed at 18·4 weeks. We recognize that our definition of relapse, defined by the date when the patient feels further active treatment is necessary, is influenced by factors other than the extent of psoriasis recurrence. Nevertheless, we felt that this definition was of more practical application, was more relevant to the patient and would detect any significant difference in psoriasis recurrence between the body sides.

Figure 2. Erythema episodes.

In the long term, any reduction in the cumulative UVB dose is worthwhile, if not at the expense of more exposures. The low increment regimen achieves this and is also associated with fewer erythema episodes; we therefore favour this regimen and have altered our clinical practice accordingly.

Narrowband UVB is more effective than conventional broadband UVB phototherapy with apparently no greater risk.[3-8] However, the long-term risk of photocarcinogenicity, which is probably less than with PUVA,[15,16] is as yet undetermined in clinical practice. In the meantime, therefore, the optimum mode of use to minimize risk needs to be defined and based on objective data. Our study comparing different dose increment regimens contributes to this definition. The low increment regimen is now in routine use in the Tayside Service.

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Photodermatology
Photoimmunology
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Original articles

Artificial hardening for polymorphic light eruption: Practical points from ten years' experience

Man I, Dawe RS, Ferguson J. Artificial hardening for polymorphic light eruption: Practical points from ten years' experience. Photodermatol Photoimmunol Photomed 1999: 15: 96–99. © Munksgaard, 1999.

The conservative approach of sunlight avoidance and broad-spectrum sunscreen is often disappointing in patients with moderate to severe polymorphic light eruption. A springtime course of prophylactic artificial hardening with ultraviolet B (UVB) phototherapy or psoralen plus ultraviolet A (PUVA) photochemotherapy will often allow patients to tolerate more sunlight and give them greater freedom during the summer. In this retrospective study we describe ten years' experience of such "desensitization" treatment. Individualized therapy with attention to detail will maximize the effectiveness of this treatment.

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Key words: polymorphic light eruption (PLE); narrowband UVB phototherapy; PUVA photochemotherapy: desensitization

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Polymorphic light eruption (PLE) is a common idiopathic photodermatosis, with higher prevalence in the temperate climates (1, 2). Patients present with a pruritic, often papular, eruption of photoexposed sites occurring usually between spring and autumn. Therapeutic intervention has been mainly aimed at preventive measures with the use of broad-spectrum sunscreen and behavioural sunlight avoidance. This approach to management may be effective in patients with mild PLE (3), but is often unsatisfactory in more severely affected individuals.

It is commonly observed that PLE frequency and severity decreases as the summer progresses (4, 5). Although the mechanism is not fully understood, this "hardening" process has been put into therapeutic use. Desensitization with artificial sources in early spring has been shown to be an effective prophylactic treatment (6–9). Early studies (10, 11) indicated that psoralen plus ultraviolet A (PUVA) was superior to broadband ultraviolet B (UVB), but more recently Bilsland et al. (12) demonstrated in a carefully controlled study that the newer narrowband TL-01 UVB source is as effective as PUVA.

Both UVB and PUVA are now widely used and are regarded as the treatments of choice in patients with moderate to severe PLE (13). Nevertheless treatment regimens vary greatly between centres, as revealed by a recent Scottish Audit of phototherapy and photochemotherapy (14).

In this retrospective study we describe ten years' experience of UVB and PUVA desensitization in the prophylactic treatment of PLE. This may guide others using, or intending to use, these forms of therapies.

Method

Patients

Between 1986 and 1995, within the Tayside region, northeast Scotland, 287 patients with PLE were seen and investigated at the photodermatology clinic. The diagnosis was established by history, monochromator and UVA provocation testing, lupus serology, porphyrin scan and histology, as appropriate. Desensitization treatment was offered in early spring to 170 patients with moderate to severe PLE (i.e. those whose condition causes significant disruption of normal life). Each course of treatment was carefully documented. Notes were reviewed on all patients who had UVB and/or PUVA between 1986 and 1995. The total number of treatment courses administered, the frequency

of provoked PLE and each subject's response to treatment during the subsequent summer months were tabulated and analysed.

Treatment regime

Our standard treatment protocols for UVB and PUVA throughout the period of study are shown in Table 1. The starting dose was 70% of the predetermined minimal erythema dose (MED – defined as minimal perceptible erythema) for UVB and 70% of the minimal phototoxic dose (MPD) for PUVA. This was followed by a 10–20% incremental increase depending on erythema or PLE response (Table 1). Treatment was administered daily for inpatients or three times weekly for outpatients for 10 to 15 treatments. If PLE was provoked, topical steroid was used and the dose adjusted accordingly, as shown in this table.

Although the majority of patients received whole body irradiation, over recent years, especially in those with severe PLE, we have treated habitually exposed sites only, i.e. patients wore short-sleeved shirt and shorts during treatment. In extremely photosensitive patients, potent topical steroid was applied to treated sites immediately after exposure. Such measures were introduced either prior to or during the course of treatment.

Post treatment advice. Following each course of treatment, patients were encouraged to cautiously seek sunlight exposure to keep their artificial photoprotection 'topped up'. Broad spectrum sunscreen, however, should be applied if they intended to stay outdoors for longer periods of time.

Patients were followed up in autumn or the following spring. If successful, treatment was repeated yearly, in early spring. In patients who failed to respond satisfactorily to TL-01, PUVA was offered the following year.

Results

The majority of PLE patients had a normal action spectrum on monochromator phototesting. Abnormal photosensitivity was demonstrated in 32 (11%), 25 of whom had sole involvement of the UVA wavelengths (335–365±30 nm). PLE lesions were induced in 16.3% of cases following 25 J/cm^2 UVA provocation on two consecutive days (Dr Honle Portable Dermalight 2000, filter H1, high-pressure metal halide lamp, spectral output 320–400 nm).

Between 1986 and 1995 170 PLE patients (152 female, 18 male; age range 9–73 years) were treated. Of these, 133 patients received UVB treatment (128 TL-01 and 5 broadband), 8 patients received PUVA and 29 patients had both UVB and PUVA. A total of 330 courses of UVB (325 TL-01 and, in 1986/7, 5 broadband), and 109 courses of PUVA were administered (Fig. 1).

Evaluable data were obtained for 281 courses of

Table 1. TL-01 and PUVA treatment protocol in PLE desensitization

TL-01 UVB desensitization
- determination of minimal erythema dose (MED) with readings at 24 h
- initial irradiation dose – 70% of MED
- 20% increments at each visit if no erythema[1] or provoked PLE[2]
- outpatients – 3 times weekly for 5 weeks (total 15 treatments)
  inpatients – daily for 2 weeks (total 10 treatments)

PUVA desensitization
- 8 MOP or 5 MOP
- determination of minimal phototoxic dose (MPD) with readings at 72 h
- initial dose – 70% of MPD
- 20% increments at each visit if no erythema[1] or provoked PLE[2]
- 3 times weekly for 5 weeks (total 15 treatments)

[1]If erythema
- Grade 1 – previous dose repeated
- Grade 2 – postpone 1 treatment and same dose repeated, followed by 10% increments
- Grade 3/4 – no treatment until recovery, then dose reduced by half followed by 10% increments

[2]If provoked PLE
- itch or mild PLE – topical steroid if required
- moderate – same dose and moderate/potent topical steroid, followed by 10% increments
- severe – postpone 1 or 2 treatments, potent topical steroid and restart with penultimate dose followed by 10% increments
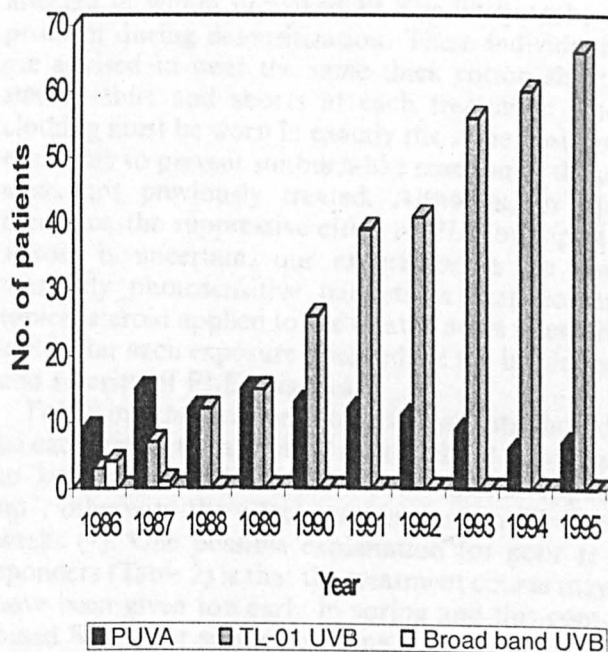

Fig. 1. No. of PLE patients "desensitized" with UVB and PUVA between 1986 and 1995. Total no. of courses administered: 325 narrowband TL-01, 5 broadband UVB and 109 PUVA.

Table 2. Subjective response following each treatment course

Patient response	UVB (%)	PUVA (%)
Good[1]	176 (63)	57 (58)
Moderate[2]	73 (26)	30 (30)
Poor/no response[3]	32 (11)	12 (12)

[1]no PLE; [2]mild PLE; [3]recurrent PLE.

UVB and 99 courses of PUVA. At follow-up, the majority of patients obtained either good benefit (63% UVB, 58% PUVA) with no PLE episodes, or moderate improvement (26% UVB, 30% PUVA) with reduction in severity and frequency of PLE compared to pretreatment years. There was a failure rate of 11% of UVB and 12% of PUVA treatment courses, following which patients continued to have recurrent PLE during the summer (Table 2). Of the 29 patients who received both PUVA and TL-01, 21 reported an overall preference: 12 favoured PUVA, 4 preferred TL-01 and the remaining 5 responded equally well to both forms of therapies.

The responses to 49 courses of UVB and 10 courses of PUVA were excluded from the study because patients either failed to attend the follow-up clinic or the response had not been clearly documented in the notes. However, of those 49, 11 patients had since had a further course of UVB and 2 had PUVA with good response. Four patients had moved from the Dundee area and were uncontactable.

Desensitization was well tolerated by most patients, although mild PLE was often provoked during treatment. At least 1 episode of PLE was induced during 48% of UVB and 44% of PUVA treatment courses. As most were mild, subsequent adjustment of doses with or without the addition of topical steroid allowed completion of the course of treatment. Systemic steroids were not required.

Discussion

In moderate to severe PLE, when sunscreen and sunlight avoidance fails to offer satisfactory protection, desensitization phototherapy and photochemotherapy should be considered. Successful outcome was noted in the majority of patients, irrespective of a history of hardening.

Despite its widespread use, treatment regimens vary greatly between centres (14). In our department, narrowband TL-01 has gradually replaced broadband UVB and PUVA in most cases of psoriasis and atopic eczema patients, and is now the treatment of choice in PLE desensitization. PUVA is generally reserved for the minority who failed

to gain satisfactory photoprotection from TL-01. Advantages of TL-01 include 1) absent psoralen and its associated gastrointestinal upset, 2) avoidance of wearing photoprotective glasses in the post-treatment period, and 3) the ability of use in children and pregnancy. It may also be quicker and cheaper to administer. Furthermore, TL-01 UVB is probably safer than PUVA in terms of the risk of non-melanoma cutaneous malignancy (15, 19).

The mechanism of action of phototherapy and photochemotherapy artificial "hardening" in the prophylactic treatment of PLE is not fully understood. Thickening of the · stratum corneum, hyperpigmentation and alteration of cellular immunity may play a role (16–18).

When discussing a desensitization course with a PLE patient, it is important to highlight that each patient will respond differently and as such treatment will be individualized. In our experience, at least one episode of mild PLE was provoked in half the treatment courses. The first course is often exploratory and patients should be forewarned of a 50% chance that PLE may be provoked but that it should not prevent them from continuing treatment. In the few cases where PLE episodes were more troublesome, greater caution in the incremental dose steps, along with the use of topical steroid, usually allowed the patient to continue to completion. Although systemic steroid has been used concurrently with PUVA to suppress induced PLE (16), we have not required this approach.

In recent years we have tended to treat sunlight-exposed sites only, especially in those severely affected in whom provoked PLE is likely to be a problem during desensitization. These individuals are advised to wear the same thick cotton short-sleeved shirt and shorts at each treatment. The clothing must be worn in exactly the same position each time to prevent sunburn-like reaction in those areas not previously treated. Although, in the literature, the suppressive effect of PLE by topical steroid is uncertain, our experience in the few markedly photosensitive patients is that potent topical steroid applied to the treated areas immediately after each exposure does reduce the incidence and severity of PLE episodes.

Following the treatment course, patients should be encouraged to cautiously seek sunlight exposure to keep their artificial photoprotection "topped up", otherwise the effect may be lost within 4–6 weeks (7). One possible explanation for poor responders (Table 2) is that the treatment course may have been given too early in spring and this combined with poor spring sunshine, a situation common in Scotland, may result in loss of photoprotection. In this study, 65% of the poor responder group was treated between March and May. The

remaining 35% was treated, at patients' request usually prior to holidays, earlier or later in the year. In these individuals, it is possible that over-exposure to foreign sunshine might account for some who reported treatment failure.

The photoprotective effects of phototherapy and PUVA are temporary and treatment needs to be repeated yearly. A total of 59 of our patients had 3 or more courses of successful yearly treatment, 15 of whom had 5 or more treatment courses. There appears to be no loss of benefit with subsequent courses. In our practice, patients who have had 3–4 years of successful desensitization are encouraged to try a year without treatment. The natural history of this condition is unknown but from our experience a proportion of patients do spontaneously improve with time.

The concern with repeated yearly UVB phototherapy is the long-term skin cancer risk. A previous study by Larkø & Diffey (20) suggests that the cumulative UVB dose, and therefore skin cancer risk, received by patients undergoing regular phototherapy for psoriasis, is approximately 2–3 times that of a yearly three weeks' Mediterranean holiday. It is probable that PLE subjects, through their behavioural avoidance of sunlight and the lower cumulative dose used in desensitization compared to a course for psoriasis, may in fact be at a lower risk than normal subjects and UVB-treated psoriatic patients.

Desensitization adapted to individual patient's needs, such as dose incremental regimen, exposed-site treatment with or without topical steroid use, can produce a successful outcome for the majority of PLE patients.

Acknowledgements

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settled immediately on withdrawal of isotretinoin. The second patient was a 16-year-old boy who had mild asthma and who developed nocturnal symptoms and exercise-induced wheeze during the first month of treatment with isotretinoin. It improved on withdrawal of the drug and recurred when it was started again for a further flare of acne.

Although uncommon, there have been 20 reports to the Committee on Safety of Medicines of isotretinoin causing asthma-related side-effects. In one controlled study, a proportion of patients with acne taking isotretinoin showed a significant reduction in their forced expiratory flow rate.[3] The mechanism by which isotretinoin exacerbates asthma is not known, but drying of the tracheobronchial tree leading to increased irritability has been proposed.[1,2]

We wish to draw this rare side-effect of isotretinoin to readers' attention and urge that a history of asthma is sought in patients starting the drug. If positive, a baseline peak flow measurement is useful, and an appropriate warning should be given.

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Photosensitizing drugs may lower the narrow-band ultraviolet B (TL-01) minimal erythema dose

SIR, Does it matter if patients attending for narrow-band (TL-01, 311–313 nm) ultraviolet (UV) B phototherapy are on known phototoxic systemic therapy? Many patients attending for treatment of psoriasis, atopic dermatitis and other conditions are taking potentially photoactive medication including non-steroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, quinine, phenothiazines and fluoroquinolones. Such agents are known to be photoactive within the UVA wavebands, with extension into the UVB region in some.[1–4] Stern *et al.* have examined the use of these drugs during PUVA,[5] and found a slightly increased risk of burning, resulting in the need for discontinuation of PUVA therapy, particularly in older patients. No work which examines the effect of photoactive medication during UVB has been published.

A prospective study was established to record current medication and minimal erythema dose (MED) in all patients starting UVB (TL-01). The MED was measured by irradiating eight 1.5×1.5 cm squares on the patient's back with a series of UVB TL-01 doses (25, 50, 70, 100, 140, 200, 280 and 390 mJ/cm^2 in skin types I and II, and 50–550 mJ/cm^2 in skin types III and IV) using a unit consisting of eight TL-01 tubes, the output of which was measured monthly with an IL1400A radiometer/photometer. Calibration is traceable to the National Physical Laboratory. The MED was defined as the dose required to cause just perceptible erythema at 24 h. Patients with known abnormal photosensitivity were excluded.

In total, 401 patients were studied between November 1995 and June 1997. Ninety-five (24%) were receiving medication considered to be potentially photoactive. Of these, 31 (8%) were taking more than one potentially photoactive medication. One hundred and thirty-one (33%) were receiving other drugs and 175 (44%) were taking no medication.

The MED values for patients either taking no medication or taking drugs from 10 groups of suspected photosensitizers are shown in Figure 1. The Kruskal–Wallis equality of populations rank test was used to determine whether or not differences in MEDs across the groups of patients on no drugs and on suspected photosensitizers could be explained by chance. When this showed a significant difference between the groups ($P = 0.002$), the Wilcoxon rank-sum test was applied to compare the MED values for individual drug groups with those on no medication. This showed significant lowering of the MED for patients on NSAIDs, phenothiazines and calcium-channel blockers (Table 1). Similar results were found when patients on more than one suspected photosensitizer were excluded (data available on request from authors). There was no significant difference in distribution of skin phototypes between those taking and not taking potentially photoactive medication ($P = 0.22$).

The numbers involved were small, but our findings suggest that some photoactive medications may influence the UVB TL-01 MED. In particular, NSAIDs, calcium-channel blockers and, probably, phenothiazines are associated with a lower MED. Lowering of a patient's MED by photoactive medication should, on current knowledge, not contraindicate the use of TL-01 (narrow-band) UVB phototherapy. It is, however,

Table 1. Minimal erythema dose (MED) values for patients on no medication and those on suspected photosensitizers (where there were 10 or more patients on individual medications)

Medication	No. patients	Median MED (mJ/cm^2)	P-value[a]
No medication	175	140	
NSAIDs	36	100	0.0027
H2-blockers	28	140	0.74
Phenothiazines	23	140	0.0096
Calcium-channel blockers	19	100	0.0041
Thiazides	13	140	0.36
Tricyclic antidepressants	10	140	0.97

NSAIDs, non-steroidal anti-inflammatory drugs; [a] Wilcoxon rank-sum test comparing those on medication with those on no medication.
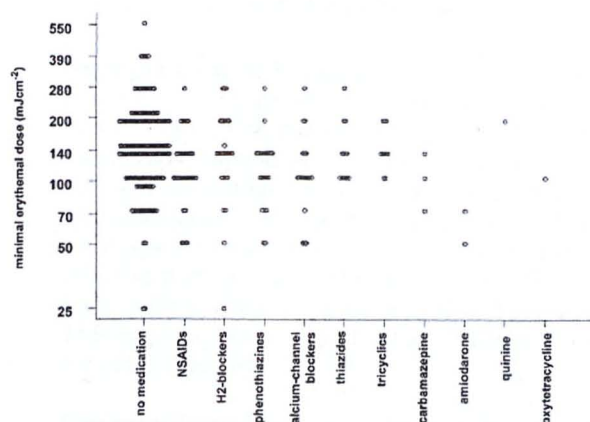
Figure 1. TL-01 minimal erythema dose values for patients on no medication and on drugs within groups of suspected photosensitizers, NSAIDs, non-steroidal anti-inflammatory drugs.

another reason for performing MED testing prior to treatment.

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Reactive perforating collagenosis associated with underlying malignancy

SIR, We were interested in the recent report by Chae *et al.* of a patient with reactive perforating collagenosis (RPC) and periampullary carcinoma.[1] The authors suggest RPC should be considered a paraneoplastic condition. We report a further case of RPC associated with underlying malignancy.

A 75-year-old lady presented with a 6-month history of nausea, anorexia, 10 kg weight loss and an itchy rash on her back. There was a history of hysterectomy and bilateral salpingo-oophorectomy for endometrial carcinoma 20 years previously and also a 20-year history of non-insulin-dependent diabetes. Her medications consisted of metformin,
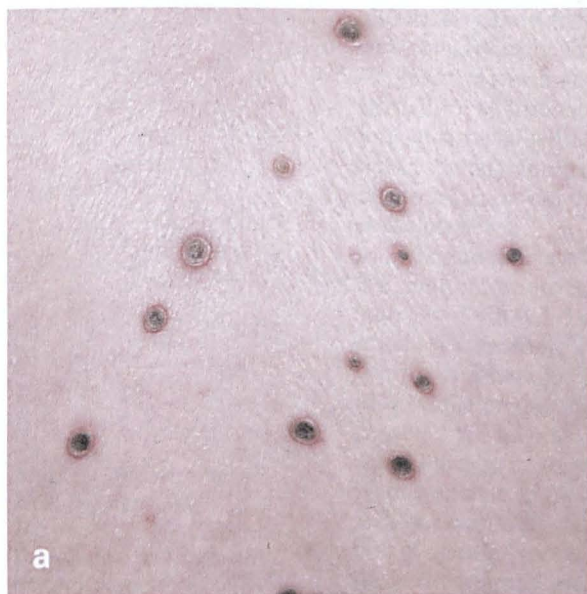

Figure 1. (a) Multiple dome shaped papules with saucer-like rims and distinctive central dark brown crusts are evident on the back. (b) A photomicrograph of a lesion on the back shows hyperkeratosis, hypergranulosis, acanthosis and a plug of debris with necrotic collagen fibres suggestive of transepidermal elimination.

Narrowband TL-01 Phototherapy for Patch-Stage Mycosis Fungoides

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Background: Although patch-stage mycosis fungoides (MF) has a generally good prognosis, and long-term survival rates with current therapies (UV-B, photochemotherapy, topical nitrogen mustards, electron-beam therapy) are similar, there is concern regarding their potential adverse effects. Narrowband or TL-01 UV-B phototherapy (311 nm), in use for more than 10 years, is more effective than broadband UV-B for the treatment of psoriasis, with an efficacy approaching that of psoralen UV-A. This open study assesses TL-01 as an alternative therapy for patch-stage MF.

Observations: Eight white patients (4 men, 4 women; age range, 66-83 years) with histologically proven patch-stage MF received TL-01 phototherapy 3 times weekly using a standard protocol. Complete clearance of MF was achieved in 6 cases in a mean of 9 weeks or 26 treatments (range, 20-37 weeks) and 4 patients have had prolonged remissions. Mean duration of clinical improvement has been 20 months (range, 11-40 months). Partial response to TL-01 or poor histologic improvement was associated with rapid relapse.

Conclusions: TL-01 is an effective, convenient therapy that may have less risk of long-term adverse effects than current alternatives. Although larger prospective studies are necessary, for some patients intermittent courses of TL-01 may offer effective long-term therapy.

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MYCOSIS fungoides (MF) is an uncommon T-cell lymphoma, initially confined to the skin, that can evolve from limited to widespread cutaneous disease. Progression from patch, plaque, and tumor stages may, in a few cases, culminate in disseminated lymphoma with visceral and lymphatic involvement. In patch-stage MF, the malignant clone of T helper cells demonstrates epidermotropism with abnormal cells evident in the epidermis and superficial dermis. The accessibility of this site for local treatment in conjunction with the failure of studies to demonstrate prolonged survival with more aggressive systemic therapy confirms topical therapeutic modalities as the treatment of choice for patch-stage MF.[1]

Commonly used treatments for early MF include photochemotherapy (psoralen UV-A [PUVA]) and topical nitrogen mustard (mechlorethamine) or carmustine chemotherapy. Total-skin electron-beam radiation therapy is also used in some centers.[2] All have been reported to have equal efficacy in stage 1 MF with a complete response to treatment in more than 70% of cases.[3] Although the median duration of disease-free remissions reported for these therapies is variable, the long-term survival rates are not significantly different.[3] Broadband UV-B has also been shown to have similar efficacy for skin clearance, with a 23% sustained disease-free remission on discontinuation of maintenance therapy in stage 1a disease (mainly patch-stage disease).[4] Although several studies have suggested that narrowband TL-01 is more effective than broadband UV-B in the treatment of psoriasis,[5-8] there is only 1 report of its use in MF.[9]

RESULTS

Eight patients received a total of 11 TL-01 courses (Table 2). TL-01 was well tolerated, but toward the end of most courses dose increments were reduced to 10% when higher TL-01 doses were being used. All patients achieved a rapid and clinically significant improvement in their condition with abolition or reduction of pruritus. Six patients achieved complete clearance of the eruption (**Figure 1**), and the other 2 responded satisfactorily with partial clearance. For those patients who achieved complete clinical clearance (patients 1, 2, 3, 6, 7, and 8), a mean of 26 treatments (9 weeks) was required. While some of the residual areas were in sanctuary sites such as the gluteal cleft, others were not. One patient has had repeated prolonged clinical remissions without maintenance therapy (patient 1). Patient 2 relapsed soon after initial TL-01 clearance but has achieved prolonged re-

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PATIENTS AND METHODS

Eight white patients (age range, 66-82 years) with histologically proven patch-stage MF received narrowband TL-01 phototherapy. All histologic analyses were done independently by 2 of us (J.G.L. and A.T.E.), and patients with preMF or doubtful histologic findings were excluded.[10] Pretreatment and posttreatment skin biopsy specimens were taken from patches, residual areas, or treatment-cleared sites. All had normal full hematologic and biochemical profiles (full blood count, urea and electrolyte, and liver function tests) and urinalysis and chest radiograph findings. None had palpable lymphadenopathy or organomegaly, but 1 patient (case 3) with an atypical acute presentation underwent bone marrow examination and an abdominal computed tomographic scan, both of which produced normal results. Cutaneous involvement was classified by recognized TNMB and clinical staging protocols[11] (**Table 1** and **Table 2**). All of the patients had clinical stage 1 disease (T1 or T2, N0, M0), with cutaneous involvement consisting of patch-stage disease of limited extent in 4 cases (stage 1a) and more widespread in the others (stage 1b) (**Table 3**). Although a Sézary preparation was not available for all patients, the b classification does not affect the clinical staging. Patients were offered TL-01 treatment when prior therapy (topical steroids, PUVA) had either failed or produced adverse effects or if they were reluctant to have systemic medication. There was a minimum of 3 months between TL-01 treatment and previous phototherapy. Patients used emollients during treatment, and topical steroids were limited to use at sanctuary sites.

All treatments were carried out in a purpose-built cubicle constructed by the medical physics department of Ninewells Hospital, Dundee, Scotland, containing 50 100-W TL-01 fluorescent lamps (Philips Electronics, New York, NY). The irradiance within the cubicle changed from 3.53 mW/cm² to 2.22 mW/cm² during the study period, and exposure times were adjusted accordingly. Irradiance was measured monthly, by a standard protocol, with an international light meter (IL-4000; Able Instruments, Reading, England) calibrated using a spectroradiometer.

Patients received TL-01 phototherapy by our standard protocol.[13] The minimum erythemal dose for each patient was determined prior to starting treatment by irradiation of a template of eight 1 × 1-cm² apertures on the upper back with a TL-01 source 20 cm from the patient. Two standard ranges of doses were administered: 25 to 390 mJ/cm² for phototypes 1 and 2 or 70 to 770 mJ/cm² for phototypes 3 and 4.[14] Therapy commenced with 70% of the minimum erythemal dose. Treatment was administered 3 times weekly with 20% increment at each exposure unless modified by the erythemal response assessed at 48 hours after treatment. Phototherapy was continued until complete clinical clearance or minimal residual activity was achieved. Minimal residual activity and partial response were defined as a greater than 90% and 50% improvement, respectively, with persistent skin disease despite continuing treatment (ie, sanctuary sites). Relapse was defined as clinically significant disease requiring further therapy. A face shield and gloves were used to minimize UV-B exposure to areas habitually exposed to sunlight but unaffected by MF (cases 2, 3, 5, and 7).

Table 1. TNMB Classification for Mycosis Fungoides*

Classification	Description
T (Skin)	
T1	Limited patch/plaque (<10% of total skin surface)
T2	Generalized patch/plaque (≥10% of total skin surface)
T3	Tumors
T4	Generalized erythroderma
N (Nodes)	
N0	Lymph nodes clinically uninvolved
N1	Lymph nodes enlarged, histologically uninvolved (includes "reactive" and "dermatopathic" nodes)
N2	Lymph nodes clinically uninvolved, histologically involved
N3	Lymph nodes enlarged and histologically involved
M (Viscera)	
M0	No visceral involvement
M1	Visceral involvement
B (Blood)	
B0	No circulating atypical (Sézary) cells (<5% of total lymphocytes)
B1	Circulating atypical (Sézary) cells (≥5% of total lymphocytes)

*Reprinted substantially from Kim et al.[12]

Table 2. Clinical Staging System for Mycosis Fungoides*

Clinical Stages	TNMB Classification†		
	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T1-2	N1	M0
IIB	T3	N0-1	M0
IIIA	T4	N0	M0
IIIB	T4	N1	M0
IVA	T1-4	N2-3	M0
IVB	T1-4	N0-3	M1

*Reprinted substantially from Kim et al.[12]
†B classification does not alter the clinical stage.

and extensively and on whom a posttherapy biopsy was not done. Diagnosis relied on the presence of typical histologic features on hematoxylin-eosin–stained sections. All pretherapy specimens demonstrated a superficial dermal mononuclear cell inflammatory infiltrate containing phenotypically abnormal lymphocytes (**Figure 2**). All showed epidermotropism, Pautrier microabcesses, and variable acanthosis. T-cell marker studies were available in 4 cases, showing predominant T helper (CD4+) cell infiltrates (cases 2, 3, 4, and 6). T-cell receptor gene rearrangement studies were not routinely performed.

Although no posttreatment biopsy findings showed entirely normal histologic characteristics, most showed a

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mission following a second course. Three of our 8 patients remain in clinical remission without maintenance therapy at this time.

Pretherapy and posttherapy biopsy results were available for study except for patient 5, who relapsed rapidly

Table 3. Clinical Characteristics of Study Patients With Patch-Stage Mycosis Fungoides (MF)*

Case No./ Age,y/Sex	Phototype	Duration of Pre-MF Skin Eruption, y	Duration of MF, y	Stage, TNM	Previous Treatment	Complications
1/67/M	II	29	3	1a	PUVA, topical steroid	PUVA pain
2/77/M	I	19	4	1b	PUVA, topical steroid	PUVA pain, basal cell carcinoma × 2
3/82/M	III	4	3	1b	PUVA. topical steroid	
4/71/F	I	5	1	1b	PUVA, topical steriod	Basal cell carcinoma
5/78/M	II	1.5	1	1a	Topical/systemic steroid	
6/72/F	II	70	1	1a	PUVA, topical steroid	Solar keratoses, lentigenes, basal cell carcinoma
7/71/F	I	10	2	1b	Topical steroid	
8/66/M	III	19	1	1a	PUVA, topical steroid	Psoralen-associated nausea

PUVA indicates psoralen–UV-A. The psoralen used in all previous treatments was oral 8-methoxsalen.
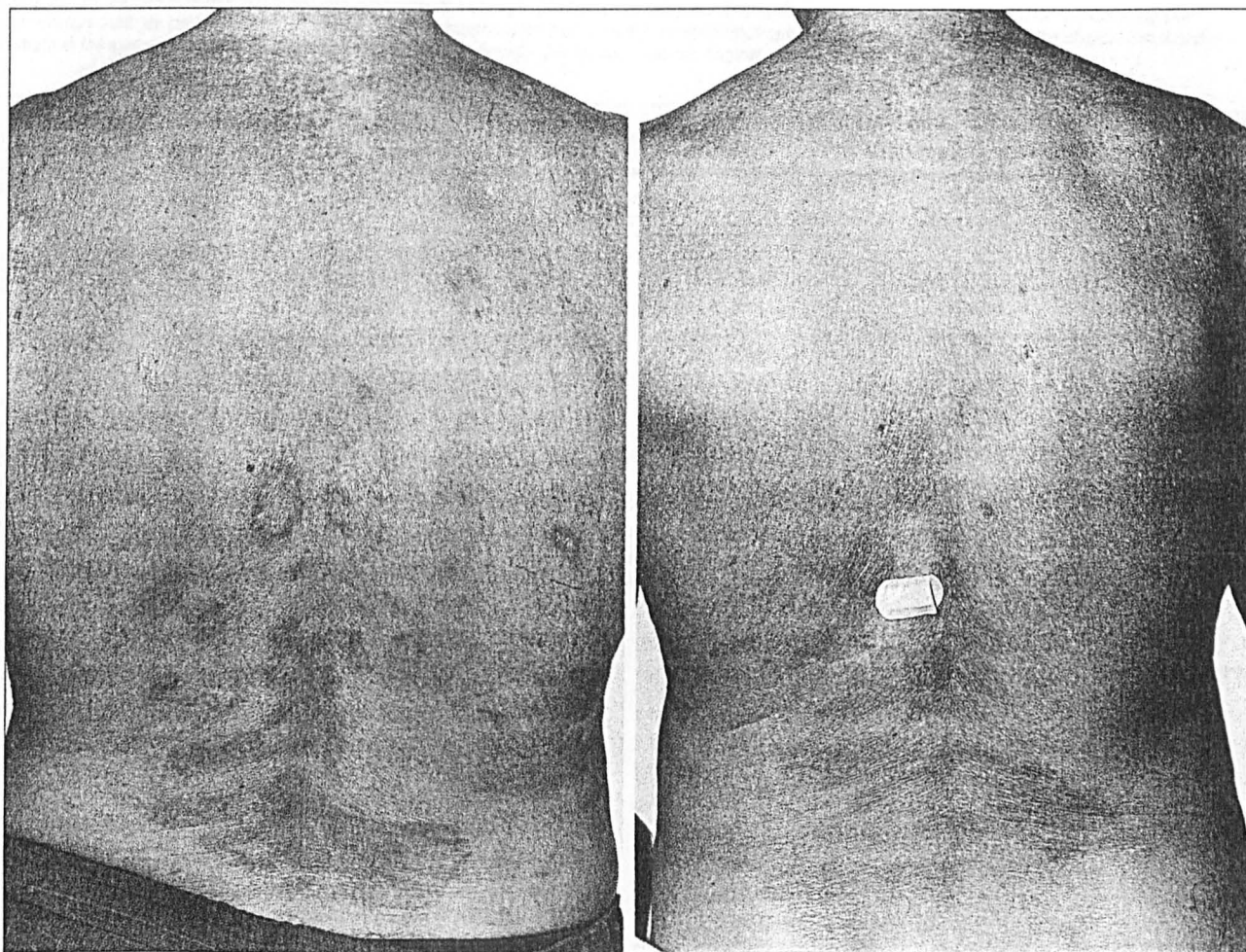

Figure 1. *Left, Patch-stage mycosis fungoides (case 2) with pruritic, superficial, scaly, erythematous patches on the lower trunk. Right, Complete clinical remission in the same patient following narrowband TL-01 phototherapy.*

reduction of the inflammatory infiltrate (cases 1, 2, 3, 6, 7, and 8). Marked reduction of the inflammatory infiltrate with loss of epidermotropism and Pautrier microabcesses was found in those who achieved a prolonged remission (patients 1 and 2), but acanthosis and a mild chronic atypical dermal inflammatory infiltrate remained (Figure 2). In case 3, despite apparent clinical clearance, the atypical lymphocytic infiltrate was only moderately reduced after treatment, and the subsequent remission was short lived. Partial response (case 4) was associated with a persistent, atypical lymphoid cell infiltrate, epidermotropism, Pautrier microabcesses, and acanthosis.

COMMENT

The most important prognostic indicators for MF are the extent and type of skin involvement and whether extracutaneous spread has occurred.[15] Failure to achieve complete remission following initial therapy is also a risk factor for progression.[12,16] The outlook for most patients receiving treatment for limited patch MF (stage 1a) is good, with a life expectancy similar to the normal population (cases 1, 5, 6, and 8).[12] More extensive patch/plaque disease (stage 1b) is associated with disease progression and mortality. One study reports disease progression in 24%
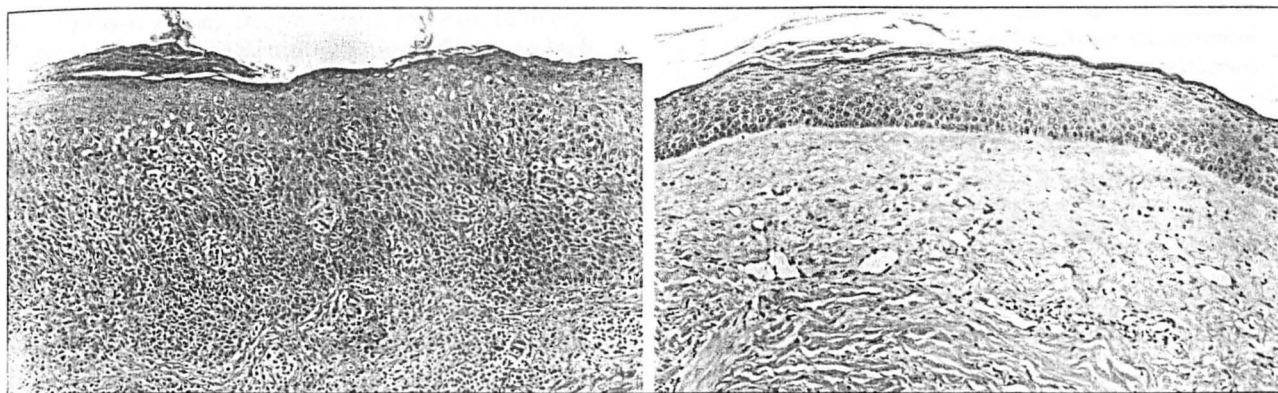
Figure 2. *Left, Patch-stage mycosis fungoides pretreatment histologic photomicrograph (case 2) showing acanthosis, a superficial dermal mononuclear cell inflammatory infiltrate containing phenotypically abnormal lymphocytes that demonstrate epidermotropism. Right, Marked reduction of the atypical lymphocytic infiltrate in the same patient following narrowband TL-01 phototherapy. (Hematoxylin-eosin; original magnification × 166 for both photographs.)*

Table 4. Response to TI-01 Phototherapy in Patch-Stage Mycosis Fungoides*

Case	TL-01 Courses	No. of Treatments	MED, mJ/cm²	PEAK TL-01 Dose, mJ/cm²	Clinical Response	Histologic Improvement†	Time to Relapse, mo‡
1	May 1992	20	140	673	Clear	...	40
	May 1996	20	140	814	Clear	...	11
	November 1997	20	200	1192	Clear	Marked	24
2	August 1996	34	280	2111	MRA	...	<3
	February 1997	37	200	1919	Clear	Marked	18
3	January 1996	33	280	1442	Clear	Moderate	1
4	May 1997	42	70	1083	Partial response	Minimal	...
5	June 1997	30	70	1919	Partial response	...	...
6	June 1998	20	200	895	Clear	Marked	Remission
7	July 1998	19	100	285	Clear	Marked	Remission
8	August 1998	33	280	1442	Clear	Moderate	Remission

*MED indicates minimum erythemal dose; ellipses, not available; MRA, minimal residual activity; and NA, not applicable.
†Moderate improvement indicates residual mycosis fungoides; marked improvement is not diagnostic for mycocis fungoides.
‡Relapse is defined as return of clinically significant disease.

of those with generalized patch/plaque MF, and 20% of patients ultimately died of their disease.[16] However, clinical staging fails to differentiate between patch-stage MF and the more advanced plaque-stage disease. As a result, it is difficult to directly compare outcome and treatment efficacy between studies of stage 1 MF and those where only patch-stage disease has been included. Despite this, when controlled for the disease stage, the efficacy of currently available topical therapies is similar in respect to complete response and long-term survival rates, although the reported duration of disease-free remission is variable.

Although the ability of UV-B to clear patch-stage MF has been known since the 1950s, it seems to have been rarely studied.[17] Two reports of broadband UV-B phototherapy for "early" MF have shown similar effectiveness. Most of these patients had limited patch-stage disease, and complete remission was achieved in more than 80% in a median of 5 months to clearance, results comparable with other topical therapies.[4,18,19] Both studies used maintenance regimens following complete remission and noted high relapse rates when this treatment was stopped. Nevertheless, 23% of patients in 1 study had a long-term sustained remission (>58 months).[4] Ultraviolet-B phototherapy was most effective with patch-stage or thin-plaque disease, and the authors concluded that this might be due to the limited ability of UV-B to penetrate thicker

lesions. This may also be reflected in an Italian retrospective study where PUVA was reported to be more effective than broadband UV-B for stage 1 MF.[20]

Narrowband phototherapy uses the Philips TL-01 lamp, which has an emission spectrum (311-313 nm) within the therapeutic action spectrum for psoriasis. In many centers it has replaced traditional broadband UV-B phototherapy as the treatment of choice for psoriasis and other dermatoses.

In this study, the response to TL-01 was best when there was a long history of premycotic eruption suggestive of an indolent and less aggressive disease more susceptible to this therapy. No correlation between skin phototype and therapeutic response was found (Table 3 and **Table 4**). Although persistent histologic abnormalities were demonstrated in all cases, similar findings have been reported with PUVA.[21] Without maintenance therapy, 3 patients relapsed rapidly and required alternative therapy. One patient had extensive, indurated MF patches and her partial response to TL-01 and subsequent relapse was, perhaps, predictable (case 4).

Although current topical therapies are effective, they can have clinically significant adverse effects. High cumulative numbers of PUVA treatments in patients with psoriasis have been associated not only with an increased incidence of nonmelanoma cutaneous carcino-

mas,[22] but also a small but important increase in malignant melanomas.[23] Topical nitrogen mustard causes a high incidence of allergic contact dermatitis, an increased incidence of cutaneous and internal malignancies, and environmental contamination.[24] Carmustine is associated with marrow suppression, intertrigo, and telangectasia.[25] Total-skin electron-beam radiation therapy can produce serious adverse effects including erythema, edema, desquamation, total alopecia and nail loss, blistering, pigmentation, telangectasias, and chronic xerosis.[26]

When compared with PUVA, TL-01 phototherapy has several advantages. As systemic psoralen is not required, related acute adverse effects (nausea, headaches, and lightheadedness) and the need for protective glasses after treatment are avoided. TL-01 phototherapy usually has shorter irradiation times, which aids compliance since patients with MF are often elderly and infirm. It can also be used in the rare instance where therapy is required during pregnancy.

Although we have achieved sustained remissions in 50% of our patients (mean, 20 months), others have reported more transient remissions.[9] Unlike PUVA, with which maintainance is effective, once-weekly treatment with TL-01, attempted for 1 patient (case 3), proved difficult because painful posttreatment erythema developed despite UV-B dose reduction.

Acute adverse effects from TL-01 phototherapy can include erythema and pruritus. The major chronic adverse effects are photoaging and photocarcinogenisis. Despite the absence of long-term prospective studies, the photocarcinogenic risk of TL-01 seems to be less than that associated with PUVA.[27,28] Of concern is the recent discovery of p53 tumor suppressor gene mutations in some MF tumors (40%).[29] These mutations were predominantly in C:T and CC:TT transitions, which are characteristic of UV-B–induced DNA damage and were not found in plaque-stage disease. This might suggest a role for UV radiation therapy in the progression of the later stages of MF. However, in the absence of epidemiological evidence for the association of UV radiation and MF progression, further work is necessary to determine the significance of these findings.[30,31]

Narrowband phototherapy offers the potential for prolonged remission for some patients with patch-stage MF. Although our study cohort was small (8 patients), we believe TL-01 treatment should be included among the initial therapeutic options in view of its efficacy, convenience, and likelihood of fewer long-term adverse effects. Clearly, larger prospective, long-term follow-up studies are necessary to define the role of TL-01 in patch-stage MF. However, our experience has shown TL-01 to be effective when PUVA therapy has been unsatisfactory or curtailed because of adverse effects. The optimum therapeutic regimen for TL-01 therapy in MF is still to be determined, but a more prolonged induction phase or the use of maintenance therapy may improve its efficacy while retaining a favorable adverse-effect profile.

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