Clinical Studies to Broaden the Application and Improve the Safety of Psoralen and Ultraviolet A (PUVA) Phototherapies

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A thesis submitted in candidature for the degree of MD in Clinical Dermatology

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And

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Dedicated to my family

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SUMMARY

This medical doctorate thesis contains clinical studies to broaden the application and to improve the safety and efficacy of ultraviolet (UV) A phototherapies, the main focus being to enhance the current clinical practice of topical psoralen photochemotherapy (PUVA. The thesis includes three studies:

1. **The validation of a semi-automated Minimal Phototoxic Dose (MPD) Tester for topical photochemotherapy**

Thirty seven psoriasis patients referred to the phototherapy unit at St. Woolos, Newport were recruited. Patients had two sets of minimal phototoxic dose (MPD) tests performed on symmetrical, contralateral sites on the lower back. MPD test results from a panel of PUVA-lamps with a UV-opaque template and windows were compared to those from the modified hand-held MPD tester. The hand-held MPD results were linearly related to the PUVA-panel MPD results and this was therefore shown to be a convenient and reliable method of assessing MPD. However, the difference in MPD between the PUVA lamp and the modified handheld MPD tester (CFL TL-10 lamp) was much less than predicted from the PUVA action spectrum of previously published studies suggesting that formal re-evaluation of the erythema action spectrum for PUVA was now appropriate.

2. **The re-evaluation of the erythema action spectrum of topical psoralen sensitised skin.**

Re-evaluation of the PUVA erythema action spectrum using aqueous 8-methoxypsoralen (8-MOP) as used routinely in current clinical practice, involved the recruitment of 20 healthy volunteers with so-called skin phototypes I – V. Six UVA irradiations at 10nm intervals between 325 and 375 nm were randomly allocated to forearm sites and were applied using a 10-nm bandwidth irradiation monochromator. The visual minimal phototoxic dose (MPD) was recorded on each site at 96 h. This study established the erythemal action spectrum for bath/soak PUVA therapy as is currently performed and showed the therapeutic action spectrum for topical PUVA appeared to be similar to the action spectrum of topical PUVA erythema, with a peak sensitivity at 325 nm.

3. **A comparison of topical PUVA regimens in the treatment of chronic inflammatory disorders of the hands and feet.**

This study was a within-patient, randomised, assessment-blinded (i.e. single-blind), comparison of two treatment regimens involving immediate illumination with UVA after immersion in psoralen solution or a delay of 30 minutes between soaking hands and/or feet and UVA

irradiation in the treatment of palmar-plantar dermatoses (psoriasis/eczema). Recruitment was slow for this study; Nevertheless 7 patients completed the protocol. All patients showed significant improvement of their dermatoses during 4-weekly assessments and all showed improvement following immediate irradiation though one patient with hyperkeratotic psoriasis affecting his soles noted a greater improvement following a 30 minute delay. The sample size was too small to draw statistically sound conclusions but strongly suggested immediate irradiation was generally suitable, except perhaps in hyperkeratotic conditions where the 30 minute delay allowed perfusion to the viable epidermis. A larger patient cohort is now required for confirmation

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ABBREVIATIONS

5 – MOP	5-Methoxypsoralen
8 – MOP	8-Methoxypsoralen
AD	Atopic dermatitis
AE	Adverse event
bbUVB	Broadband ultraviolet B
CAD	Chronic acinic dermatitis
CFL	Compact fluorescent lamp
CTCL	Cutaneous T-cell lymphoma
ECP	Extracorporeal photochemotherapy
EPP	Erythropoietic protoporphyria
GA	Granuloma annulare
GVHD	Graft Versus Host Disease
HV	Hydroa vacciniforme
LCH	Langerhans cell histiocytosis
LP	Lichen planus
LS	Localised scleroderma

LyP	Lymphomatoid papulosis
MED	Minimal erythema dose
MPD	Minimal phototoxic dose
nbUVB	Narrowband ultraviolet B
PL(C)	Pityriasis lichenoides (chronica)
PLE	Polymorphic light eruption
PPD	Pigmented purpuric dermatoses
PPP	Palmoplantar pustulosis
PRP	Pityriasis rubra pilaris
PUVA	Psoralen photochemotherapy
Re-PUVA	Retinoid and psoralen photochemotherapy
SD	Standard deviation
TMP	Tri-methyl psoralen
UVA	Ultraviolet-A
UVB	Ultraviolet-B

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1.1 History of PUVA

Psoralens and ultraviolet radiation have been used in the treatment of cutaneous disease since antiquity. The “Ebers Papyrus” (circa 1550 BC), is one of the oldest preserved medical documents. [1] It is currently stored in the University of Leipzig library, Germany. The 110-pages contain more than seven hundred remedies for various ailments including descriptions of how the seeds of the *Psoralea corylifolia (*family *Leguminosae)*, were used for the treatment of vitiligo.[1,2]

Physicians and herb specialists from early times used boiled extracts of seeds, roots and leaves of these plants to formulate preparations which were either applied topically as a paste or ingested two hours prior to sun exposure.[3]

A similar method of managing vitiligo, was described in the Indian sacred book “Artharva Veda” 1400 BC.[2] This practise continues to be used today by peasants in India where vitiligo remains a major medical and social problem.

The thirteenth century AD, saw the rise of Ibn al-Baitar, one of the greatest scientists of Al-Andalus (Andalucia) and a highly regarded botanist and pharmacist of the Middle Ages.[4]

Ibn al-Baitar described the use of powdered seeds of another plant, *Ammi majus* Linnaeus (which grows throughout the Nile valley as a weed), in his book *Mafardat Al Adwiya* as a “cure” for leukoderma.[4]

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Aatrillal (*Ammi majus)* was commonly used by Ben Shoeib, a Berberian tribe, dwelling in the north-western African desert as a remedy for leukoderma. Aatrilal, a yellow-brown powder, is still used by Egyptian herbalists today as a treatment for vitiligo.[5]

Photoactive furocoumarin compounds are contained in many plants including lemon, lime, fig, parsnip, parsley, clove and the fruits of *A. majus* and *P. corylifolia.*[2] However, it was 3 millennia later, in 1938 that Kuske, a Swiss dermatologist, first described photosensitization of the skin by plants due to the presence of natural furocoumarin compounds. Kuske isolated bergapten, 5-methoxypsoralen (5-MOP), from the oil of bergamot.[6]

In 1947 Fahmy, an Egyptian pharmacologist and his student Abu-Shady, isolated the psoralen compound 8-MOP from Ammi majus.[7] Following on from this work, El Mofty, an Egyptian dermatologist, successfully pioneered the use of crystalline 8-MOP both topically and orally (40-50mg) followed by sun exposure, achieving repigmentation of vitiliginous macules.[8] The 1960s and 70s were an era where the basic pharmacology of the psoralens was studied. In 1974, Parrish successfully introduced a treatment for psoriasis, combining orally administered 8-MOP and UVA radiation (320-400nm) using a newly developed high intensity artificial UVA light.[9]

Honigsmann *et al.*[10] in 1979 reported 5-methoxypsoralen as an alternative to 8-methoxypsoralen but with less adverse gastro-intestinal

side-effects. For those patients unable to tolerate oral 8-MOP due to nausea and vomiting, 5-MOP PUVA is another alternative. Berg[11] *et al.* conducted a double-blind PUVA study to compare efficacy and side-effects of 5-MOP versus 8-MOP in 38 patients. At six weeks, patients treated with 8-MOP showed greater response than those treated with 5-MOP. However, at nine weeks there was no significant difference between the two groups.

Two classic multicentre studies paved the way for the widespread use of PUVA in psoriasis. The study by Melski *et al*. (US Cooperative Clinical Trial 1977)[12] was conducted in 16 academic dermatology departments in the USA. The study assessed efficacy of oral methoxsalen photochemotherapy in the treatment of psoriasis. Although all centres used the same protocol including dose, light source and monitoring of patients, results varied considerably between centres. Some centres reported 90% clearance of psoriasis whereas others recorded only 40% clearance. Henselar *et al*.[13] reported the results of the multi-centre European PUVA study 1981, which assessed efficacy of PUVA in achieving remission of psoriasis. Their findings supported those of the US Cooperative Clinical Trial. In particular, they commented that PUVA maintenance therapy may not prevent relapse of disease for prolonged periods of time and hence may not be required in most patients.

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Regarding the US cohort and European cohort study the apparent differences in skin cancer rates should be viewed with caution. In USA they used systemic PUVA whereas in Europe mainly bath PUVA was used. Maintenance therapy for psoriasis patients in the US cohort was more commonly used. The patients in the US cohort also received regular follow-up if they had been treated with PUVA, there was no control group of patients who did not receive PUVA. This leads to a lead-time bias as the US cohort patients who were more likely to be diagnosed earlier with skin cancers. There was also an ascertainment bias as patients with dermatological disease were more likely to be diagnosed with skin cancers. In the European cohort, patients received lower PUVA exposure. PUVA was used for many indications and there was little maintenance treatment. No increased incidence of melanoma was found in the European cohort, unlike the US cohort where there appeared to be a five-fold annual incidence risk of melanoma in 1997 and a nine-fold risk of melanoma in 2001. Furthermore, in the Swedish study data from a cancer registry for PUVA treated patients could be compared to a control population. Both European and US studies show that the risk of non-melanoma skin cancers increase thirty-fold if a patient received more than 200 treatments. However, the high prevalence of Phototypes I and II in the US cohort studies may be a significant factor for the cancer difference.

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TABLE 1 SHOWING PUVA HISTORICAL LANDMARKS

Date	Source	Finding
	ANCIENT HISTORY	
1550 B.C	Eber's Papyrus	Psoralea Corylifolia seeds ingested/ applied topically as a paste for the treatment of leukoderma followed by sun exposure
1400 B.C	Artharva Veda	
13th Century A.D.	Ibn al-Baitar Mafradat Al Adwiya	*Ammi Majus* Linnaeus abundantly found in Nile Valley – "cure" for leukoderma
	MODERN HISTORY	
1938	Kuske (Swiss Dermatologist)	Isolated Bergapten (5-MOP) from oil of bergamot. Skin photosensitization due to furocoumarin compounds
1947	Fahmy (Egyptian Pharmacologist) and his student AbuShady	Isolated 8-MOP from *Ammi Majus*
1948	El-Mofty (Egyptian Dermatologist)	Pioneered use of crystalline 8-MOP (topically and orally) achieving repigmentation of vitiliginous macules
1955	Fitzpatrick *et al.*	Randomised double-blind cross-over trial involving 63 volunteers assessing dose-reponse to sunlight exposure. Max. Phototoxic effect 1.5-2hr following oral 8-MOP
1960	Buck *et al.*	Action spectrum of 8-MOP localised to 360nm
1965	Mussajo *et al.*	Evidence of covalent photobinding of furocoumarin molecules to DNA
1974	Parrish *et al.*	Oral 8-MOP and high intensity UVA used to treat Psoriasis
1977	US Co-operative Trial Melski *et al.*	16 Academic Dermatology Departments in USA recruited 1308 psoriatic patients to assess efficacy of PUVA
1978	Fritsch *et al.*	Oral retinoid (etrinate) combined with PUVA Therapeutic efficacy of PUVA greatly potentiated
1981	European PUVA Study Henselar *et al.*	Cooperative study - 18 European centres, assess efficacy of PUVA in psoriasis. PUVA maintenance therapy little effect on remission
1987	Edeleson *et al.*	Extracorporeal photochemotherapy (ECP) evaluated for CTCL
1997	Stern *et al.*	Follow-up study: carcinogenic risk reported on US cohort of 1380 patients
2001	Stern *et al.*	Follow-up study: increased risk of melanoma found in original US patient cohort.

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Fritsch[14] introduced the concept of retinoid and PUVA, which he termed "Re-PUVA" in1978. The combination of PUVA with oral etretinate, an aromatic retinoid, potentiated the therapeutic efficacy of PUVA significantly by reducing the time, dose of UVA (J/cm^2) and number of treatments required to achieve clearance of psoriasis.

Psoralens have also successfully been used as systemic immune-modifying agents in photopheresis. Extracorporeal photochemotherapy (ECP) was first evaluated by Edelson *et al*.[15] in 1987, for the management of erythrodermic cutaneous T-cell lymphoma (CTCL). ECP was found to provide high response rates and to improve overall survival for the disease. ECP is currently practised in over 150 centres worldwide for multiple indications[16] including pemphigus vulgaris, atopic dermatitis, type I diabetes mellitus, inflammatory bowel disease, scleroderma[17], systemic lupus erythematosus, epidermolysis bullosa acquisita, morphoea[18] and nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis[19]. ECP may also be used to treat acute and chronic organ transplant rejection as well as preventing acute organ rejection.

The procedure involves extracorporeal photoactivation (photopheresis) of 8-MOP by passage of blood containing CTCL cells through a UVA

exposure system. The irradiated blood is then re-transfused back into the patient. The mechanism of action of ECP remains an area of on-going research. One theory is that the combination of 8-MOP and UVA results in preferential apoptosis of abnormal or activated T-cells thus targeting the pathogenic cells of CTCL or graft-versus-host disease (GVHD). There is also evidence that ECP promotes differentiation of monocytes into dendritic cells which phagocytose and process the apoptotic T-cell antigens. Following reinfusion of activated dendritic cells into the systemic circulation, a resultant systemic cytotoxic $CD8^+$ T-cell immune response to the processed apoptotic T-cell antigens ensues.

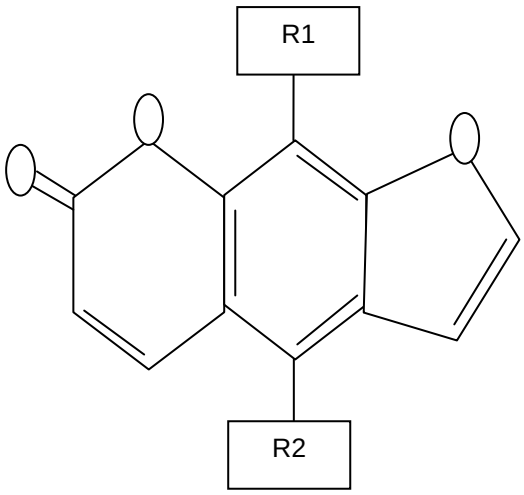
A major disadvantage of PUVA is the increased risk of skin cancer compared to UVB phototherapy. In 1997, Stern *et al*.[20] published data on a cohort of 1380 psoriasis patients treated with PUVA in 1975/6. They found that the risk of malignant melanoma increased more than five-fold particularly in patients who had received 250 treatments or more. A further follow-up study by the same authors in 2001[21], confirmed their initial findings and they described additional melanomas in their original patient cohort. The risk of melanoma increases with time in this patient population.

The use of PUVA has declined significantly with the emergence of narrow-band (nb)UVB. This decline is largely due to the cancer risk, which is so much lower for UVB. PUVA, however still has an important

therapeutic role in cases of dermatoses recalcitrant to conventional phototherapy and in dermatoses that penetrate deep into the skin.

1.2 Psoralen Photobiology

Psoralens are planar, tricyclic compounds composed of a furan ring bound to a coumarin moiety.



R1 = H	R2 = H	Psoralen
R1= OCH_3	R2 = H	5-Methoxypsoralen (5-MOP)
R1 = H	R2 = OCH_3	8-Methoxypsoralen (8-MOP)

Fig. 1 Chemical Structure of Psoralen[22]

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The planar, aromatic structure of psoralens together with their hydrophobic nature, facilitate their intercalation with DNA bases.[23] Psoralen has been shown to enhance the generation of reactive oxygen species and free radicals in the absence of light and to possess pro-oxidative effects[24]. However, psoralen alone in the absence of ultraviolet light has no effect on the function of DNA synthesis of human cells grown in vitro[25]. This finding is supported by a study of S-180 (murine sarcoma) cells, in which neither the psoralens nor UVA light alone inhibit cell growth but together act synergistically[26].

The principle theory of psoralen photobiology revolves around the impact of adduct formation on cellular properties and function. The most frequently occurring adducts are those with thymine-psoralen; cytosine-psoralen adducts occur less efficiently. When irradiated with UVA light, a 2 + 2 photocycloaddition reaction occurs with pyrimidine bases, particularly thiamine. This occurs between the 4',5'double-bond furan-side of psoralen and the 5,6 double-bond of thymine. This may involve one or both strands of DNA resulting in 2 types of lesions: monoadducts or interstrand cross-links, which are responsible for the short and long-term effects of PUVA respectively. Interstrand cross-links occur following cycloadditions between one psoralen molecule and two pyrimidine bases on two complementary DNA strands. The cross-linking process depends upon the structure of the psoralen. Linear furocoumarins form cross-links more efficiently than angular furocoumarins.[23]

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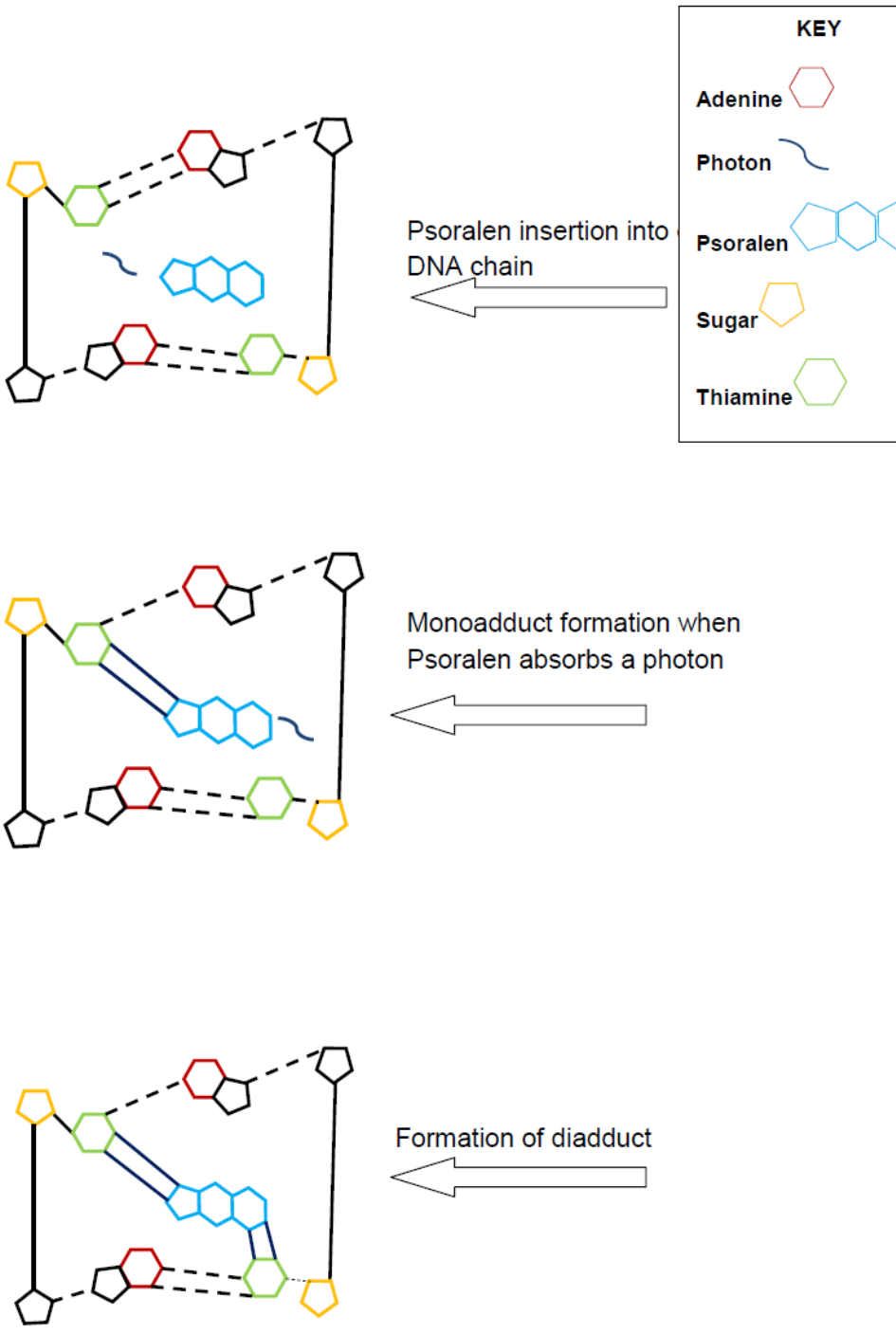

Adapted from Medical applications of photochemistry. Merchan M, Serrano-Andres L, Serrano-Perez P. http://www.uv/es/qcexval/research/pdt.html

Figure 2: Illustrating Monoadduct Formation and Interstrand Cross-linking between psoralen and DNA

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The initial hypothesis was that these reactions had an anti-proliferative effect. In psoriasis, therefore, PUVA therapy would induce 8-MOP DNA photoadduct formation slowing cellular replication. However, Johnson *et al*.[27] showed that keratinocytes were very resistant to the effects of PUVA therapy whilst cytokine-releasing lymphocytes in the epidermis of psoriasis patients were much more sensitive. In addition, there was virtual elimination of epidermal $CD3^+$ T-cells in psoriatic skin.[28]

Whilst comparing the effects of Trimethyl Psoralen (TMP) to 8-MOP, Coven *et al*.[21] found TMP to be nearly 10,000-fold more lymphotoxic compared to 8-MOP. Further work needs to be carried out to establish the carcinogenicity risk of TMP. Coven *et al.* suggest this "potent lymphotoxic treatment may prove to be one of the safest and most effective treatments for psoriasis."[28]

Although DNA psoralen photochemistry is well characterised, psoralens also react with proteins and other cellular constituents. Studies to determine the affinity of 8-MOP to bind with epidermal lipids, proteins, and DNA/RNA following PUVA treatment showed 17% of the 8-MOP was bound to DNA, whilst the vast majority was bound to proteins (57%) and lipids (26%).[29] A common finding when assessing PUVA effects on proteins, however, was that much greater doses of 8-MOP and UVA are required to produce a biological effect than relatively small doses necessary to induce DNA damage.[30]

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1.3 Psoralen Erythema Action Spectrum

For PUVA to be successful, a number of elements need to be optimised. These include: choice of psoralen, mode of administration for psoralen, timing of psoralen administration relative to UVA exposure, dose of UVA, rate of application of UVA and spectrum of UVA administered. Thus, the action spectrum of psoralen within UVA is defined as the rate of physiological activity (erythemal response) plotted against light wavelength (UVA 320nm-400nm).

The published action spectrum of psoralen-induced erythema enables the calculation of the erythemal efficacy of any UV source where the emission spectrum of the lamp is known or can be measured.[25-30] However, the action spectrum of 8-MOP differs markedly from its absorption spectrum.[31] Potential reasons for this are psoralen or 8-MOP under-go chemical changes upon their incorporation into the skin and exposure to UVA and the action spectra within the skin will differ according to the absorption spectra of the chromophores they target. [31] The UV absorption spectra for psoralen and 8-MOP compounds have been reported by Fowlks[32] as having maximal absorption at approximately 220nm, 245nm, and 295nm (with a shoulder at 330nm) for psoralen and 220nm, 250nm, and 310nm for 8-MOP.

In 1940, Kuske demonstrated that topically applied psoralens led to photosensitisation with the 334nm and 366nm lines of the mercury arc spectrum from a monochromator. Stegmaier[33] (1959) showed that

following ingestion of 8-MOP, erythema developed after subsequent exposure to fluorescent lamps which emitted the majority of their energy between 320 – 360 nm. In 1960, Buck *et al.*[34] used 1% 8-MOP applied topically on human skin; Pathak[35] (1961) administered 8-MOP orally to guinea pigs. Both Buck *et al.* and Pathak localised the peak erythemal action spectrum of 8-MOP to 360nm.

Later studies conducted by Owens[36] *et al.* (1968) administering oral 8-MOP to guinea pigs and Nakayama[37] *et al* (1974) using topical application of both 8-MOP and TMP on guinea pigs both noted that maximum sensitivity occurred at 330 nm.

This discrepancy in reported erythemogenicity led to a re-evaluation of the psoralen erythema action spectrum by Cripps[38] *et al.* (1981). Cripps concluded that peak sensitivity for 8-MOP was 330nm and for TMP was 335nm. The study used 8-methoxy psoralen at 1% dissolved in acetone and then in ethanol and applied directly to the skin, followed by irradiation with various wavelengths of UVA. No details were provided for the time between application of psoralen and UVA irradiation were given.[38]

This scenario differs greatly from present clinical practice, where the skin is immersed in an aqueous solution of 8-methoxypsoralen at 37°C[39] for 15 minutes, followed by UVA irradiation within 30 minutes. The study by Schempp[40] *et al*. showed there was a marked, significant reduction in erythema after 60 minutes delay between soaking in an 8-

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MOP bath and irradiation and no erythema was detected after 180 and 360 minute delay. Thus, it is timely to re-assess the action spectrum for PUVA in the context of current clinical practice for this treatment.

A general problem in comparing studies of erythemal effectiveness is the definition of minimal erythemal or phototoxic dose, the outcome measure used to define the photosensitising potential of UV treatments on skin (both psoralen-sensitised and non-sensitised).

Early studies used a definition of minimal erythema as skin with minimal redness described as even or confluent with sharp borders. Later definitions describe minimal erythema as “barely perceptible”, dropping the requirement for the irradiated site to have confluent erythema with sharp borders.

Reported differences in psoralen formulation, application time, body site, skin phototypes and time to read erythema make the photosensitising outcome measures somewhat heterogeneous, and restrict conclusions from comparison of studies to be relatively generalised.

1.4 Pharmacokinetics of Psoralens

Three psoralens are used for PUVA therapy, the most commonly used being 8-MOP; 5-MOP and 4,5'8-trimethylpsoralen are also used.

1.41 Systemic Psoralen

Approximately 75-80% of 8-MOP is reversibly bound to serum albumin and distributed to all organs. This binding is short-lived in the absence of UVA exposure and the drug is metabolised in the liver and excreted as inactive metabolites in urine.[41] The rate of intestinal absorption of psoralens is dependent upon several factors including concomitant drugs, food intake and physical characteristics of the preparation.

Food intake, particularly of high fat content, decreases the absorption of psoralens[42]. Psoralen undergoes first-pass metabolism and may result in interindividual variability in plasma levels after a fixed dose of methoxsalen.[43] Drugs that induce cytochrome P-450 enzymes may decrease the biologic effect of PUVA. 5-MOP is less water soluble than 8-MOP and has an absorption rate approximately 25% that of 8-MOP.[44] Dissolved preparations (soft gelatine capsules) are better absorbed than crystalline formulations. The former yields peak serum levels in a relatively reproducible time whereas wide time variability occurs with crystalline formulation.[45] In contrast, the pharmacokinetics of topical 8-MOP depend on the method of application. 0.15% 8-MOP emulsion or

solution applied to large body areas results in plasma levels comparable to those achieved with oral administration, whereas plasma levels after whole body bath PUVA treatment are very low.[444]

1.42 Topical Psoralen

Topical PUVA was first used to treat palmoplantar psoriasis in 1974.[46] Further studies have been published with variable results.[47,48,49] The treatment schedules vary considerably with regards to method of psoralen application and the time interval between psoralen application and UVA irradiation. The advantage of immersion (soak) PUVA is the epidermis is fully hydrated and overcomes problems associated with variable application as occurs in paint PUVA. The degree of hydration is known to affect permeability of the stratum corneum.[50]

The optimal time for UVA irradiation on palmoplantar skin following application of topical 8-MOP psoralen or by immersion appears to be related to the lag time.[50] That is the time taken for a substance with diffusion properties to appear in considerable quantity in the viable epidermis. This is related to the thickness of the stratum corneum and the diffusion coefficient. Abnormalities of the stratum corneum as in psoriasis or eczema may lead to an increased permeability to psoralens when compared with unaffected skin. Diffusion is influenced by factors including vehicle characteristics or the presence of emollients on the surface of the skin. The greatest penetration occurs with solutions and emulsions.[51]

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Penetration kinetics of 8-MOP into human skin have been investigated using in vitro conditions.[51] 8-MOP tissue concentration increases with time. The lag time in palmoplantar skin is increased to 30-40 minutes before maximum UVA sensitivity is reached and is followed by sustained sensitivity for approximately an hour.[50] This implies that immediate irradiation of these sites is unsuitable. The increased thickness of the stratum corneum on both palmar and plantar sites compared to other body sites, acts as a drug reservoir and may explain the sustained activity providing an optimum therapeutic window from 30-110 minutes after the soak.

1.5 Minimal Phototoxic Dose (MPD)

The MPD is the lowest dose of UV radiation of psoralen-sensitised skin which causes a just perceptible erythema[52]. The MPD may also unmask previously unidentified photosensitivites due to dermatoses or phototoxicity secondary to concurrent medications. The initial UVA dose should, when possible, be based on an MPD test. This helps to identify the optimal starting dose of PUVA – thus avoiding either painful erythema or, conversely, under-treatment.[52] If the extent of disease precludes MPD testing, then the initial dose can be based on skin phototype, although this is not ideal (see below).

ASSESSING MPD

Traditionally, MPD's have been examined at 72 hours when it was believed that peak PUVA erythema was maximal[53,54,55] However, Ibbottson and Farr demonstrated that peak PUVA erythema using oral 8-methoxypsoralen (8-MOP) occurs at 96 hours.[56] Man *et al.* showed the optimal time to assess topical 8-MOP MPD is 120 hours.[57] MPD assessment during or beyond 120h is best avoided due to confounding effects of the development of pigmentation[57]. Their recommendation was that topical 8-MOP MPD should be read four days (96 hours) after exposure. 40% of the MPD is in widespread clinical usage as the initial treatment dose at the start of a course of PUVA therapy.[57] Subsequent dose increments of 20-40% are recommended, with an increase if tolerated, at every treatment.[52]

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The traditional method of assessing MPD is cumbersome and time-consuming for both patients and staff. Several small areas of skin are exposed to increasing doses of UVA from a panel of UVA lamps. This "open" source is associated with the potential for errors including UV source non-uniformity due to curvature of the test site, patient movement, incorrect positioning of the patient leading to incorrect distance between the skin and UVA lamps and exposure timing errors.

A device that overcomes many of these difficulties is the minimal erythema dose (MED) tester used for UVB. This uses a compact fluorescent tube (CFL) in a handheld housing as the source and a UVB opaque template with 10 x 1-cm-diameter apertures. The output of nine of these apertures is successively attenuated by a factor of 1.25 by steel shaver-type foils. This device will be discussed in more detail in Chapter 2.

1.6 Skin Phototypes

The concept of skin phototype was proposed by Professor Thomas Fitzpatrick the Chair of Dermatology at the Massachusetts General Hospital in Boston, in 1978 as a way to subdivide human beings by their tanning and erythemal responses to sun exposure. The Fitzpatrick Skin Type[58] (phototype), sometimes referred to as the Boston Classification of skin type, correlates an individual's skin colour with their ability to burn or tan when exposed to sunlight. Patients were asked two specific questions about their responses to three minimal erythema doses (MED) or approximately 45 – 60 minutes of noon exposure in northern latitudes (20º- 45º) in early summer.

1. "How painful is your sunburn after 24 hours?"

2. "How much tan will you develop in a week?"

However, this relies on an individual's recollection of past observations, making the accurate determination of skin types very difficult in practice.

Table1.2: Fitzpatrick Skin Phototype

Skin Phototype	Constitutive Colour* (unexposed skin colour)	Sunburn & Tanning History	Sensitivity to UV
I	Ivory White	Always Burns, never tans	Very Sensitive
II	White	Always Burns, tans minimally	Very Sensitive
III	White	Burns minimally, tans gradually and uniforml	Sensitive
IV	Light Brown, Beige-Olive	Burns minimally, always tans well	Minimally Sensitive
V	Moderately Brown	Rarely Burns, tans darkly	Rarely Sensitive
VI	Dark Brown	Never Burns, tans darkly	Least Sensitive

* The constitutive skin colour is genetically determined by the amount of cutaneous melanin.

However, Schiener *et al*.[59] showed that skin phototype is not a suitable indicator for the initial UVA dose in PUVA bath photochemotherapy. This is supported by Kraemer *et al*.[60] Mean MPD values were greater than the values attributed to those used for the different phototypes. Patients being treated with PUVA would therefore receive lower initial UVA doses than was necessary, prolonging treatment and potentially

subjecting individuals to late side effects. Therefore, phototype alone is not a good parameter to define the initial UVA dose.

1.7 ADVERSE CLINICAL EFFECTS OF PUVA

1.71 Short-term

Nausea

Nausea is the most common adverse reaction following oral 8-MOP (30% of patients) and vomiting (10% of patients). This may require reduction in the dose of oral 8-MOP or in severe cases discontinuation of treatment. These side-effects are encountered more frequently with liquid rather than crystalline preparations. Conversely oral 5-MOP is much less frequently associated with nausea.[61]

Patients are advised to take oral 8-MOP with a small amount of food with a high fat content or milk to prevent or reduce nausea. This may decrease the absorption of psoralens. Ginger has also been used to reduce the nausea.

Erythema

Excessive phototoxicity varying from intense delayed erythema to bulla formation may occur. This may occur in approximately 10% of patients during the clearance phase.[62] Management is largely symptomatic including liberal use of emollients, anti-pruritic agents and cool baths.

If large areas of skin are affected, systemic symptoms of excess photosensitivity including fever and general malaise may occur. Non-steroidal anti-inflammatory drugs and topical or systemic corticosteroids may be required to alleviate symptoms.

Subacute phototoxicity presents as a diffuse scaly erythema with intense pruritus and may occur at any time during a course of PUVA therapy even if the dose of UVA has remained stable for a period of time.[62] An important feature of subacute phototoxicity is the sparing of body areas naive to UVA during treatment e.g. axillae. Management involves conservative measures as above and possibly a temporary cessation of PUVA therapy. PUVA may be resumed at a dose of UVA 30-40% lower than the previously used dose, with gradual increments as tolerated by the individual.

Pruritus and Skin Pain

Mild pruritus secondary to dry skin during PUVA therapy is common. Liberal use of emollients is generally sufficient to relieve this. Intense pruritus “PUVA-Itch” is commonly described as a deep, burning itch occurring in the presence or absence of erythema. This usually begins on the outer aspects of extremeties, buttocks and, in women, on the breasts. An uncommon complication of PUVA therapy is persistent skin pain.[63] [64] Pruritus and skin pain have been postulated to occur as a result of phototoxic damage of the dermal nerve endings.[65]

Other Short-Term Adverse effects

This may include reactivation of herpes simplex, triggering PLE, photo-onycholysis and melanonychia.[66]

1.72 Long-Term

Photoageing

Skin ageing may be differentiated into intrinsic (chronological) ageing and photoageing[67]. Chronic exposure to PUVA results in dry skin, irregular pigmentary changes, telangiectasia, wrinkle formation, yellowish skin discolouration, loss of elasticity and actinic keratoses. Additionally, profuse dark lentigines – PUVA lentiginosis may occur.

Photoageing of darker Asian skin differs from that of whiter Caucasian skin primarily due to melanocytic function. Ethnicity, genetic differences and sun exposure habits also modify skin structure and function. Clinically the dyspigmentation and wrinkling responses associated with photoageing differ between Asian and Caucasian skin[68]. Initial beliefs that Asian skin photoageing mainly comprised of pigmentary change rather than wrinkling is disputed[69]. Further investigation is required to elucidate the inherent characteristics of Asian skin, and on the aging and photoageing processes in Asians.

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Photocarcinogenesis

The multi-centre Photochemotherapy Follow-up Studies reported by Stern et al.[70] showed that large cumulative doses greatly increase the risk of skin cancer. Interestingly, there have been no reports of such risk in vitiligo patients treated with PUVA.

Squamous cell cancer remains the primary cause of cancer morbidity and mortality in psoriasis patients with skin types I and II treated with PUVA. SCC metastases occurred in 4- 5% of these patients.[70] There is also in an increased risk of SCC in patients receiving long-term ciclosporin subsequent to PUVA.

Male genitalia are particularly high risk sites for development of SCC especially if previously treated with tar and UVB prior to PUVA, highlighting the need for shielding during treatment[71]. A retrospective study involving 5400 patients treated between 1978–1998, showed no cases of genital cancer despite no genital shielding during UVA exposure.[72] There was a significant increase in the incidence of truncal basal cell carcinomas (BCC) in patients receiving a high number of treatments. However, BCCs are easily treatable and have a low associated morbidity.

Of the 1380 patients enrolled in the U.S. multi-centre study[73], 23 patients developed 26 invasive or in-situ melanomas since first followed in 1975. This occurred in patients receiving the highest doses of therapy and the longest follow-up. These two factors may be interrelated as an

increased incidence of melanoma has not been observed in other studies of patients managed with PUVA. The study published by Hannuksela et al[74]. involving 944 Swedish and Finnish psoriasis patients receiving bath PUVA with TMP, did not show an increased risk of SCC's or cutaneous melanoma. Furthermore, no association between cutaneous carcinoma and 8-MOP bath PUVA was detected in 158 Finnish patients[75].

This variability in apparent cancer risk may be due to differences in cumulative exposure to PUVA phototherapy, ethnicity, treatment protocols, prior exposure to other carcinogens including x-irradiation, and attitudes toward sun exposure. Follow-up duration of these patients also needs to be taken into account.

Ocular Effects

UVA penetrates the lens and accelerates cataract formation by psoralen-protein photoadduct formation in animal models. However, in clinical studies, there has not been a dose-related increase in cataract formation[76]. Eye protection however, remains mandatory during treatment. UVA-opaque glasses are worn by patients receiving systemic psoralens until the evening of the day of treatment.

Other Effects

Cardiovascular disease, non-cutaneous neoplasms including lymphomas, hepatitis[77,78] or the occurrence of ANA antibodies[79] are not associated with PUVA therapy[80].

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1.8 Clinical Indications PUVA[81]

Table 1.3 PUVA RESPONSIVE DISEASE

Therapy of Disease	**Induction of tolerance in photosensitivity conditions**
Psoriasis	Polymorphic Light Eruption‡
Palmoplantar pustulosis	Solar Urticaria‡
Atopic dermatitis	Chronic Actinic Dermatitis*‡
Mycosis Fungoides	Hydroa Vacciniforme*‡
Vitiligo	Erythropoietic protoporphyria*‡
Generalised Lichen Planus	
Cutaneous Graft Versus Host Disease	
Prurigo Nodularis	
Urticaria Pigmentosa	
Generalised Granuloma Annulare	
Localised Scleroderma*	
Pityriasis Lichenoides (acute & chronic)*	
Lymphomatoid papulosis*	
Langerhans Cell Histiocytosis*	
Purpuric Pigmented Dermatitis*	
Pityriasis Rubra Pilaris*‡	

*Limited to small number of patients

‡May flare

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Psoriasis

Psoriasis is a common, chronic, inflammatory skin disease characterised by scaly erythematous papules and plaques. There are various clinical patterns of psoriasis including:

- Psoriasis vulgaris – small/large plaques occurring on extensor surfaces
- Guttate psoriasis – sudden onset widespread, crops of small, drop-like, scaly papules and plaques, usually precipitated by streptococcal tonsillitis/pharyngitis.
- Palmoplantar pustulosis;
- Generalised pustular psoriasis
- Flexural psoriasis
- Erythrodermic psoriasis

Prevalence of psoriasis varies between ethnic groups, but is estimated to affect approximately 2% of the population worldwide. Susceptibility to the condition is inherited. Approximately 30% of patients with psoriasis vulgaris have an affected first-degree relative. Although no single psoriasis gene has been identified, at least 9 chromosomal loci have been linked to psoriasis. The major genetic determinant of

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psoriasis is found on Chromosome 6p, designated PSOR 1. The absence of 100% concordance in monozygotic twins indicates that environmental factors contribute to expression of psoriasis in susceptible individuals. Patients with psoriasis are at greater risk of developing other immune-mediated diseases including sero-negative arthritis and Crohn's disease. Patients are also more likely to develop the metabolic syndrome.

Traditionally, psoriasis is managed in step-wise manner. Step 2 often gets omitted because of poor provision of phototherapy across the UK.

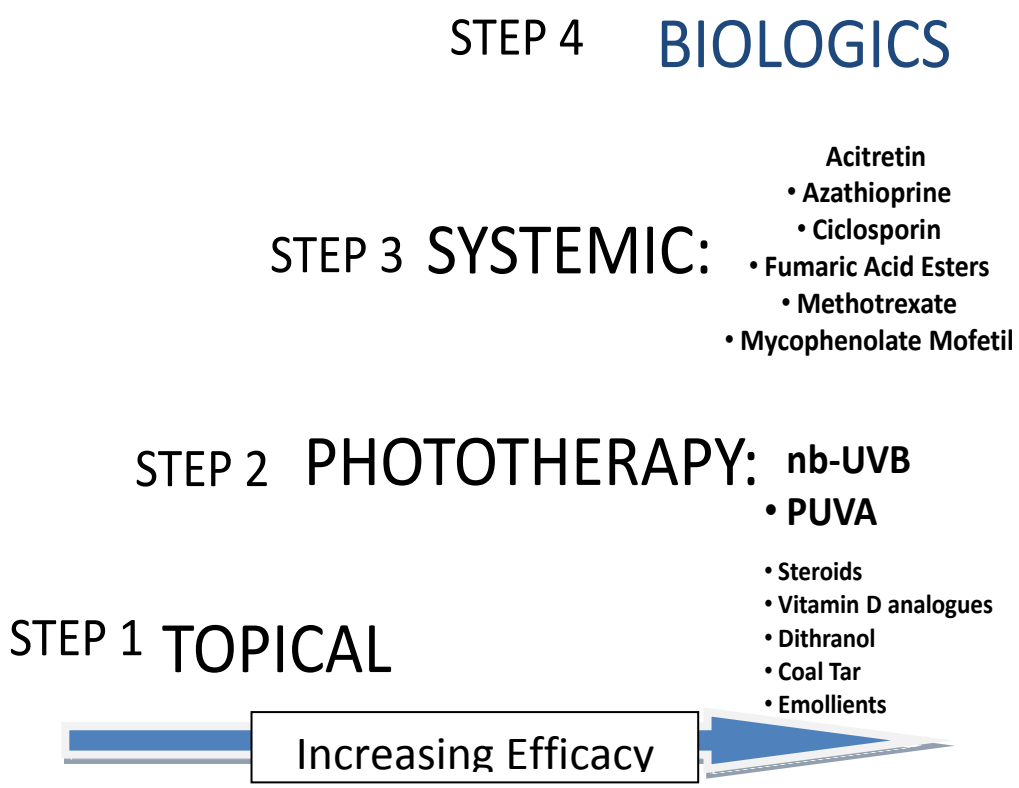

Figure 1.3 Stepwise Management of Psoriasis

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Topical treatments are suitable for limited disease. The main drawbacks are that these treatments can be time-consuming and compliance with the topical regimes may become a problem.

Patients with widespread psoriasis, in particular guttate psoriasis, often benefit from a course of phototherapy. NB-UVB therapy has been used successfully in the treatment of psoriasis and is generally accepted to be first line compared to PUVA. Furthermore due to safety nbUVB is the first-line therapy in pregnant patients with plaque and guttate psoriasis who need treatment.[82] Patients who respond poorly to nbUVB may then be offered PUVA (but not in pregnancy).

PUVA is one of the most effective therapies available for widespread psoriasis. Fourteen hundred and eight patients were included in the European Cooperative Clinical Trial assessing the efficacy of oral methoxsalen with UVA phototherapy for the treatment of psoriasis.[12] 88% of patients cleared following twice or three times weekly PUVA treatments. A course of 24 treatments with PUVA often results in clearing of psoriasis, with varying remissions lasting between 3 – 6 months.[83]

Gordon *et al.*[85] reported a randomised comparison of nbUVB and PUVA for 100 patients with plaque-type psoriasis. Patients were randomly allocated to receive twice weekly nbUVB (TL-01) or PUVA. Clearance of psoriasis was achieved in a significantly greater proportion of PUVA-treated patients (84%) compared to TL-01 (63%), with significantly

fewer treatments. Six months after completion of treatment, 35% of patients treated with PUVA compared to 12% of patients treated with TL-01 remained clear[84]. A double-blind, randomised, single-centre study comparing nbUVB with PUVA for the treatment of 93 psoriasis patients, also demonstrated that PUVA treatment achieved clearance in more patients with fewer treatment sessions than does nbUVB. In this study, PUVA resulted in longer remission time than nbUVB.[85]

There are also studies supporting similar efficacy for nbUVB and oral PUVA. Van Weelden[86] *et al*. reported that twice weekly nbUVB was as effective as twice weekly oral 8-MOP PUVA in ten patients after four weeks of treatment. Similarly, Tanew[87] *et al.* confirmed that both treatments were equally effective when administered thrice weekly but suggested that oral 8-MOP PUVA was superior for patients with severe plaque psoriasis. A further randomised parallel study by Markham[88] *et al.* involving fifty-four patients found that twice weekly PUVA was as effective as thrice weekly nbUVB in achieving clearance of chronic plaque psoriasis.

However, a retrospective study examining the remission rates between PUVA and NBUVB, found no statistically significant difference between the two. Although, PUVA-treated patients remained clear for a period of about 88 days longer than patients treated with nbUVB[89].

PUVA may be administered alone or in combination with other treatments to minimise PUVA dosage. There are conflicting reports

regarding remission periods when topical steroids are combined with oral PUVA. One study found this combination resulted in faster clearance without reducing the period of remission; whilst another study found the addition of topical steroids resulted in shorter remissions.[90,91] The combination of topical vitamin D analogues (calcipotriol) with PUVA has been reported to decrease duration of PUVA therapy with an improved clinical response.[92]

A potent therapeutic regimen for psoriasis involves the combination of PUVA with systemic retinoids (RePUVA). RePUVA reduces the number of exposures as well as the total cumulative UVA dose and is particularly useful in "poor PUVA responders." An additional advantage of systemic retinoids is that they may suppress the development of non-melanoma skin cancers.[93]

Isotretinoin and PUVA was reported to provide a good response in four young adult females. This is particularly important for women of child-bearing potential for whom acitretin is contraindicated[94]. Women are still advised to avoid pregnancy for at least 31 days after stopping isotretinoin.

A recent randomised comparison of acitretin with narrow-band (nb)UVB and acitretin with PUVA in 60 patients with moderate-severe plaque psoriasis was undertaken. Efficacy was assessed using PASI scores by a blinded observer. Clearance was achieved in 56.6% of patients with reUVB compared to 63.3% in rePUVA group. This cohort of

patients remained clear three months after completing treatment, irrespective of whether they had received nbUVB or PUVA[95].

Studies have compared bath-water delivery of 8-MOP to oral 8-MOP. Lowe[96] *et al.* found bath PUVA to be as effective as oral PUVA, requiring less UVA and no associated systemic side effects such as nausea. The study by Collins[97] *et al.* involving 44 patients confirmed these findings. The therapeutic efficacy of bath PUVA may well be due to the higher penetration of psoralens through abnormal stratum corneum over psoriatic plaques compared to normal peri-lesional skin.

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Palmoplantar Putulosis (PPP)

Palmoplantar pustulosis (PPP) is a chronic condition characterised by a vesiculopustular eruption affecting the palms and soles. PPP may be associated with autoimmune diseases including thyroid disease and diabetes mellitus. Genetic studies on PPP however, have not shown a link to the same loci as psoriasis vulgaris. The relationship between these two conditions is controversial.

Treatment of PPP is often challenging and unsuccessful. Nevertheless, a reasonable degree in efficacy of oral PUVA when compared to placebo has been established in the management of PPP. Both Murray[98] *et al.* (1980) and Rosen[99] *et al.* (1987) found that patients with PPP improved on systemic PUVA. In Murray's cohort of patients, all 22 showed improvement and 12 patients had clearance of disease. Results for placebo showed improvement in 12 patients and no patients had clearance. In Rosen's within-patient comparison of oral PUVA versus placebo, 9 of 14 (64%) and 2 of 14 (14%) PPP patients showed improvement with oral PUVA and placebo respectively. However, only 3 of 14 patients had clearance of disease with oral PUVA.

There does not appear to be any benefit of topical PUVA in PPP. Layton[100] *et al.* (1991) and Matsunami[101] *et al.* (1990) failed to show any benefit of topical PUVA over placebo. These findings are consistent with those of Lassus[102] *et al.*1985.

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There is no additional advantage of using short-term PUVA following induction of remission with topical steroid under occlusion. Nielsen[103] *et al.* 1995, showed that a third of PPP patients (3 of 9) receiving short term PUVA did not relapse within one year compared to 6 of 13 patients who did not receive further intervention.

Two studies have compared PUVA with etretinate. The study by Rosen comparing oral PUVA to etretinate did not show a definite benefit of retinoids over PUVA or vice versa. Lassus' study used topical and systemic PUVA. Lassus found the use of etretinate to be more effective. Yet the results of Lassus' study showed generally lower response rates for all PUVA modalities than other studies. Overall, there does not appear to be a significant difference between PUVA and retinoids.

This is supported by a Cochrane Systematic Review of interventions for chronic palmoplantar pustulosis in which twenty-three trials involving 724 people were included. The evidence supporting the use of systemic retinoids, showed an improvement rate difference of 44%, (95% confidence interval [CI] 28% - 59%). Oral PUVA showed an improvement rate difference of 44% (95% CI 26% – 62%). However, when the modalities are combined, retinoids and PUVA (rePUVA), the outcome is superior to a single treatment modality[104].

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Atopic Dermatitis

Atopic Dermatitis (AD) is an intensely pruritic skin condition that usually starts around three months of age. AD clears in approximately 50% of children by puberty. In others, AD is persistent or recurrent in adult life. Clinically, AD is characterised by xerosis (dry skin), pruritus, eczematous lesions and lichenification. AD is more commonly associated with a personal or family history of atopy (asthma, eczema or allergic rhinitis); however environmental factors also play a role. The pathophysiology of AD is poorly understood. Defective epidermal barrier function (due to loss-of-function mutations in the gene encoding fillaggrin) and an imbalance of T lymphocytes (T_H2 predominance) causing an increase in IgE sensitisation play a major role.

Patients with moderate to severe (including erythrodermic) eczema have benefitted from PUVA. Oral PUVA has successfully been used to treat severe atopic eczema in adolescents. 14 out of 15 children had initial clearance, nine of whom achieved complete remission. Resumption of normal growth in children previously growing poorly occurred[105]. In a subsequent update of oral PUVA, to treat severe childhood eczema, thirty-nine out of fifty-three children who received twice weekly treatment, achieved clearance or near-clearance after an average of 9 weeks[106]. Bath PUVA markedly improved pruritus, night-time rest and severity of lesions in 29 adults with severe atopic dermatitis. Three patients discontinued treatment due to aggravation of

their disease. The patients received thrice weekly treatments for a maximum of 30 sessions[107]. However, in comparison to psoriasis, atopic dermatitis is more difficult to treat and generally requires a greater number of treatments. Patients are younger and relapse rates are high.

In a randomised control trial comparing nbUVB, UVA and fluorescent light exposure for adults with atopic dermatitis, nbUVB was more effective as an adjunctive treatment for moderate to severe atopic eczema. The treatment was well tolerated by most patients.[108]

A systematic review of photo(chemo)therapy in the management of AD, including nineteen randomised controlled studies (905 participants) highlighted the need for further well-designed, adequately powered RCTs.[109] A meta-analysis was not feasible due to the heterogeneity of RCTs due to small sample sizes, varying study quality and occasionally the absence of direct comparisons. The conclusion on the evidence provided was that UVA1 and nbUVB appeared the most effective treatment modalities for the reduction of clinical signs and symptoms. There is also evidence suggesting that UVA/UVB was more effective than UVA and broadband-UVB for the improvement of clinical symptoms, but not compared with UVA1.[110]

UVA1 is a promising phototherapeutic modality for acute severe, atopic eczema. As for nbUVB phototherapy it is administered for a limited period of time (ten to fifteen exposures). Efficacy for UVA1 in eczema

appears to be dose-dependent[111]. A detailed discussion on UVA1 is beyond the scope of this thesis.

Mycosis Fungoides (Cutaneous T-Cell Lymphoma–CTCL)

Cutaneous T-cell lymphomas (CTCLs) are a group of lymphoproliferative disorders characterised by a neoplastic clonal proliferation of T-cells localised to the skin. Mycosis fungoides is the commonest CTCL. The choice of treatment and prognosis are related to the stage of the disease[112].

- Stage I – patches and plaques involving less than 10% (IA) or more than 10% (IB) of the skin
- Stage II – as stage I, with non-malignant lymphadenopathy (IIA) or cutaneous tumours (IIB)
- Stage III – generalised erythroderma
- Stage IV – malignant infiltration of blood (IVA), lymph nodes (IVA2), viscera (IVB)

Gilchrest *et al.* were the first to report successful use of PUVA for CTCL[113]. All nine patients treated with oral 8-MOP and UVA responded well; four remained in complete remission. Based on the data of five studies and a total of 244 patients, Hermann[114] *et al.* calculated the rate of complete remission after an initial course of PUVA to be 90% for IA,

76% for stage IB, 78% for stage IIA, 59% for stage IIB%, and 61% for stage III (staging according to the 1979 Bunn Classification).

The relapse rate and disease-free survival for MF treated with PUVA is less well documented. Querfeld *et al.* published data on 66 CTCL patients (stage IA – II) who achieved complete remission after an initial course of PUVA. Patients were followed-up for up to 242 months. The 5- and 10-year disease-free survival rates for patients with T1 disease were reported as 56% and 30%, respectively, and 74% and 50% for T2.[115]

The results of a recent multinational survey amongst dermatologists showed that 88% of respondents used PUVA as maintenance therapy after disease clearance has been achieved. However, there was no consensus on frequency, UVA-dose or duration of PUVA therapy.[116] This is despite the published data on carcinogenic risk associated with PUVA (Stern *et al.*). Furthermore, EORTC have recently published their consensus report and suggest avoiding maintenance PUVA.

For patients with advanced disease (tumour stage or lymph node involvement), PUVA may be used in combination with other systemic agents. These include: interferon-α (IFN-α), retinoids (isotretinoin, etretinate, acitretin) and more recently bexarotene, (a retinoid that binds to the nuclear retinoid X receptor). Although these drugs are effective monotherapeutic agents, combination with PUVA is likely to have an additive effect. However, whether any PUVA combination is superior to

PUVA alone in terms of clinically relevant endpoints (e.g. toxicity, disease-free survival, overall survival) remains unanswered[117].

Vitiligo

Vitiligo is an idiopathic, common acquired pigmentary condition and can have a profound psychosocial affect on individuals. Loss of epidermal melanocytes results in patchy or rarely complete depigmentation. The average age of onset is 20 years although vitiligo may appear in childhood. Several hypotheses have been proposed to explain the aetiology of vitiligo, including autoimmune, hereditary, neural, biochemical (including oxidative stress), and environmental, which may interact to contribute to its development.

Vitiligo was the first disease to be treated by psoralen photochemotherapy in ancient Egypt and India. The mechanism by which PUVA induces repigmentation remains speculative. There may be an immunomodulatory response suppressing the stimulus for melanocyte destruction as well as promotion of melanocyte division. PUVA had been considered the gold-standard treatment for vitiligo until recently.

Patient selection and counseling are extremely important. Oral PUVA may be considered suitable for patients with extensive disease. For patients with smaller lesions (less than 5% total body surface area),

topical 8-MOP is preferred. However, results are variable. The total number of treatments required is between 50 and 300 for extensive disease. A complete course of treatment for segmental vitiligo, on average, requires 150 treatments. If there is **no** response after 4-5 months (approximately 30-40 treatments) treatment should be discontinued.

Complete repigmentation is achieved in only a few patients. Patients with darker skin types appear to show better responses to PUVA. Furthermore, repigmented areas may remain stable for decades. However, if therapy is discontinued, partial repigmentation may reverse[118]. A 10-year retrospective study involving 97 patients found this treatment to be moderately effective in widespread vitiligo. There was a high relapse rate within a year of discontinuing therapy. Younger patients tended to retain their pigmentation longer than older patients.[119]

Khellin, a furanochromone extracted from the plant *Ammi visnaga,* is structurally similar to 8-MOP, and possesses similar photochemical and phototherapeutic properties. It has been used, both topically and orally, in conjunction with UVA (KUVA) in the treatment of vitiligo. The major advantage of khellin is its lack of phototoxicity. However, approximately 30% of vitiligo patients receiving oral khellin developed reversible increases in hepatic transaminases for unknown reasons presumably from the khellin.[120]

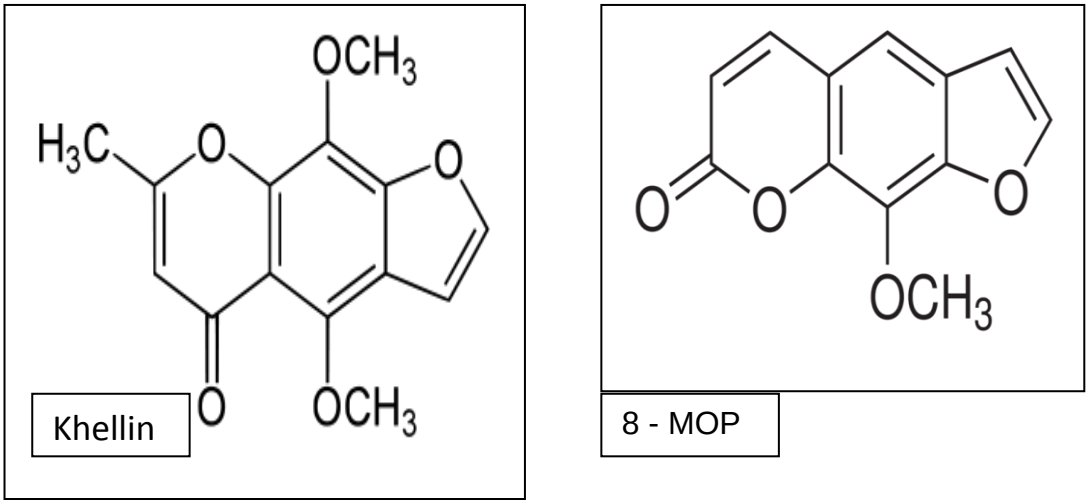

Figure 1.4: Comparing Structure of Khellin and 8-MOP

Topical khellin 4% ointment has been applied to vitiliginous skin 20 minutes before UVA or sun exposure. Although there were fewer side-effects compared with topical PUVA, topical khellin was less effective.[121]

There is growing evidence that nbUVB may be superior to PUVA for treatment of vitiligo. In 1997, Westerhof *et al.* compared 311-nm UVB and topical PUVA for the treatment of vitiligo. 28 patients were treated with topical PUVA for 4 months and 78 patients received 311-nm UVB for 4 months. Repigmentation rates were 46% and 67% for PUVA and UVB respectively.[122] The first bilateral comparison study comparing nbUVB to PUVA in 15 adult patients showed no significant difference in clinical response after 60 sessions[123]. Parsad *et al.* published their retrospective comparison of 38 patients on oral PUVA and 31 patients

on NBUVB. Their results showed a significantly better outcome for NBUVB[124]. Fifty non-segmental vitiligo patients were randomly allocated to thrice weekly treatment with nbUVB and oral TMP-UVA in an open prospective study. Although the mean treatment duration was longer for nbUVB (6.3 months) than oral TMP UVA (5.6 months), nbUVB was found to achieve superior results regarding efficacy and stability[125]. Yones *et al.* conducted the first randomised, double-blind trial comparing efficacy of nbUVB vs. oral 8-MOP (or 5-MOP) UVA in 50 patients with non-segmental vitiligo. Treatment was given twice weekly and patients were assessed after every 16 sessions. At the end of the study, the PUVA group had received a mean of 47 treatments. Patients in the nbUVB group received 97 treatments. Results showed that 64% of patients in the nbUVB group experienced >50% improvement compared with 36% of patients in the PUVA group. The colour match of repigmented skin was also excellent in all patients treated with nbUVB but in only 44% of those treated with PUVA. The authors concluded that nbUVB is superior to oral PUVA[126].

Table 1.4 Studies on Vitiligo comparing nbUVB Vs PUVA

Author	Year	No. Patients	Findings
1997	Westerhoff *et al.*	116 – Extensive Vitiligo	4 months topical PUVA (n=28) vs. 4 months 311nm UVB; Repigmentation rates 46% PUVA; 67% 311nm UVB
2006	El Mofty *et al.*	15	Bilateral comparison study nbUVB vs. PUVA; No significant difference between treatment modalities.
2006	Parsad *et al*	69	Oral PUVA (n=38), nbUVB (n=31); nbUVB significantly better results
2007	Bhatnagar *et al.*	50	Open prospective trial; Thrice weekly nbUVB vs. Oral TMP-UVA; nbUVB superior efficacy and stability
2007	Yones *et al.*	50	Double-blind Randomised Control Trial; Twice weekly Oral 8-MOP (or 5-MOP) vs. nbUVB. 36% patients PUVA group and 64% patients in nbUVB group showed >50% improvement. Repigmentation in nbUVB closer colour match than PUVA.

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Generalised Lichen Planus

Lichen planus (LP) is a chronic inflammatory idiopathic condition that manifests as a pruritic papulosquamous disease. In most cases of LP, disease severity is mild and treatment is limited to topical therapy (superpotent corticosteroids). Severe cases may have greater disability requiring more aggressive therapy such as oral steroids. nbUVB, acitretin or PUVA.

Gonzalez *et al.* treated 10 patients with oral 8-MOP PUVA in a bilateral comparison study. Five patients cleared completely and did not require further treatment during the 4-year follow-up. Three patients improved by at least 50%, however 2 patients experienced disease exacerbation on the treated side. Maintenance treatments may not be required once remission is attained[127]. Helander *et al.* found bath PUVA to be superior to oral PUVA. 13 patients received bath PUVA, 10 patients had oral PUVA. Good or excellent clearing occurred in 10 (77%) patients following eight to forty-six treatments with bath PUVA. Only 5 (50%) patients maintained similar results after eight to thirty treatments with oral PUVA. Early relapses occurred with both regimens[128]. Combined RePUVA regimen may accelerate clearance of generalised and hyperkeratotic forms of lichen planus.

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Cutaneous Graft versus Host Disease (GVHD)

Acute and chronic graft-versus-host disease (GVHD), are multisystem disorders that occur following allogeneic bone marrow transplantation. The skin, liver and gastrointestinal system may individually or collectively be affected. There are 2 forms of this condition: acute and chronic. Acute GVHD occurs within 1 – 3 weeks after transplantation. This typically presents as a maculopapular rash which may progress to erythroderma. Chronic GVHD occurs in 30% to 70% of adults and children surviving more than 100 days post transplantation and presents as a mucocutaneous lichenoid and/or sclerodermatous disease. [129,130]

PUVA was initially evaluated for lichenoid GVHD due to clinical and histological similarities with lichen planus[131]. Beneficial effects were observed in patients who were non-responsive to conventional immunosuppressive therapies. Unlike other conditions, PUVA may exert systemic effects. Improvement of mucosal erosions has been observed during treatment of chronic lichenoid GVHD. However the results of PUVA treatment for sclerodermoid GVHD are controversial.

PUVA has also been used in acute GVHD. Reinauer *et al.* treated six acute cutaneous GVHD grade II III (n=2 grade II, n=4 grade III) patients with PUVA. All patients improved markedly after 5-12 sessions of irradiation. 5 patients had complete resolution of skin disease with 8-18 treatments. Following clearance of acute cutaneous GVHD, 2 patients

developed chronic GVHD after therapy-free intervals of 3 and 12 months, respectively. PUVA confers a protective effect against chronic GVHD[132]. Oral 8-MOP PUVA has also been successfully used to manage severe erythrodermic acute GVHD, in a 34 year-old male due to myeloid leukaemia.[133]

Prurigo Nodularis / Pruritus

Prurigo nodularis is an intensely pruritic condition characterised by multiple papules/nodules occurring on extensor aspects of limbs and the trunk. The cause is unknown. Topical antipruritic agents including menthol or the use of potent topical corticosteroids (under occlusion) are often inadequate.

The antipruritic effect of UV light appears to be effective in the management of this chronic inflammatory skin disease. Fifteen patients with prurigo nodularis reported a dramatic improvement of their itching within 4 – 6 days following treatment with trioxsalen baths and UVA[134]. Hans *et al.* treated two patients with thrice weekly UVB to a maximum of 30 treatments. Residual lesions were treated with intralesional corticosteroids and topical PUVA[135]. However, patients frequently relapse following short-term treatment. Hammes *et al.* found the combination of UVB 308nm excimer light and bath PUVA to be an effective treatment modality. 22 patients were included in their prospective study. They received either PUVA alone or in combination with excimer UVB. Patients were followed-up four weeks after

completion of treatment. The cumulative PUVA-only dose was greater (23.7 ± 4.5 J/cm^2) than the combination group (16.9 ± 2.7 J/cm^2). One patient remained in remission in both groups; however, all patients showed a long-term benefit with a notable reduction of itching[136].

Urticaria Pigmentosa

Urticaria pigmentosa is one of the most common forms of mastocytosis, due to an excessive accumulation of mast cells in the skin of uncertain cause. Multiple organs (including the bone marrow, spleen, lymph nodes, gut, lungs and bone) may also be involved.

The disease is more common in children than in adults. The exact incidence is unknown. About 75% of cases occur during infancy or early childhood. Incidence peaks again in mid-adulthood (30 to 49 years). Adults are more likely to develop systemic disease.[137] The skin lesions are characterised by brown macules or papules that urticate when rubbed (Darier's sign).

Oral PUVA may be an effective long-term treatment of urticaria pigmentosa as well as systemic mastocytosis. Godt *et al.* [138] investigated the long-term efficacy of oral PUVA treatment and bath PUVA in urticaria pigmentosa and systemic mastocytosis. Twenty patients treated by oral PUVA and four patients treated by bath PUVA, were examined retrospectively for a period of up to 18 years. 70% of patients treated with oral PUVA therapy showed an improvement.

Remission rates ranged from a few weeks to more than 10 years. 25% of the patients showed an improvement for more than five years. There was no difference in the response rate between urticaria pigmentosa and systemic mastocytosis nor was there a correlation with the total PUVA dosage. Younger patients (children and early adolescents) with skin types I and II responded better to treatment. Bath PUVA however was ineffective[138].

Other

Generalised Granuloma Annulare

Granuloma annulare (GA) is an idiopathic disorder with several clinical variants, of which generalised GA is one. Generalised GA tends to be seen in older patients and is characterised by numerous (>10) flesh-coloured or erythematous papules. The histological hallmark is necrobiosis surrounded by a lymphohistiocytic infiltrate.

There have been reports of complete clearance of generalised GA following PUVA[139] however, long-term maintenance treatment on a weekly or twice monthly basis was required to maintain remission. Browne *et al.*140 conducted a retrospective study of 33 patients with generalised GA over 13 years (1995 – 2008). Patients were treated twice weekly with oral 8-MOP PUVA (38 treatments), while bath PUVA was used in six treatments. Patients who were intolerant of oral 8-MOP

received 5-MOP. The maximum dose of UVA administered was 12 J/cm^2. Although, there was a good initial response, the majority (68%) relapsed within 2 years.[140]

Localised Sceroderma

Localised Scleroderma (LS), also known as morphoea, is a chronic, localised hardening and thickening of the skin. Lesions are categorised according to their appearance: morphoea (guttate, profunda, pansclerotic) or linear (with/without melorheostosis or hemiatrophy). There is a female:male preponderance 2:1. Characteristic features include skin ischaemia, lymphocytic infiltrates, swollen collagen bundles, and thickening of the dermis with reduction of subcutaneous fat.

Localised scleroderma and pansclerotic morphoea have both been successfully treated with bath PUVA and oral PUVA. In 1994, Kerscher *et al.* reported the first two cases of LS treated with bath PUVA. Patients received 30 treatments over 10 weeks (maximum single dose of 20J/cm^2) leading to almost complete clearance of lesional skin.[141] Evaluation of 17 patients receiving bath PUVA, revealed a marked improvement in 13 patients who had received 15 treatments[142]. The maximum dose ranged between 1.2J/cm^2 - 3.5J/cm^2. Pasic *et al.* found bath PUVA useful in the treatment of childhood LS[143].

CHAPTER ONE

Introduction

Pityriasis Lichenoides (acute and chronic)

Pityriasis lichenoides (PL) is a self-limiting papulosquamous skin disease with a spectrum of clinical manifestations. These range from pityriasis lichenoides et varioliformis acuta (PLEVA), characterised by rapid development of necrotic lesions associated with fever and systemic involvement, to pityriasis lichenoides chronica (PLC), a chronic relapsing variant. There are also overlapping forms of the condition. Phototherapy has commonly been employed in the treatment of patients with PL.

Fifteen patients were randomised to receive either oral 8-MOP PUVA (8 patients) or nbUVB (7 patients). Patients receiving nbUVB had 200 mJ $/m^2$ initially and then three times weekly. The dose was increased by 10% at each visit. For PUVA, doses for patients with Fitzpatrick skin type I-III was 1–1.5 J $/m^2$ and 2 J $/m^2$ for patients with skin type IV–V. The dose increment was 2 J $/m^2$ every two sessions. Results were equivocal in bothgroups, 87.5% patients treated with nbUVB and 71.4% patients treated with PUVA showed good response.[144]

CHAPTER ONE

Introduction

Lymphomatoid Papulosis

Lymphomatoid papulosis (LyP) is part of a spectrum of CD30 (Ki-1)–positive cutaneous lymphoproliferative diseases. Histologically, LyP has features suggestive of a malignant lymphoma. However, there is on-going debate whether to classify this chronic papulonecrotic or papulonodular skin disease as a true malignancy due to its spontaneous resolution and benign clinical course.

Experience with PUVA is limited to a small case series. 5 patients with lymphomatoid papulosis were treated with PUVA. 4 patients had classical lymphomatoid papulosis; the other patient had 1-2 cm tumours. Doses ranged between 51-124 J/cm^2 for the patients with classical lymphomatoid papulosis, whereas the patient with tumours received 481 J/cm^2. The total number and life-cycle of the lesions decreased in all patients. One patient, who had the disease for one year prior to PUVA treatment, entered complete remission whilst the remaining patients had partial remissions. The authors suggested that early treatment equated to a better response. However, there was no subsequent follow-up data to comment on long-term prognosis[145].

CHAPTER ONE

Introduction

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a rare disease characterised by clonal proliferation of Langerhans cells and cytokine over-production. This results in inflammation and tissue destruction. LCH may affect a single or multiple organ systems. Commonly involved sites include bone, skin, lung, reticulo-endothelial system and other organs. Treatment is dependent on the organ(s) affected and severity of disease. LCH may occur at any age.

A 32 year-old Caucasian female with generalised eruptive histiocytoma (GEH) was treated with systemic PUVA. Following 20 treatments, the skin lesions completely resolved with no relapses[146]. A 23-year-old man with LCH was treated with oral 8-MOP PUVA three times weekly for two months and then once or twice with maintenance phototherapy. There was no recurrence of lesions during the four-month follow-up period.[147] A 74-year old male with LCH skin disease was successfully treated with PUVA.[148]

CHAPTER ONE

Introduction

Purpuric Pigmented Dermatoses

Pigmented purpuric dermatoses (PPD) are a group of chronic recurring disorders of unknown aetiology. They are characterised by purpuric lesions mainly involving the lower extremities.

Treatment of this condition is generally unsatisfactory. There have been case reports of successful treatment following PUVA therapy, with patients being maintained in remission. Krizsa *et.al* managed seven patients who had pigmented purpuric lichenoid dermatosis (Gougerot-Blum) with PUVA. All patients cleared after seven to twenty treatments. The cumulative dose of UVA dose ranged between 16–49 J/cm^2. 5 patients remained in remission (7 - 76 months). Two relapsing patients responded to a second course of PUVA therapy. Similar outcomes were reported in another series involving eleven PPD patients (five had Schamberg's disease, five had Gougerot-Blum and one had eczema-like purpura of Doucas and Kapetanakis) [149,150,151]

CHAPTER ONE

Introduction

Pityriasis Rubra Pilaris

Pityriasis Rubra Pilaris (PRP) is an uncommon group of papulosquamous skin diseases of which there are 6 types. The most common is the adult classical type (type I). This is characterised by follicular keratoses, palmoplantar keratoderma and abrupt onset of erythroderma with islands of sparing of normal skin.

There is inconsistency regarding results of PUVA as a treatment modality for PRP. Some patients have successfully been treated with bath PUVA whilst others may flare requiring treatments with methotrexate or retinoids. [152,153]

CHAPTER ONE

Introduction

Induction of tolerance in photosensitivity disorders

Polymorphic Light Eruption (PLE)

PLE is the most common photodermatoses and develops within hours and may persist for days following exposure to sunlight. However, with repeated exposures to sunlight, the tendency to develop PLE in most patients diminishes with time by a phenomenon known as hardening (tolerance).

PUVA and UVB were compared in a double-blind trial involving 42 patients between April-September 1983. Patients were randomly allocated to three groups, PUVA (with oral 8-MOP), UVB with oral placebo, and control low-dose UVA with oral placebo. The treatment groups commenced treatment with a third of the predetermined MPD or MED. Patients received thrice weekly treatments for six weeks. At each visit, doses incremented by an eighth in the PUVA group and by a seventh in the UVB group. Patients' were followed-up at 4months. PUVA appeared to be more effective than UVB from patient's subjective reports.[154]

Narrow-band UVB was compared with oral PUVA in 25 patients thrice weekly for five weeks in the spring. There was no significant difference between treatment groups. 85% of patients in each treatment group were adequately protected from developing PLE in the summer.

However, nbUVB may be a more convenient effective treatment for PLE.[155]

Solar Urticaria

Solar urticaria is a rare form of urticaria occuring within minutes of exposure to sunlight or an artificial light source emitting the appropriate wavelength.

If antihistamines are ineffective then PUVA is indicated. However, pre-PUVA desensitization with UVA is often necessary as patients have been reported to flare with PUVA[156]. Alternatively, PUVA treatment may be fractionated, with small doses of UVA (0·1–0·25 J/cm^2, for example) given every 15 minutes, starting 1 hour after psoralen ingestion. The result is a therapeutically useful cumulative dose, yet individual exposures remain below the threshold required to trigger urticaria.[157]

Omalizumab, an anti-IgE antibody approved for use in chronic spontaneous urticaria, has also been used in solar urticaria with variable results. A 24-year-old patient with solar urticaria received four doses of Omalizumab 150mg subcutaneously at four weekly intervals but had no demonstrable changes in phototesting at the end of the brief study.[158] Three cases of solar urticaria were reported to have been successfully treated with Omalizumab at differing doses.[159] Further

studies are required to investigate the optimal dose and injection interval for such patients.

Chronic Actinic Dermatitis

Chronic actinic dermatitis (CAD) is a condition mainly affecting men over the age of 50 years. It is intensely pruritic and is characterised by inflamed, erythematous, thickened eczematous skin, mainly occurring in sun-exposed areas. Some patients also react to artificial light sources. Patients may have co-existing contact allergic dermatitis, particularly to plants or photo-contact dermatitis for many years before the sensitivity develops. Occasionally, CAD occurs as a persistent eczematous rash following withdrawal of a photosensitizing drug.

Four male patients with severe CAD were treated twice weekly with PUVA. The starting dose of UVA was 0.25J/cm^2 with increments of 0.25J/cm^2 to 1J/cm^2. The maximum dose was 10J/cm^2. Topical steroids were applied to the rest of the body immediately after the first six treatments. All patients responded very well and were maintained on twice monthly PUVA therapy (10 J/cm^2).[160]

CHAPTER ONE

Introduction

Hydroa Vacciniforme (HV)

Hydroa vacciniforme is a very rare, idiopathic photodermatosis occurring in childhood. Patients develop recurrent crops of papulovesicles or vesicles on sun-exposed skin that heal with characteristic varioliform scarring. One male patient received PUVA therapy with good control of his disease.[161] However, in a review of 10 cases, there was a flare of HV in the one patient treated with PUVA whereas there was improvement in two patients who were treated with UVB.[162]

Erythropoietic Protoporphyria

Erythropoietic Protoporphyria (EPP) is a non-acute porphyria due to deficiency in ferrochelatase, the final enzyme in haem biosynthesis. This results in the accumulation of protoporphyrin, the two principal manifestations of which are: acute cutaneous photosensitivity typically occuring in childhood and hepatobiliary disease. Although nbUVB, has been shown to be an effective preventative treatment for photodermatoses and is more commonly prescribed, PUVA may also increase sun tolerance.[163]

CHAPTER TWO

Minimal phototoxic dose (MPD) measurements for topical photochemotherapy using a semiautomated MPD tester

CHAPTER TWO

2.1 Background

Psoralen–ultraviolet A (PUVA) phototherapy has an important therapeutic role in cases of dermatoses recalcitrant to conventional narrowband UVB phototherapy, and is still used particularly in psoriasis, atopic eczema and mycosis fungoides.[80] Initial treatment doses are limited by the sensitivity of unaffected, normal skin. To optimise PUVA phototherapy, it is important to establish the lowest dose of UV radiation that causes a just perceptible erythema – the minimal phototoxic dose (MPD). This enables determination of a safe initial dose. Recommended start doses are 40% of this MPD.

The British Photodermatology Group guidelines[52] also recommend subsequent dose increments based on a percentage (20 – 40%) of the previous dose. The MPD also establishes that sufficient psoralen is present in the patient's skin. If the extent of disease is so widespread as to preclude MPD testing, the initial dose is based on skin phototype.

The traditional method of assessing MPD is cumbersome and time consuming for both patients and staff and requires a separate source of UVA. It involves applying UVA light to skin sensitised with psoralen via eight square apertures through a panel of UVA lamps. A typical patient with psoralen-sensitised skin is required to be seated 20cm from the panel of UVA lamps. The template consisting of 8 square apertures is put on to the patient's lower back and the remainder of the patient's skin is covered to protect from UVA light. Seven of the 8 apertures are

covered with dense removable tape. Each one of the apertures is exposed at a specific time to deliver the appropriate dose of UVA. A timer is set to the maximum time required to deliver the dose sequence (see below) and initiated concurrently with the UVA panel irradiation.

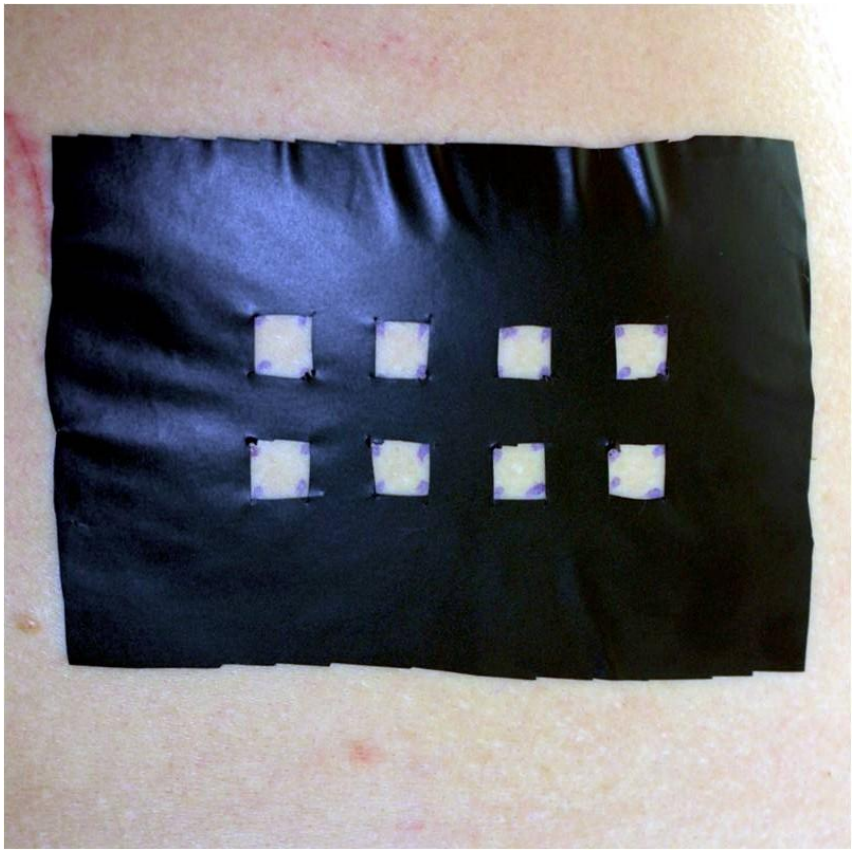

Figure 2.1 MPD Template

Figure 2.2 Template on Back, protection of surrounding skin

Figure 2.3 Patient sitting 20cm from UVA lamps

The dose sequence comprises of the maximum dose as determined by the protocol, with a factor of square root of 2 (1.41) between adjoining areas. Each dose is set in a table with the time requirements to deliver that dose at 20 cm distance from the face of the calibrated output from the UVA panel.

A typical dose sequence is shown below:

2.2 J/cm^2, 1.55 J/cm^2, 1.10 J/cm^2, 0.78 J/cm^2, 0.55 J/cm^2, 0.39 J/cm^2, 0.28 J/cm^2 and 0.20 J/cm^2.

In our unit, this would take 15 - 20 minutes. This 'open' source Is associated with the potential for errors, including UV source non-uniformity due to curvature of the test site, patient movement and exposure timing errors. The difficulties (due to time required, equipment and training) of performing MPD testing discourage its widespread adoption. We are interested in establishing how many phototherapy centres use MPD testing prior to a course of topical PUVA. An easier, safer method of establishing the MPD may encourage more centres to perform this check. A device that overcomes many of these difficulties is the minimal erythema dose (MED) tester used for UVB.[164] This uses a compact fluorescent lamp (CFL) in a handheld housing as the source and a UVB opaque template with 10 x 1-cm-diameter apertures. The output of nine of these apertures is successively attenuated by a factor of $\sqrt[3]{2}$ by steel shaver-type foils. Our previous study established that the test–retest reliability of this method was high.[164] The kappa measure of agreement was calculated for the comparison of two MED tests prepared on the same patient at the same time, and for two MED tests on the same patient but

administered 24 h later. Both scenarios gave agreement of 0.8 or higher, indicating excellent agreement.

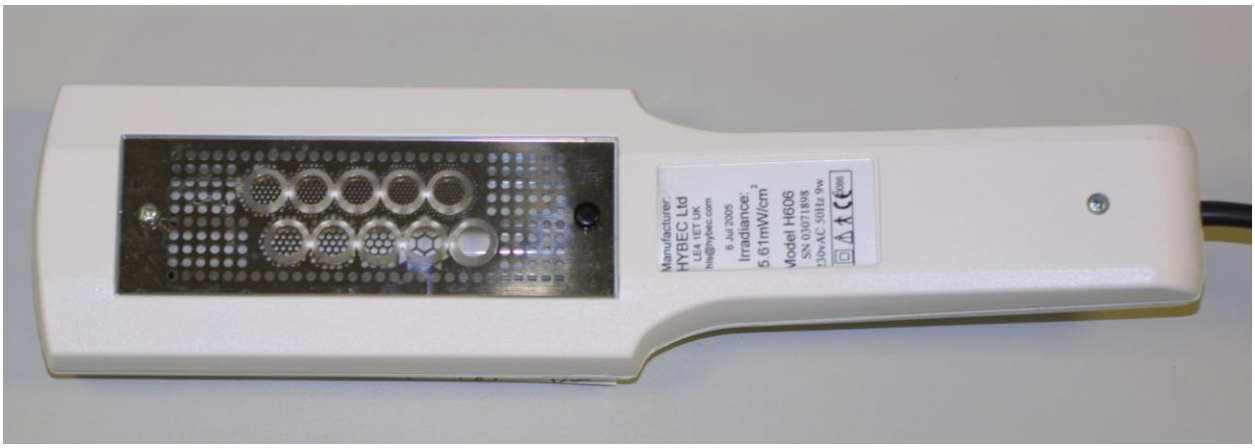

Figure 2.4 Modified Hand-Held Tester

Differences in photosensitivity responses to the same UV dose administered using different magnitudes of irradiance (testing 'reciprocity') have been checked by our group using a high-intensity UVA-1 light-emitting diode source. We found no differences in MED using 100mW/cm^2 and 200 mW/cm^2 intensities. This indicates that there are unlikely to be significant differences between our two MPD methods, which differed in applied UVA-1 irradiance by a factor of 2 (approximately 8 mW/cm^2 for PUVA panel vs. approximately 16 mW/cm^2 for a modified UVA MPD tester).

CFLs with the same UVA spectrum as phototherapy lamps (Philips Cleo series lamps; Philips, Amsterdam, The Netherlands) are not available. As industrial, consumer and medical users of UVA require larger irradiation areas, this has been achieved using traditional 6-foot (180-cm) and 2-foot (60cm) fluorescent tubes. Manufacturers have little

commercial incentive to choose UVA CFL spectra that are exactly the same as those of the larger tube lamps. The nearest equivalent CFL to a PUVA lamp is the Philips TL-10 CFL, which has a narrower spectrum centred around a longer wavelength (370nm).

As PUVA photochemotherapy uses only psoralen as the sensitiser and only PUVA-designated lamps, it should theoretically be possible to establish a fixed factor to convert the observed MPD using the TL-10 CFL to a PUVA-equivalent MPD for all patients. This would be convenient and repeatable, ameliorating many of the disadvantages of the traditional method.

2.2 Aims

1. To assess the results of an MPD measurement technique, using a hand-held UVA lamp with a built-in template with varying attenuators and compare these to those from the standard method of MPD determination using an open UVA light box as the source of UVA.
2. To calculate a fixed factor to convert the observed MPD with the handheld device to a PUVA-equivalent MPD.
3. To assess routine practice concerning MPD testing prior to PUVA therapy in UK phototherapy units.

CHAPTER TWO

2.3 Design of the Study

This was a randomised, left-right comparison study within patients. Patients with psoriasis referred to the phototherapy unit for PUVA treatment at St. Woolos Hospital, Newport were recruited for this study.

2.4 Ethical Approval

Before commencement of this study, ethical approval was obtained from the South East Wales Local Research Ethics Committee. Approval was also sought and obtained from the Aneurin Bevan Healthcare NHS Trust Scrutiny and Risk Review Committee. (Ref No. 05/WSE03/168)

2.5 Written Informed Consent

An information sheet describing the study and procedures to be performed was supplied to each patient prior to their starting the study. The study was fully explained and patients were then required to provide their written, witnessed consent. A copy of the information sheet and consent form is included in appendix I.

CHAPTER TWO

2.6 Study Subjects

A minimum of 30 patients, at least 18 years old referred to the phototherapy unit at St Woolos Hospital for PUVA treatment were selected. Patients were pre-treated with topical psoralen soaking before exposure to UVA.

2.61 Inclusion criteria

1. Aged at least 18 years.
2. No recent sun exposure to lower back / upper buttock skin.
3. Has been referred for PUVA treatment
4. Has signed the consent form after the nature of the study has been fully explained.

2.62 Exclusion criteria

1. Pregnant or lactating females, or females of reproductive potential not using a medically approved form of contraception.
2. Use of medication likely to interfere with the study.
3. Use of an experimental drug within the previous 30 days.

4. History of skin disease or allergy likely to interfere with the study.

5. Unwilling or unable to give written consent.

6. Recent psoriatic plaque at the site of measurement.

2.7 Materials and Method

Dose Range Determination

The lamp used in the handheld MPD tester (Philips TL10, 370nm) differs in its spectrum from the PUVA tubes used for phototherapy treatment. Using the published topical psoralen erythema action spectrum of Cripps *et al*[38], the new lamp spectrum can be weighted to estimate its erythemal potential in psoralen sensitised skin. This technique is described in more detail in Chapter 3.

When the psoralen-equivalent erythema action spectrum was calculated for the TL10 lamp, the predicted erythemal efficacy would be 0.15 times the erythemal efficacy of the PUVA lamps. Dosing schedules for the hand-held MPD tester were calculated using this factor.

A prospective randomised left–right comparison study was carried out on 31 patients with psoriasis due to commence topical PUVA phototherapy. All patients soaked in 30mL 1·2% 8-methoxypsoralen bath lotion (Puvasoralen; Crawford Pharmaceuticals, Knutsford, U.K.), in 140L water (2·6mgL^{-1}psoralen) for 10min at 37°C. All patients

recruited had a template with 8×1-cm or 10×1-cm square apertures with removable covers applied to an uninvolved area of skin of the lower back. The remainder of the patient's skin was fully protected from UV exposure.

A panel of UVA lamps, calibrated for UV irradiance, was positioned 20cm from the patient and was used to illuminate the test site after a warm-up period of 10min. The covers on the test sites were removed sequentially at specific intervals enabling a graduated decrement of UVA dose by a factor of $\sqrt{2}$ between successive sites. The modified handheld MPD tester was used on a symmetrical contralateral site on the lower back. A randomisation table was produced using the random number function in Microsoft Excel to determine the method of MPD testing, i.e. “hand-held” MPD tester versus panel of PUVA lamps, to either right or left side of lower back. Precise positioning of each test was further influenced by the extent and position of the uninvolved skin on that side of the lower back.

The modified handheld MPD tester was calibrated for UV output using a Bentham DM150 spectroradiometer. The DM150 was calibrated against a tungsten lamp which had a calibration from 250nm – 800nm traceable to the National Physical Laboratory. For a calibration with a margin of 8% uncertainty, the compact MPD tester requires a two minute warm-up and 15 minute cool-down between successive MPD tests. MPD test results from a panel of PUVA lamps were compared with the MPD from the modified Durham MPD tester (10 apertures with

1·26 factor between doses). Erythema was assessed 96h later (bath PUVA). Phototherapy nurses assessed MPD reactions according to usual practice. They were not blinded to the test method allocation. Blinding of the assessors was not possible due to the visible characteristic pattern of MPD erythema from the two methods. The hand-held tester was manufactured with circular apertures, whereas the 'homemade' template used square cuts in the self adhesive plastic template. Also, it would have been very difficult to reproduce the tight spacing of the manufactured aperture plate of the Durham tester in adhesive backed plastic.

A questionnaire survey was sent to 78 phototherapy units around the U.K. to gauge current practice concerning usage of MPD testing in phototherapy treatment protocols. Responses from 43 phototherapy units were obtained. The survey comprised five questions including the following:

CHAPTER TWO

1. Which hospital(s) are you based at?

2. Does your department provide a phototherapy service?

Yes ☐

No ☐

3. Do you offer:

(whole-body) Bath PUVA ☐

(localised) Hand/Foot PUVA ☐

Systemic PUVA ☐

4a. Do you routinely assess Minimal Phototoxic Dose (MPD) prior to PUVA phototherapy?

Yes ☐

No ☐ (go to 4b)

4b. Is this because (please circle as appropriate):

i) Treatment is commenced based on Fitzpatrick skin type

ii) MPD assessment is time-consuming

iii) MPD assessment is inconvenient

5. When treating patients with localised topical PUVA (hand/foot) do you:

a) dry the area and irradiate immediately with UVA following immersion in psoralen

b) dry the area and wait 30 mins after immersion in psoralen before irradiating with UVA

c) other (please specify)

It was estimated that accurate completion of the questionnaire would take no more than 3 minutes.

2.8 Results

Thirty-seven patients with psoriasis (17 women and 20 men) aged 18–65years were recruited. Six had inconclusive MPD reactions and were excluded from the studies. This meant that the patient did not have two comparable MPD reactions, only one MPD was visible. In the first patients tested the dose range applied with the modified Durham tester was based on the expected erythemal reaction calculated using the data from Cripps. Some of these applied dose ranges did not elicit an erythemal reaction. For subsequent patients the applied dose range was increased. In other patients the reaction was not present on the handmade template sites. This could have been because of the inherent variability in patient positioning using the older method, or because the patient had been assigned a skin phototype which did not accurately reflect their true psoralen-sensitised skin photosensitivity.

The phototypes of the remaining 31 patients included:

Table 2.1 Phototypes of 31 patients

Skin Phototype	Number of Patients
I	4
II	11
III	12
IV	4

Linear regression was performed on logarithmically transformed data, as a geometric dose series was used, as shown in figure 2.5

The handheld MPD results were linearly related to the PUVA panel MPD results as follows:

PUVA MPD = 0.48 x handheld tester + 0.17 J/cm^2

The measured PUVA MPD was 0·48 times the handheld MPD, not 0·15 as predicted by the published PUVA action spectrum. The ratios of the PUVA MPD to the handheld MPD ranged from 0·43 to 1·08. The PUVA-equivalent MPD differed by a maximum of 0·28Jcm^{-2}higher and 0·26Jcm^{-2}lower than the panel MPD; in 90% of cases the difference was one or fewer MPD categories.

The results of our survey revealed that only six of 43 phototherapy centres (14%) that responded to our survey routinely performed MPD testing. The remainder found the practice was time consuming, and commenced treatment based on Fitzpatrick skin type

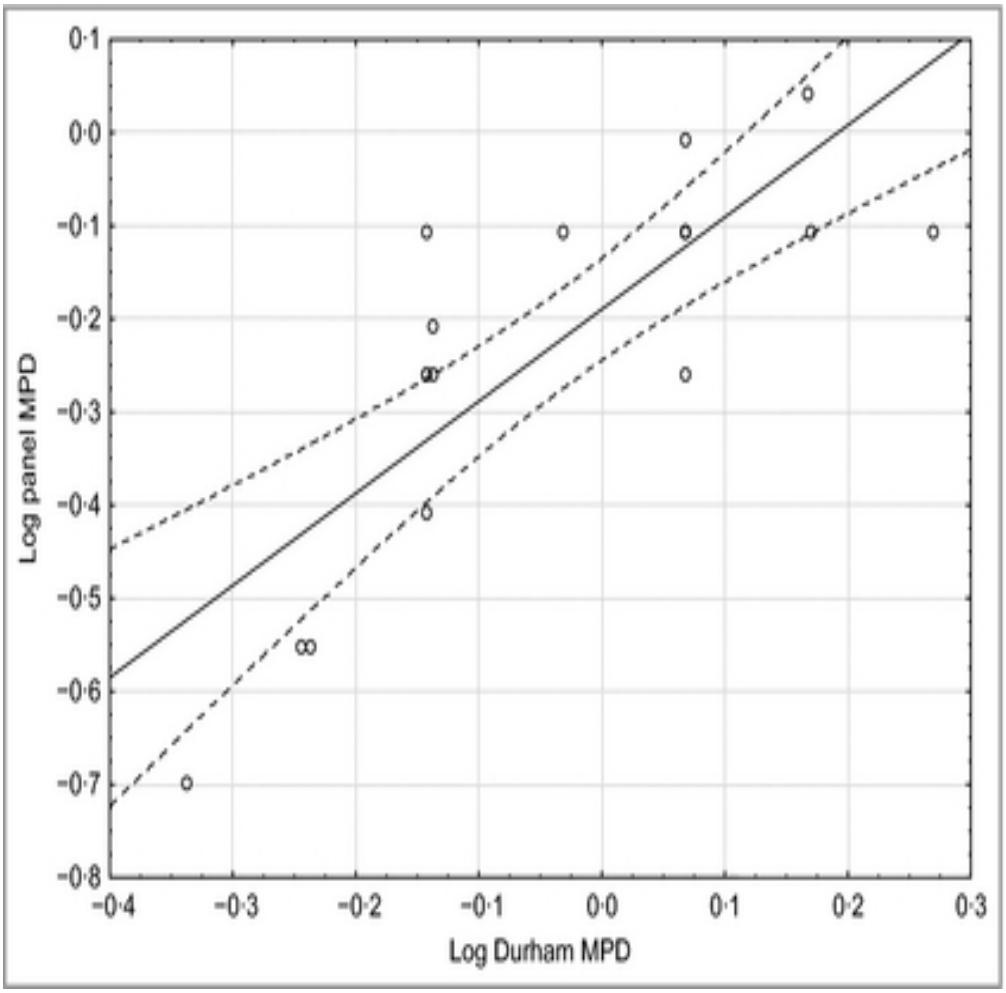

Figure 2.5: Relationship between the logarithmic transformed minimal phototoxic dose (MPD) values determined by the handheld MPD tester and from a panel of psoralen–ultraviolet A lamps. Pearson's correlation coefficient, r = 0·82,P<0·001. Dotted lines represent the 95% confidence intervals about the line of best fit. Overlapping data points are not shown.

2.9 Discussion

The handheld MPD results are linearly related to the PUVA panel MPD results. However, the difference in MPD between the PUVA lamp and the modified handheld MPD tester (CFL TL-10 lamp) was much less

than predicted from the PUVA action spectrum[37]. The erythemal effectiveness of the TL-10 lamp, calculated using the PUVA erythema action spectrum of Cripps *et al*[38], is 2·48, compared with the PUVA lamp effectiveness of 16·33 (arbitrary units). Thus PUVA MPDs should be 0·15 of the TL-10 MPDs. This suggests that formal re-evaluation of the erythema action spectrum for PUVA is now needed. We conclude that the small handheld MED tester, being convenient and reliable, could be made available for MPD testing by replacing the UVB tube with a CFL TL-10 tube. The MPD dose is then adjusted according to our results to indicate a PUVA-equivalent dose.

Furthermore, only 14% of phototherapy centres surveyed routinely assess MPD prior to photochemotherapy, the principle reason being that it is too time consuming.

Results of Questionnaire Survey

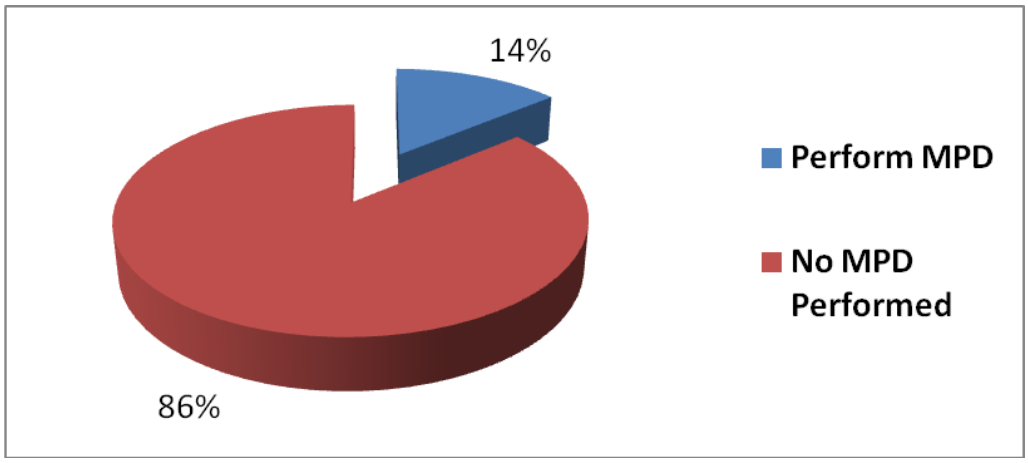

Figure 2.6 Routine Measurement of MPD prior to PUVA exposure

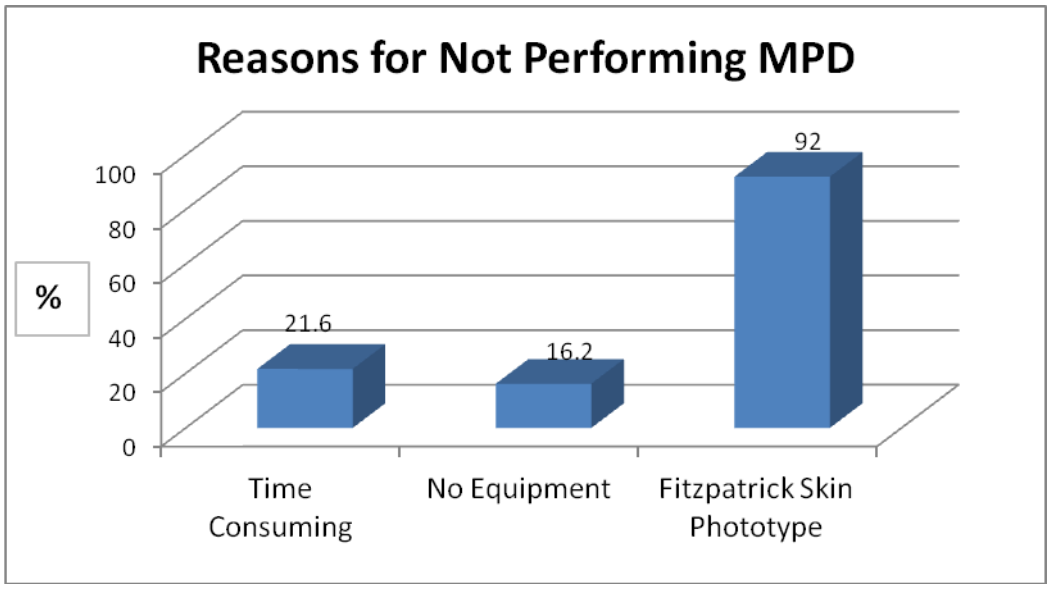

Figure 2.7 Reasons for Not Performing MPD assessment

CHAPTER THREE

Erythema Action Spectrum of Topical Psoralen-Sensitised Skin Re-evaluated

CHAPTER THREE

3.1 Background

Published research on the topical psoralen ultraviolet A (PUVA) erythemal action spectrum has used methods that do not reflect current clinical practice for psoralen sensitization. The study by Cripps *et al.*[38] used 8-methoxy psoralen at 1% dissolved in acetone and then in ethanol and applied (via pipette) directly to the skin of the lower dorsum trunk of 6 Caucasian males. This was then followed by irradiation with various wavelengths of UVA. No details were provided for the time between application of psoralen and UVA irradiation. MPDs were read at 72 hours. Their findings were a peak sensitivity between 330-335nm for 8-MOP, 6 times more effective than 365nm. In the study by Buck *et al.*[34] there was a delay of between 1½ - 2 hrs between application of 1% 8-MOP solution in chloroform and illumination with UVA.

This scenario differs greatly from present clinical practice in the UK, where the skin is immersed in an aqueous solution of 8-methoxypsoralen at 37ºC[39] for 10 minutes, followed by UVA irradiation within 30 minutes. The study by Schempp[40]*et al*. showed there was a marked, significant reduction in erythema after 60 minutes delay between soaking in an 8-MOP bath and irradiation and no erythema was detected after 180 and 360 minute delay. Man *et al*[57] showed that time to develop topical 8-MOP induced erythema had a broad peak at 120 hours. However, MPD assessment during or beyond 120 hours is

best avoided due to confounding effects of the development of pigmentation. Their recommendation was that topical 8-MOP MPD should be read four days (96 hours) after exposure.[52,57] We therefore re-evaluated the PUVA erythema action spectrum using aqueous psoralen at 2.6mg/L concentration as is used routinely in current clinical practice in the UK and assessed MPDs at 96 hours. We then used our action spectrum to estimate the "PUVA equivalent" output of a range of UVA sources.

3.2 Aims

1. To determine a range of the erythema action spectrum of topical 8-MOP solution between 325nm to 375nm on normal skin under the same conditions as used in current clinical practice.

2. To determine the dose-response characteristics of topical PUVA erythema in normal skin.

4. To establish the relative erythemal efficacy of a range of UVA lamps on topical psoralen sensitised skin.

3.3 Design of the Study

This was a dose-response and dose-ranging study involving 20 healthy volunteers. MPD's were established at 6 wavelengths between 325nm

and 375nm at 10nm wavelengths (325nm, 335nm, 345nm, 355nm, 365nm and 375nm). Three defined wavelengths of UVA (325nm – 375nm) were tested on each forearm of each subject. Subjective assessment of erythema and objective assessment of erythema (using an erythema meter, Mexameter MX16, Courage & Khazaka, Cologne, Germany) were recorded for each site at 96 hours.

3.4 Ethical Approval

Before commencement of this study, ethical approval was obtained from the South East Wales Local Research Ethics Committee. Approval was also sought and obtained from the Aneurin Bevan Healthcare NHS Trust Scrutiny and Risk Review Committee. (Ref No. 14/WA/0029)

3.5 Written Informed Consent

An information sheet describing the study and procedures to be performed was supplied to each patient prior to starting the study. The study was fully explained and patients were then required to provide their written, witnessed consent. A copy of the information sheet and consent form is included in appendix II.

CHAPTER THREE

3.6 Study Subjects

Twenty healthy volunteers were recruited.

3.61 Inclusion criteria

1. Age range 18 – 65 years.
2. Normal skin.
3. No significant illness.
4. Has signed the consent form after the nature of the study has been fully explained.

3.62 Exclusion criteria

1. Presence or history of significant skin disease.
2. Significant concurrent illness likely to interfere with the study including malignancy.
3. Use of medication likely to interfere with the study, including immunosuppressant and photosensitising drugs.
4. Pregnant or lactating females
5. Unwilling or unable to give written consent.

CHAPTER THREE

3.7 Method

Following approval by the South East Wales Local Research Ethics Committee, a prospective randomised single-blinded study was carried out on 20 healthy volunteers with skin phototypes I-V. A randomisation table was produced using the random number function in Microsoft Excel to determine the location of each wavelength to either right or left forearm. The position of each wavelength test area was not blinded to the assessors. The Boston classification of skin phototype was determined in all volunteers.[58] Their forearms were soaked in 2.5mL 1·2% 8-methoxypsoralen bath lotion (Puvasoralen; Crawford Pharmaceuticals, Knutsford, U.K.). in 10L water (2·6mgL^{-1}psoralen) for 10min at 37 C. After drying the area, a template made from opaque Fablon (sticky backed plastic) with 18 holes (6 mm diameter) in a grid pattern was applied to the volar forearms 2cm from the antecubital fossae to facilitate accurate irradiation of the test sites, and again at the time of reading to help identify the previously irradiated sites. UVA irradiation was then applied. Six UVA irradiations at 10nm intervals with centre wavelengths between 325nm – 375nm were administered to each volunteer's volar forearm skin (3 wavelengths per forearm) using a 1Kw xenon arc irradiation monochromator (components from Newport Oriel, USA) with a full width at half maximum (FWHM) bandwidth of 10nm. A water filter removed infra-red radiation. A Schott WG320 filter was used to reduce the UVB content. The UVB content at each

wavelength band was checked from their measured spectra. The 325nm spectrum contained less than 0.1% UVB, while all other wavebands used contained less than 0.01% UVB

For each volunteer at each wavelength the irradiance at the application face of the light guide was measured using a calibrated radiometer. This was used to calculate the times (minutes:seconds) required to apply the dose sequence for that wavelength to the volunteer's skin.

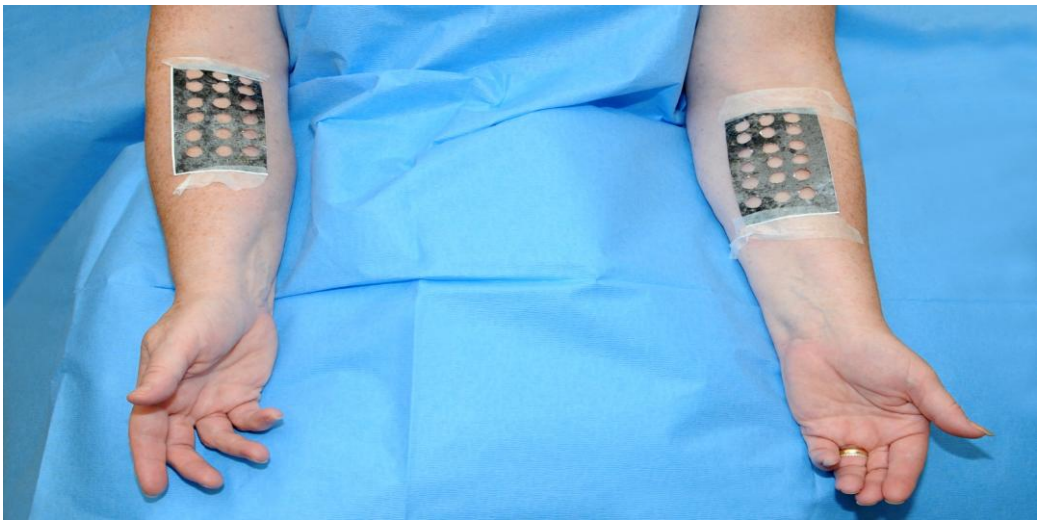

Figure 3.1 Templates on volunteer's forearms

CHAPTER THREE

Measured irradiances at each centre wavelength ranged as follows:

Table 3.1 Measured Irradiance for each wavelength

Centre Wavelength (nm)	Irradiance (mW/cm^2)
325	24.2 – 36.6
335	33.6 – 49.6
345	39.8 – 59.5
355	48.9 – 66.6
365	52.5 – 71.8
375	58.0 – 75.2

Figure 3.2 Application of dose sequence for wavelength

Each site was irradiated with a sequence of geometrically increasing (40% increment) doses via a liquid light guide with a circular area of 5mm diameter. Erythema was measured using an erythema/melanin meter (Mexameter, Courage and Khazaka) at each of the 6 sites. One measurement of non-irradiated skin at each of the 6 sites was also recorded. Visual assessments of erythema were recorded agreed by 2 observers and recorded for each site at 96 hours. At each wavelength the dose required to elicit a barely perceptible erythema was designated as the MPD for that particular wavelength.

3.8 Results

Boston phototypes in the 20 volunteers (14 females, 6 males) with mean age 44.5 years (range: 23-67years) were as follows:

Type I; two;

Type II; six;

Type III; six;

Type IV; five

Type V; one.

The mean MPD (J/cm^2) for all subjects at each wavelength was as follows:

325nm-0.64(SD 0.37); (0.27 – 1.77)

335nm–0.80(SD 0.58); (0.27 – 2.5)

345nm–0.96(SD 0.55); (0.35 – 2.5)

355nm–1.50(SD 0.85); (0.44 – 3.2)

365nm–2.19(SD 0.90); (0.53 – 4.5)

375nm–2.89(SD 1.06). (0.53 – 4.5)

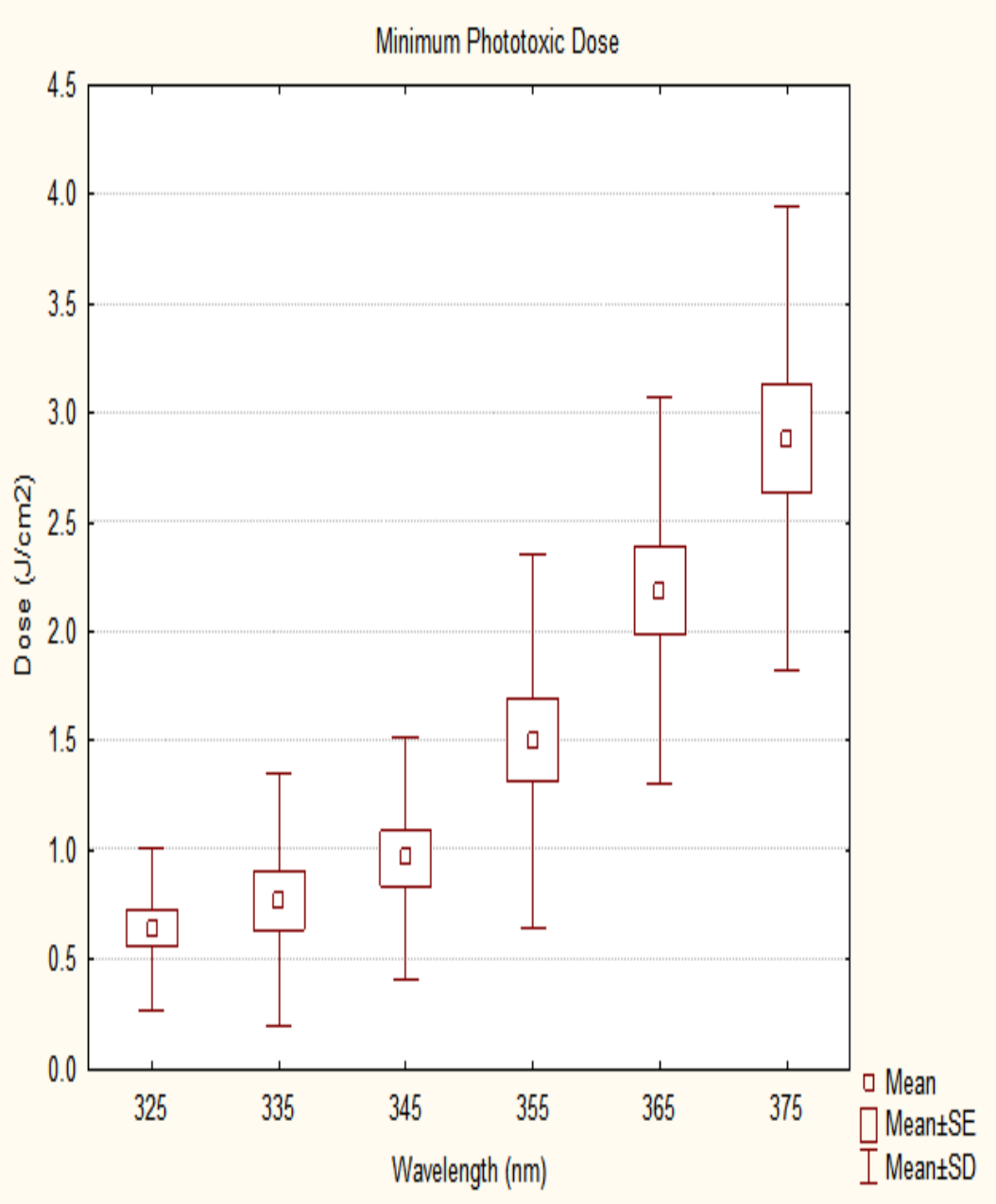

Figure 3.3: Minimal Phototoxic Dose (MPD) of all volunteers at each wavelength

PUVA erythemal effectiveness was determined by wavelengths (ANOVA $p<0.05$).

There were no significant differences between the PUVA erythema action spectrum and skin types.

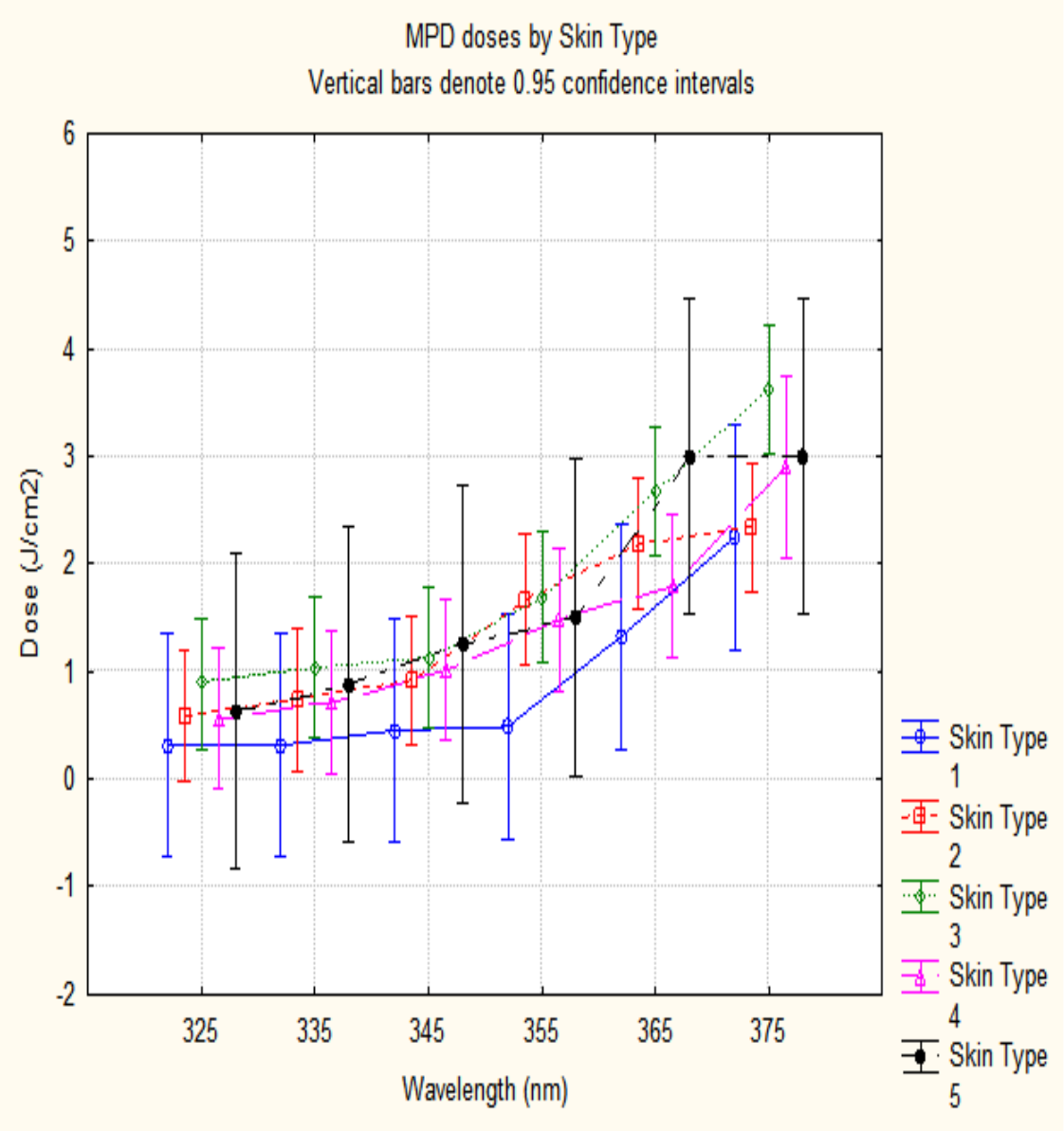

Figure 3.4: MPD by Skin type at each wavelength

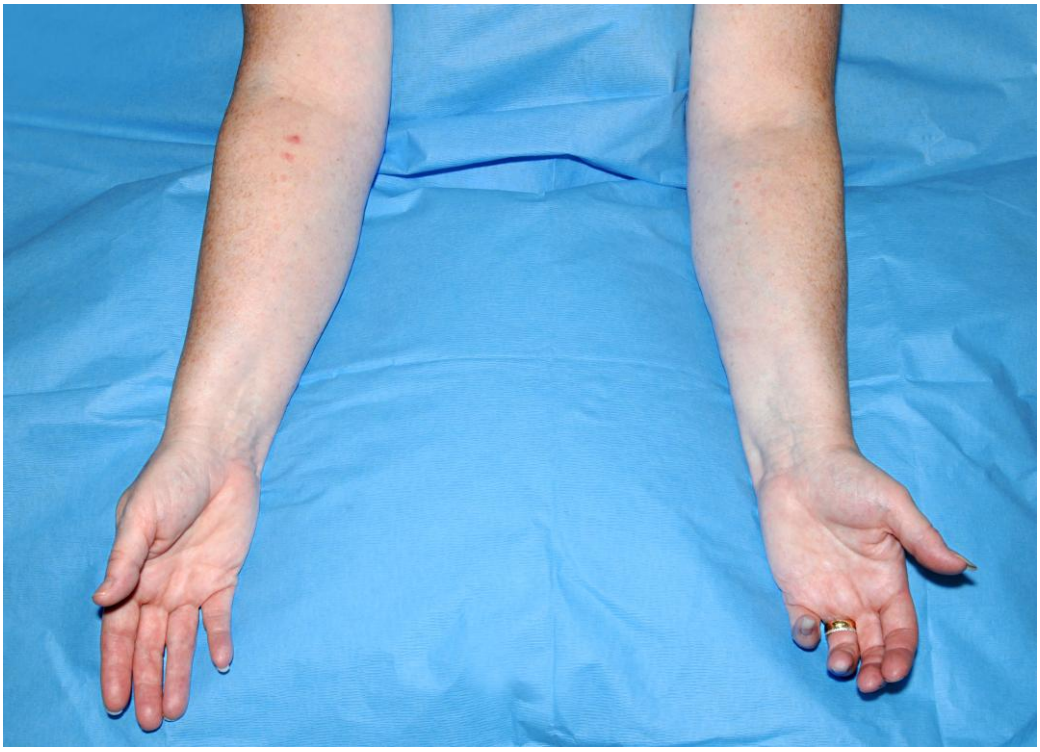

Figure 3.5: MPD at each wavelength in a volunteer

The mean MPD values can be used to calculate the relative sensitisation at each wavelength (the erythemal action spectrum). The action spectrum for topical PUVA erythema at 10nm intervals between 325nm and 375nm was: 1, 0.8, 0.67, 0.43, 0.29, and 0.22. Using Microsoft Excel at linear least squares best fit was applied to these values. The best fit equation was:

$y = -0.0162x + 6.2383 \quad R^2 = 0.98$

The equation was used to interpolate values of the action spectrum at 1nm intervals between 320nm and 400nm. All calculated values of the action spectrum were constrained to lie between 0 and 1, since values outside these limits are not possible.

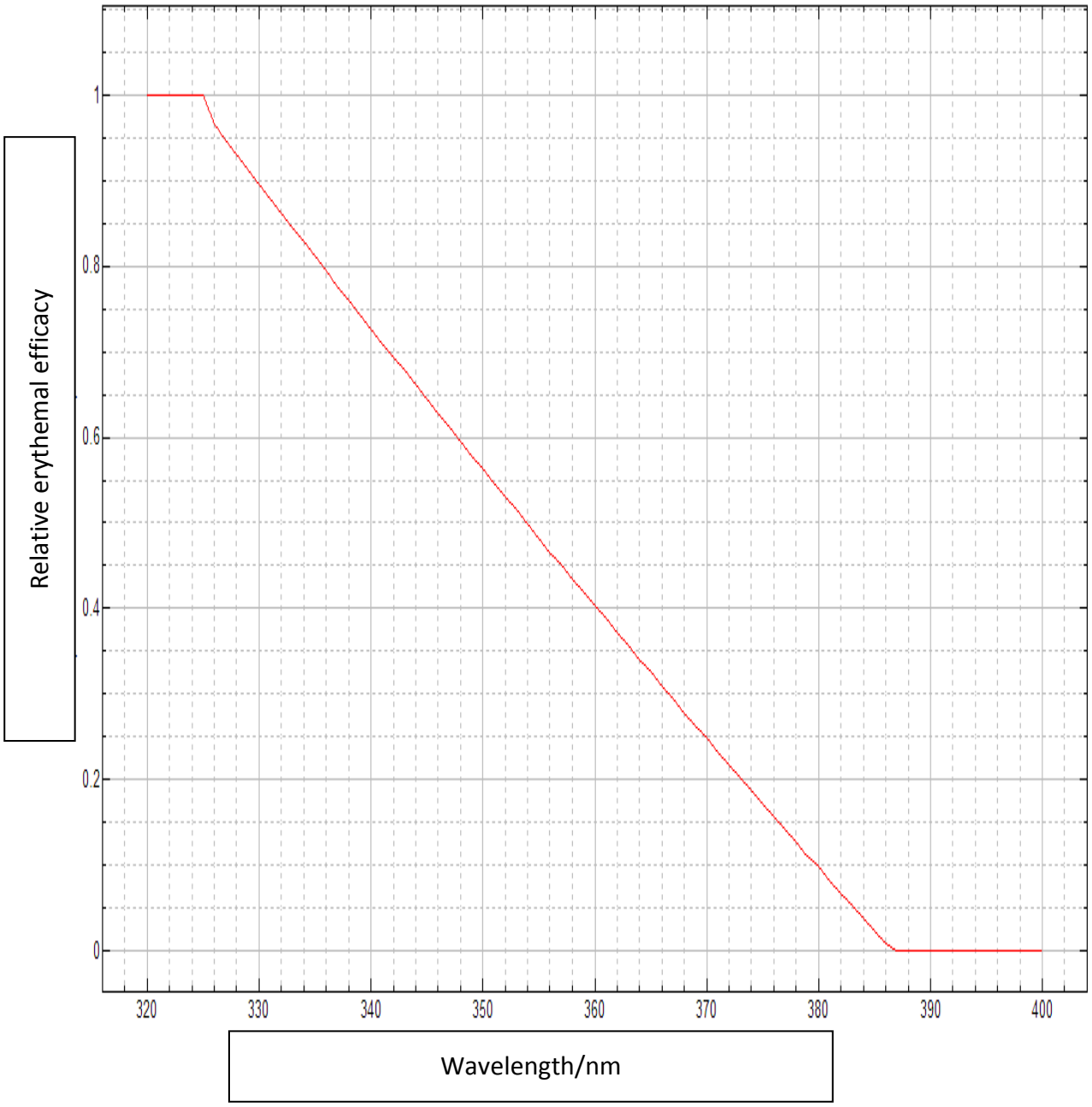

Figure 3.6: Topical PUVA Erythema Action Spectrum

Table 3.2 Action Spectrum at 5nm Intervals

Wavelength(nm)	Relative Erythema Action Spectrum Topical PUVA
320	1.00
325	1.00
330	0.90
335	0.80
340	0.72(5)
345	0.67
350	0.57
355	0.43
360	0.40
365	0.29
370	0.25
375	0.22
380	0.10
385	0.02(5)
390	0
395	0
400	0

CHAPTER THREE

Discussion

It has been shown that the action spectrum of oral 8-MOP PUVA for clearance of psoriasis follows the PUVA erythema action spectrum[165]. If we realistically assume that this will also be the case for topical PUVA, this topical PUVA action spectrum can be used to assess the relative efficacy, or efficiency, of any lamps used for topical PUVA phototherapy. For example, typical fluorescent lamps that are used for whole-body and extremities PUVA can be compared to newer UVA sources.

Applying the PUVA erythema action spectrum relative sensitivities at each wavelength to those measured in any UVA lamp spectrum allows the calculation of the “PUVA equivalent” output from that lamp. The ratio of PUVA equivalent outputs between any two UVA lamps can be used to describe the “PUVA efficiencies” of one lamp compared to another. Table 3.3 shows the PUVA effective ratio of typical PUVA sources used in clinical practice and other UVA lamps that may also be used for PUVA phototherapy.

Table 3.3 PUVA effective ratio of typical PUVA sources used in clinical practice.

Lamp	Irradiance / PUVA erythemal irradiance	PUVA effective ratio
UV800K 2-ft fluorescent lamp	2.145/4.465	0.48
Philips Cleo PUVA 6-ft fluorescent lamp	7.43/16.29	0.456
UVA1 LED	0.754/6.23	0.12
Blacklight compact fluorescent lamp	1.196/2.565	0.466
PhilipsTL10 compact fluorescent lamp	3.929/16.62	0.236
PUVA 180 UVA compact fluorescent lamp	2.956/7.461	0.396
TP4 UVA compact fluorescent lamp	10.64/22.25	0.478
Enfis UNO light engine 365nm LED	12.44/55.93	0.22

In a previous study[166] we used the action spectrum published by Cripps *et al*.[38] to predict the PUVA erythemal efficacy of a Philips TL10 UVA1 compact fluorescent tube lamp compared to our standard PUVA lamps used to establish the MPD of patients in our phototherapy unit. We predicted that the TL-10 lamp should be 0.15 as effective as the PUVA

lamp. However, when we performed MPD assessments using each of these lamps in 37 of our patients we found that the TL-10 lamp was in fact 0.48 as effective. We concluded that the published action spectrum was unreliable, and should be re-assessed. We can now examine the effectiveness of these same lamps calculated using the action spectrum we have established in this study. The table gives PUVA efficiency of the 2-ft fluorescent tube as 0.48, and that of the TL-10 UVA1 CFL lamp as 0.236. The ratio of these gives our prediction of the relative erythemal efficacy of the UVA1 lamp compared to the PUVA lamp. This value (0.236/0.48) is 0.49, which is almost exactly the value (0.48) that we measured from the MPD results from our volunteer patients. This gives strong evidence of the validity of the action spectrum measured in this study.

The therapeutic action spectrum of 8-MOP differs markedly from its absorption spectrum.[31] Potential reasons for this are psoralen and 8-MOP, undergo chemical changes upon their incorporation into the skin. Exposure to UVA and the action spectra within the skin will differ according to the absorption spectra of the chromophores they target. The UV absorption spectra for psoralen and 8-MOP compounds have been reported by Fowlks[32] as having maxima in their absorption spectra at approximately 220nm, 245nm, and 295nm (with a shoulder at 330nm) for psoralen and 220nm, 250nm, and 310nm for 8-MOP.

This study has established the erythemal action spectrum for bath or soak PUVA therapy for the first time, using an aqueous application of

psoralen as is used in routine clinical practice. In all volunteers, the action spectrum for 8-MOP induced erythema has its maximum activity (peak sensitivity) at 325nm. All volunteers showed a similar trend across the wavelengths studied irrespective of skin type. The PUVA induced clearance of psoriasis study by Farr *et al.*[1655] involving 24 patients with psoriasis, found that lamps with peak emission at 325nm were significantly superior to lamps with peak emission at 352nm or 370nm for clearance of psoriasis over a 6-week period. Equally erythmogenic doses from each of the lamps were used. They concluded that the therapeutic action spectrum for PUVA is not the same as the action spectrum for PUVA erythema. However, our topical PUVA erythema action spectrum would more closely agree with their psoriasis clearance action spectrum.

The output of lamps conventionally used in PUVA whole-body units have peak emissions at around 365 nm. A lamp with peak emission at 325nm, would enable clearance of psoriasis with a lower cumulative UV dose over a shorter time period and would improve the efficacy and efficiency of PUVA.

Our measured action spectrum for topical 8-MOP PUVA-induced erythema differs from previously published erythema action spectra[34,38]. This is most probably due to the use of strong solvents to deliver the psoralen in different concentrations, and differences in timings in application of psoralen and reading of erythema in previous studies. Our study was designed to test sensitisation of skin as would be

experienced after topical (bath) 8-MOP sensitisation as performed in routine clinical practice today. Our action spectrum was confirmed by the results of our previous study on MPD values established from PUVA lamps and TL-10 CFL. This result, of an independent study using different methodology, confirming the relative effectiveness of the two lamps used in the two MPD methods, is strong evidence to support the introduction of the simpler, safer hand-held MPD method into clinical phototherapy practice[166]. It is well recognised that the effects of electromagnetic radiation on the skin vary in a continuous fashion with wavelength. The CIE defined three regions within the UV part of the spectrum as UVA, UVB and UVC.

Therapeutically UVB and UVA are used in phototherapy. UVB has a greater erythemal effect on the skin than UVA by a factor of around 1000. In many older studies on photodermatology the UV sources were poorly defined, and some may have been inadequately filtered. Thus effects that may have been wholly or partially attributed to UVA may have been in some ways 'contaminated' by the effects of UVB leakage. This could be important especially in longer wavelength UVA spectral regions where psoralen-sensitisation of skin is less erythmogenic. In this study we were keen to isolate the effects of UVB from our observed outcome effect of erythema, and so we used a Schott glass WG320 high-pass filter to remove UVB from all wavelength studied. Since 320nm is on or very near the border between UVB and UVA, we used 325nm as our shortest wavelength.

Future studies could examine the response of psoralen sensitisation into the UVB, where Diffey and Farr[165] demonstrated an extra sensitisation due to psoralen sensitisation.

As such, our action spectrum is most relevant in establishing the potential effectiveness of novel lamps for PUVA phototherapies.

This enables accurate assessment of new UVA lamps, such as light emitting diodes or plasma screen sources, which may be used for PUVA in the future. Larger studies are required to assess differences in the PUVA erythema action spectrum between skin types.

CHAPTER FOUR

Topical Regimen in Hand/Foot PUVA

CHAPTER FOUR

Background

Palmoplantar dermatoses such as psoriasis or eczema are frequently encountered in dermatology. They are often resistant to conventional topical therapies including coal tar preparations, topical corticosteroids, vitamin D analogues and anthralin. There is no consensus about the ideal topical phototherapy to treat palms and soles. Accurate comparison of response to topical PUVA between studies is hampered by variations in topical psoralen formulation, time between application/immersion of psoralen and illumination with UVA, UVA regimes and clinical response grading.

In the right-left comparison study by Shephard *et al.*[167] 37 patients received ethanolic 0.15% 8-MOP lotion for the right hand/foot and aqueous 1mg/L 8-MOP for the left hand/foot. The treated areas were exposed to UVA within 20 minutes of bathing or painting thrice weekly. Although both therapies were effective, the concentration of 8-MOP within the ethanolic lotion was 1000 times greater than in the bath (aqueous) PUVA regimen. Patients required a lower cumulative dose of UVA. The authors advocated aqueous PUVA for fissured skin and ethanolic 8-MOP lotion for hyperkeratotic dermatoses.

Comparison studies involving the use of 0.0006% Psoralen cream (0.0006% 8-MOP containing water in oil emulsion (30% H_2O)) to 0.5mg/L 8-MOP solution (bath-PUVA) four times/ week[168], 0.005% 8-MOP gel to 1.0mg/L 8-MOP solution three to four times/week[169] were

undertaken. Despite variations in the time of soaking in PUVA solution or applying Psoralen cream or gel to acral surfaces followed by illumination with UVA, the results were equivocal. Potential advantages of PUVA-gel therapy are the ability to photosensitise select skin areas, reduction of organizational efforts and expenses compared to bath-PUVA.

In 1994, Hawk and Le Grice retrospectively reviewed the efficacy of oral PUVA versus topical PUVA in the treatment of chronic hand and foot dermatoses over an eighteen-month period and found both treatment modalities equally effective.[170] There is weak evidence to support superiority of oral PUVA versus bath PUVA. The study conducted by Hofer *et al*.[171] involved 8 patients with moderate-to-severe palmoplantar psoriasis treated thrice weekly for 4 weeks with either bath PUVA (one side) or oral PUVA (contralateral side). Although there was no significant difference in reduction of severity indices (erythema, infiltration, scaling and vesicles) between the two modalities, the authors claim that there was a significantly better effect in lesions treated with oral PUVA compared with soak PUVA.

Both a retrospective safety and efficacy study comparing oral PUVA to nbUVB[172] and a prospective comparison of PUVA paint to nbUVB in the treatment of palmoplantar psoriasis[173], each delivered thrice weekly, show that PUVA is superior to nbUVB in achieving improvements and clear skin. However, nbUVB was associated with less adverse effects

compared to oral / topical PUVA. This should remain a treatment option reserved for patients who experience phototoxic reactions to psoralens.

The British Photodermatology Group (BPG) guidelines[52] for topical PUVA recommend a delay of 30 minutes between soaking hands and/or feet and UVA irradiation in the treatment of palmar-plantar dermatoses. This recommendation is based on a single study[50] , and is not universally adopted. This study presented measurements of the time course of erythema on 6 healthy subjects, noting the presence, but not severity, of erythema at 72 hours after a single standardised dose of UVA on psoralen-sensitised hands and feet. Peak sensitivity occurred between 30 – 40 mins after removal from the psoralen solution. The authors concluded that it seemed reasonable to suppose that the therapeutic response of palmoplantar psoriasis would follow a similar time course, although this remained to be demonstrated. A study involving 30 patients (10 patients had eczema, 13 had psoriasis (plaque or hyperkeratotic), 6 had psoriasiform dermatitis and one had localised pustular psoriasis) found that 10% of the patients demonstrated a marked benefit from delaying irradiation (of whom two of three had hyperkeratotic psoriasis)[174]. A larger study is required to investigate the relationship between hyperkeratosis and improved response to delayed irradiation. This remains the case to this day.

A 30-minute wait between soaking hands and/or feet and UVA irradiation is inconvenient and time-consuming, and many centres claim

adequate clinical response with no delay between soak and irradiation. This study aims to demonstrate whether the clinical response follows the demonstrated erythemal response, and whether this holds for a larger population with palmoplantar dermatoses (both psoriasis and eczema).

Rationale

In the absence of controlled studies to provide a universally accepted protocol for the treatment of palmoplantar dermatoses with topical PUVA, phototherapy units throughout the UK have adopted protocols varying in the length of time-lapse between immersion and illumination, from 0 to 30 minutes. This study aims to determine whether the time-lapse affects the treatment outcome. If there is no difference between outcomes, this could have widespread implications in the time taken to treat patients and the number of patients that could be treated.

4.2 Aims

To determine the optimal treatment protocol for treating hand and foot dermatoses with topical PUVA in terms of delay between soak and UVA exposure and reduction of severity, or time to clearance.

To assess safety in terms of the number of treatment induced adverse events reported for each regimen.

CHAPTER FOUR

4.3 Design of the Study

Sample size calculation:

This was a within patient study to evaluate the efficacy of two treatment regimens.

All published studies of hand/foot soak PUVA present data on time to clearance and reduction in severity scores for groups of independent patients. There is thus no previous work to suggest a within-patient standard deviation of treatment outcomes. Therefore an assumption of time to clearance of 40 treatments, with a standard deviation of 4 will be used to estimate the number of subjects required. Using a two-sided test, with a power of 0.8 and setting significance at p = 0.05, 34 patients would be required).

If we chose to use a published severity score, then a study[169] indicates a typical score of 26.5, SD 11, reducing to 1.5 after clearance. If we assume a significant difference in score between treatment regimens of 5, then the number of subjects required is 41. We therefore chose to recruit 42 patients.

The study was a within-patient, randomised, assessment-blinded (i.e. single-blind), comparison of 2 treatment regimens in 42 patients with eczema or psoriasis of either their hands or feet who have been referred for topical PUVA therapy.

Two sites (either hands or feet) were pre-treated with topical psoralen according to the local (Newport) protocol. One site was then illuminated immediately with UVA light and the other site was illuminated 30 minutes after removal from PUVA solution. Assessments of symptoms and signs (Erythema, Thickness, Scaliness, Fissures, Pruritus/Pain, Vesiculation and Oedema) and Physicians Global Assessment, by an independent assessor, were made before the first treatment, then every 4 weeks throughout the treatment period and at the final visit. Photographs will be taken at baseline and final visits.

4.4 Ethical Approval

Before commencement of this study, ethical approval was obtained from the South East Wales Local Research Ethics Committee. Approval was also sought and obtained from the Aneurin Bevan Healthcare NHS Trust Scrutiny and Risk Review Committee. (Ref No. 12/WA/0043)

4.5 Written Informed Consent

An information sheet describing the study and procedures to be performed was supplied to each patient prior to starting the study. The study was fully explained and patients were then required to provide

their written, witnessed consent. A copy of the information sheet and consent form is included in appendix III.

4.6 Study Subjects

42 patients with palmoplantar psoriasis / eczema were planned to be recruited. All patients will have been referred in the normal way to the phototherapy unit at St.Woolos Hospital, Newport, or the phototherapy unit at University Hospital of Wales, Cardiff.

4.61 Inclusion criteria

1. Aged at least 16 years.
2. Has either eczema or psoriasis with involvement of either both hands or both feet
3. Has signed the consent form after the nature of the study has been fully explained

4.62 Exclusion criteria

1. Has pustular psoriasis of the hands / feet as this tends to be recalcitrant to topical PUVA.
2. Significant concurrent illness likely to interfere with the study including malignancy.
3. Use of medication likely to interfere with the study, including immunosuppressant and photosensitising drugs.

4. Pregnant or lactating females

5. Unwilling or unable to give written consent.

4.7 Method

Patients had their Boston Skin Phototype assessed by the phototherapy nurse practitioner, as is normal practice before a course of treatment. The first PUVA dose was based on the Phototype according to the treatment dose protocol common to Cardiff and Newport.

Treatment

The affected sites (both hands and/or both feet) were pre-treated by local immersion (8-MOP at a concentration of 3mg/L and a temperature of 37°C for 15 minutes), to sensitise them to UV light.

The allocation of right or left hand/foot to receive treatment A or B will be randomised. A randomisation schedule was calculated using the "random" function in Microsft Excel. The code was kept by a team member (CE) and each subject was allocated left or right, wait or immediate UVA exposure according to a printed table supplied by CE.

Treatment A: One side was illuminated immediately after immersion was complete.

Treatment B: The other side was illuminated 30 minutes after immersion was complete. Treatments were continued until clearance was achieved, or for a maximum of 30 treatments for hands and 40 treatments for feet.

Assessments

Severity assessments using validated severity tools –for psoriasis and eczema (assessing global severity, Erythema, Thickness, Scaliness, Fissures, Pruritus/Pain, Vesiculation and Oedema) were made by an independent assessor at baseline, every 4 weeks throughout treatment, and at the final visit. The primary efficacy measure for therapeutic response was whether a delay of 30 minutes prior to illumination with UVA was therapeutically effective as determined by the physician's global assessment (PGA) of overall chronic hand dermatosis performed at baseline, every 4 weeks throughout treatment schedules and at the final visit. PGA criteria, based on a previous study[175] were defined as follows:

Global Severity:

0 = **no** symptoms of disease

1 = **very slight** symptoms of disease

2 = **slight** symptoms of disease

3 = **moderate** symptoms of disease

4 = **severe** symptoms of disease

5 = **very severe** symptoms of disease

Symptoms included in this assessment included: Scaling, redness, extent and severity of hyperkeratosis (thickening), patient-reported itch, fissuring, area of involvement. The extent of disease was estimated by the physician as the total percentage involvement of the palms.

Secondary efficacy measures were the modified total lesion symptom score (mTLSS), The mTLSS was adapted from a previous TLSS scale,[176,177]and calculated as the sum of scores (0 = absent, 1 = mild, 2 = moderate, 3 = severe) assigned by the physician for the following 7 parameters: erythema, oedema, vesicles, desquamation, hyperkeratosis, fissures, and pruritus/pain.

Standardised digital photographs were taken of each site at baseline and final visits.

4.8 Results

Eight patients (4 females and 4 males) were recruited for the study. Their ages ranged between 44 – 67 years (mean 52 years). One patient withdrew from the study. The remaining seven patients had phototypes as follows: two patients – skin type II, five patients – skin type III. Three patients had eczema and four patients had psoriasis affecting their hands/feet.

CHAPTER FOUR

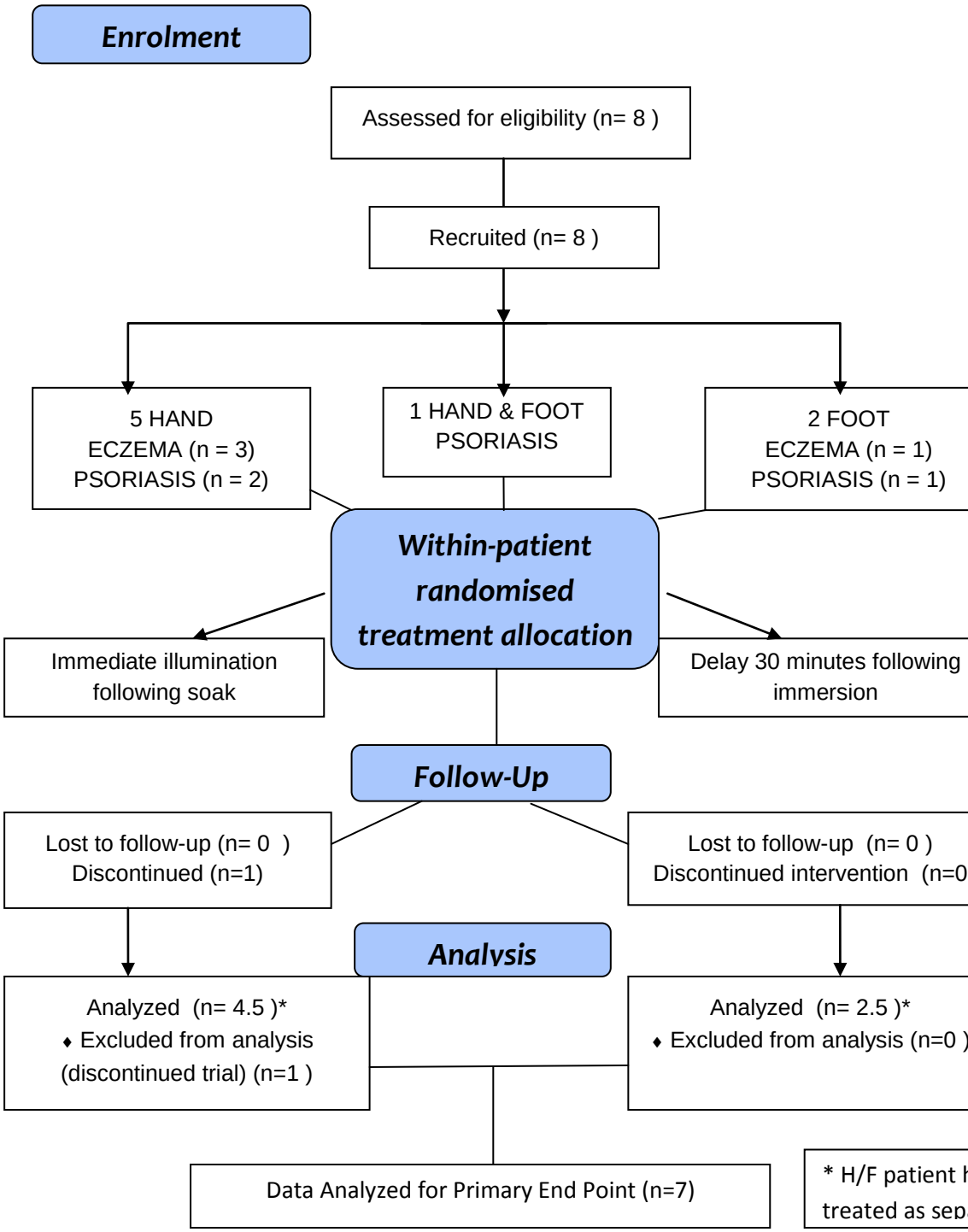

Figure 4.1 Study Flow Chart

The results show that patients with both hand/foot eczema and psoriasis improved during the course of treatment with regards to the Total Score (Erythema, Thickness, Scaliness, Fissures, Pruritus/Pain, Vesiculation and Oedema) and Physician's Global Assessment. 1 patient with eczema and 1 patient with psoriasis were clear by week 20.

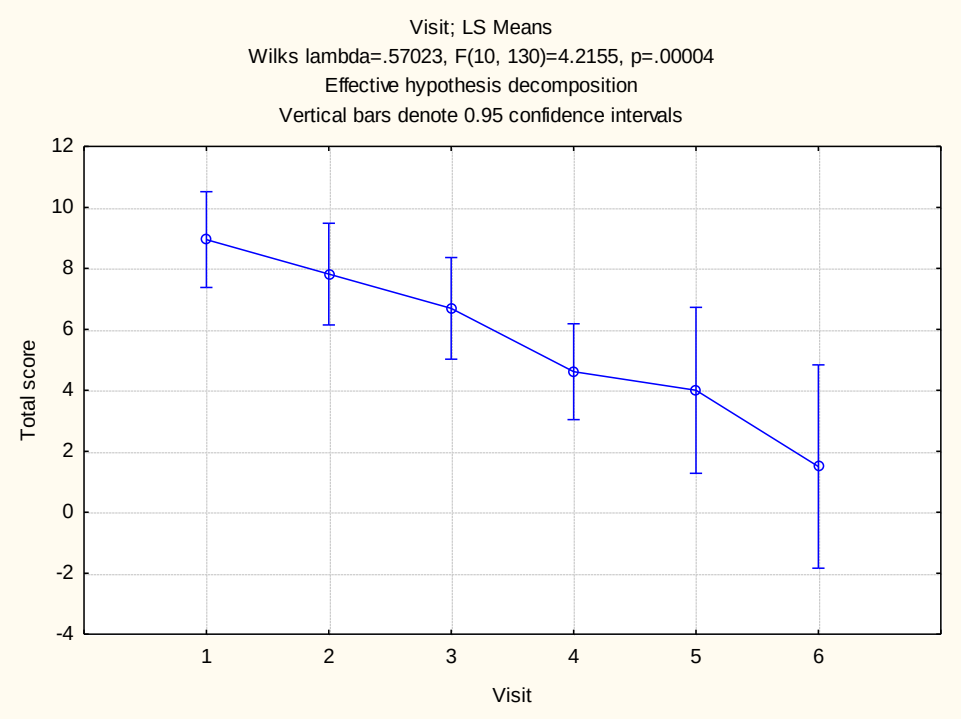

Figure 4.2 Mean Total Score with visit number

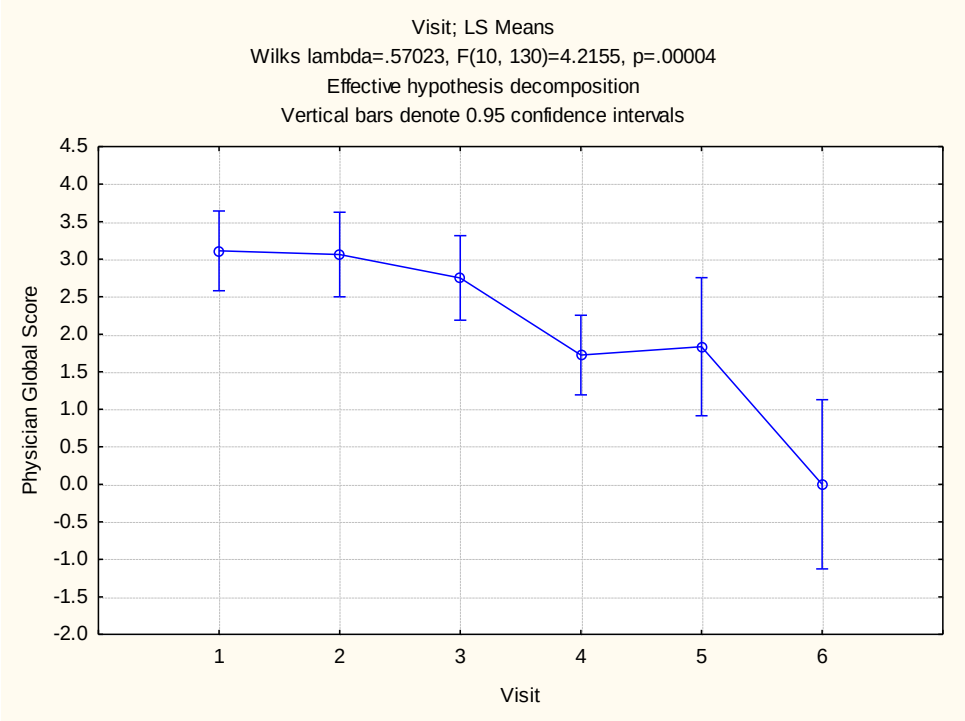

Figure 4.3 Mean Physician Global Score with visit number

The analysis of variance test showed that the length of treatment had a significant effect on the total score. There was a statistically significant reduction in Physician's Global Assessment and Total score as length of treatment progressed and assessments undertaken at 4-weekly intervals.

CHAPTER FOUR

Table 4.1 Univariate Test of Significance for Physician Global Score

Effect	Univariate Tests of Significance for Physician Global Score (Deana Hand Sigma-restricted parameterization Effective hypothesis decomposition SS	Degr. of Freedom	MS	F	p
Intercept	238.5645	1	238.5645	197.3233	0.000000
Visit	51.1351	5	10.2270	8.4591	0.000003
Delay	0.3205	1	0.3205	0.2651	0.608234
Error	85.8392	71	1.2090		

Table 4.2 Univariate Test of Significance for Total Score

Effect	Univariate Tests of Significance for Total score (Deana Hand Foot PUV Sigma-restricted parameterization Effective hypothesis decomposition SS	Degr. of Freedom	MS	F	p
Intercept	1771.629	1	1771.629	168.0228	0.000000
Visit	376.389	5	75.278	7.1394	0.000018
Delay	3.494	1	3.494	0.3313	0.566672
Visit*Delay	10.063	5	2.013	0.1909	0.965126
Error	759.167	72	10.544		

The results indicate however that there was no statistically significant difference in the Total Score and Physician's Global Assessment between waiting for 30 minutes or immediate UVA illumination.

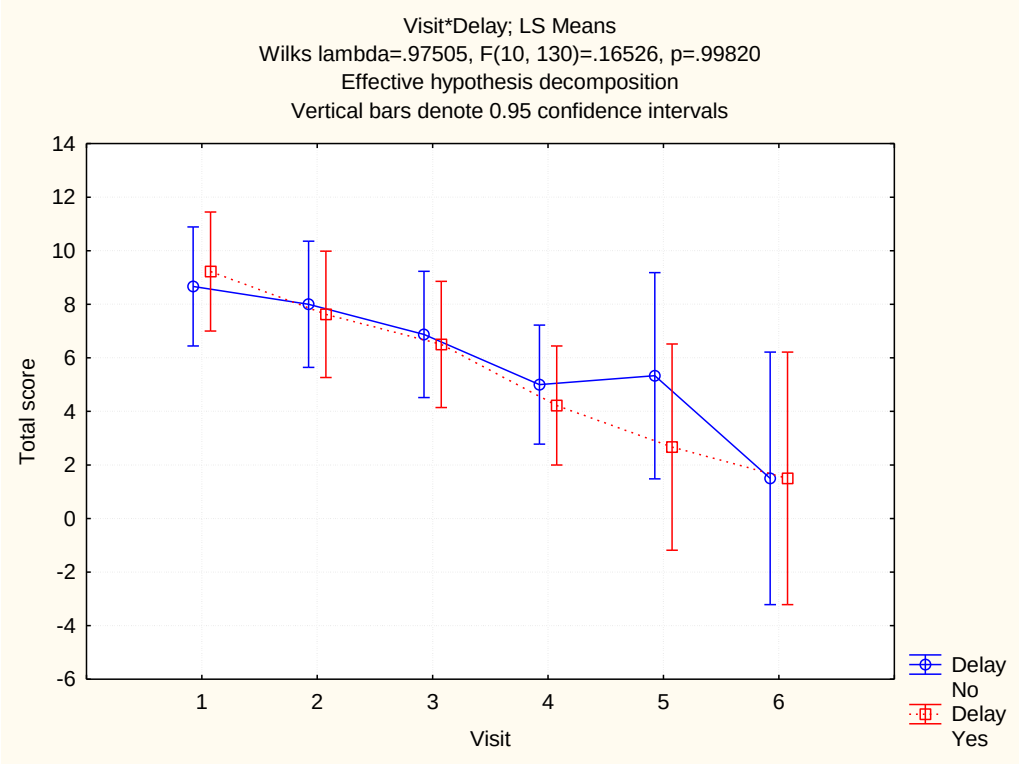

Figure 4.4 Comparing immediate and 30 minute delay before UVA illumination with Total Score

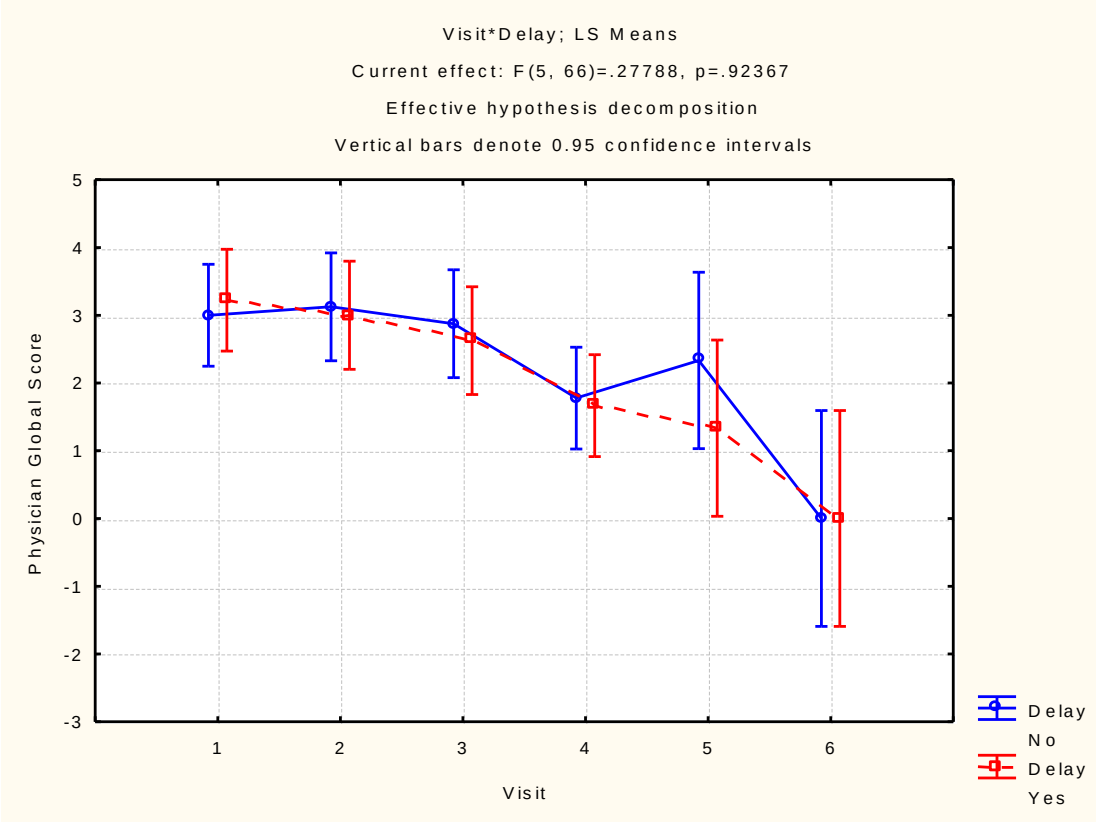

Figure 4.5 Comparing immediate and 30 minute delay before UVA illumination with Physician Global Assessment

CHAPTER FOUR

4.9 Discussion

The results of this left-right within patient comparison study show that patients with hand/foot eczema and psoriasis continued to show improvements with soak PUVA during the study period 24 weeks. Two patients were completely clear of dermatoses at 20 weeks, the remainder showed significant improvement. Although there was no statistically significant difference between waiting for 30 minutes after soaking in 8-MOP solution or immediate illumination with UVA, one patient with hyperkeratotic psoriasis affecting the soles of his feet showed a definite improvement after waiting for 30 minutes, in keeping with results from an earlier study[173]. The sample size in this study is small and only seven subjects were included within the time-frame. Planned analyses of this study included multiple regression analysis for exploring the effect of diagnosis, site (hands/feet) and severity on the outcome measures. However, because of the failure to recruit the planned number of patients, these analyses are not feasible. It could be anticipated that the delayed exposure treatment may be more effective for hyperkeratotic (thick) disease, and if data from the planned number of subjects indicated that this was found, then a larger study would have been proposed to further confirm that finding. The patient who withdrew from the study had eczema affecting her hands; she was unable to wait for the thirty minutes duration required prior to UVA illumination due to personal commitments. This patient also had a history of recurring episodes of infected hand eczema, potentially due to poor hand care,

requiring systemic antibiotics. Recruitment for this study was slow and difficult. Potential reasons for this are the inconvenience and time-commitments required for patients to attend their phototherapy sessions impacting on work and carer commitments. Furthermore, if having achieved a satisfactory response to immediate UVA treatment following a soak in psoralen, there may be little incentive for patients to try a novel approach. However, this study failed to anticipate the impact of alitretinoin on the number of patients with chronic vesicular hand eczema referred for PUVA therapy. These patients have reduced significantly in number in the PUVA unit.

This study also impacts on the phototherapy staff nurses who are required to deliver safe and effective treatment to an increasing patient population. A delay of 30 minutes prior to treatment may have also been a contributing factor to poor recruitment.

Recruitment could have been improved by targeting both the patients and the treating physicians. If research nurses were available, then they could have administered the treatments, removing reluctance from busy phototherapists who did not usually treat with delayed exposure.

Patient advertising in general dermatology clinics may have raised awareness and thus increased recruitment. Also, involving patient groups such as the Gwent Dermatology Patient Group may also have helped to raise the profile of the study. However, due to the study being run on multiple sites this was not attempted.

These strategies would have required the submission of an amendment for Ethical Opinion, and this would have introduced a delay in the study.

A larger study is required to formally investigate the efficacy of waiting for 30 minutes following a soak in 8-MOP prior to illumination with UVA.

Due to the premature ending of this study because of poor recruitment, any statistical conclusions must be viewed with caution. The completed study, with the numbers actually analysed should be regarded as a pilot study, which may encourage the design of a larger study, perhaps concentrating on “thicker” (hyperkeratotic) dermatoses, or the differences in effectiveness between acral (palmar/plantar) and other thinner (dorsal) sites. Our results have been interpreted with caution since recruitment was poor and fewer than planned patients were included in the study.

However, our limited results did confirm Desai and Halperns[174] results that for non-hyperkeratotic conditions the 30 minute delay before UV exposure is unnecessary.

For each of the clinical assessments (erythema, thickness, scaliness, pruritus/pain, fissures, vesiculation, oedema), for the composite total score (the sum of the individual symptom scores), and for the Physicians Global score we performed an Analysis of Variance for the effects of visit number and delay status. The visit number (representing

progression into the treatment schedule) was highly significantly effective on influencing every outcome measure, with p-values less than 0.001. None of the outcome measures was affected by delay status, with all p-values >0.9.

This result is strongly supportive of the conclusion that delay was not significant in this study.

However it must still be noted that we only had one patient with hyperkeratotic disease. So our strong conclusion may be stated that for non-hyperkeratotic skin conditions included in this study a delay between psoralen solution immersion and UVA exposure is unnecessary.

CHAPTER FIVE

Discussion

In the age of new systemic agents and increasingly targeted biologic therapies, is there still a role for PUVA in dermatology? Biologics are predominantly used in the management of psoriasis and psoriatic arthritis. APRICOT is a UK double-blinded randomised placebo controlled trial, assessing the efficacy of Anakinra (anti IL-1) for palmoplantar pustulosis. This trial was not published when the present trial was designed, and we have excluded pustular disease as this tends to be recalcitrant to topical PUVA.

However, all types of phototherapy are effective in a variety of dermatoses including atopic dermatitis, vitiligo, Cutaneous T-cell Lymphoma and polymorphic light eruption, to name but a few.

There remains a paucity of studies directly comparing PUVA to biologics. A comparative blinded study between these modalities would not be practical as PUVA induces erythema and pigmentation. A retrospective data analysis from a psoriasis registry comprising 172 adults, between 2003 – 2010 by Inzinger *et al*.[178] compared complete remission, PASI 90 and PASI 75 at completion of treatment for oral 8-MOP and 5-MOP (median time 10.3 and 9.2 weeks respectively) to response to biologics at week 12. Their results suggest that the primary efficacy of PUVA is superior to certain biologics. An important limitation of this study is the fact that clinical response to PUVA and biologics

were evaluated at different time points. Optimal response to certain biologics e.g. Adalumimab, occurs beyond 12 weeks.

The adverse effects of PUVA are well documented. In contrast, side-effects of biologics are only now becoming clearer. These include invasive mycoses, progressive multifocal leukoencephalopathy, lymphoproliferative disorders and lupus-like syndrome.[179]

A further strength of PUVA is that it may be used intermittently once remission has been achieved. In contrast with biologics, the efficacy appears to decrease with prolonged use due to antidrug antibody formation[180]. This is not the case with PUVA where no evidence of antibody formation has been demonstrated.

PUVA is clearly more time-consuming and sometimes inconvenient for patients. However, one study showed that PUVA guided by weekly MPD-testing in order to adjust the dose (i.e. MPD-guided PUVA), was successfully used in 89% of patients who reached PASI 75 within four weeks.[181]

There remains widespread variation regarding how phototherapy is delivered in the U.K. A questionnaire survey (Chapter 2) was completed by 72 individuals working in 43 U.K. phototherapy units across the United Kingdom, to assess routine practice concerning MPD testing prior to commencing PUVA phototherapy. Only 14% of phototherapy centres surveyed routinely assessed MPD prior to

photochemotherapy. The remaining centres found this practise too time-consuming, had no equipment to perform MPD testing or used the patient's skin phototype.

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MPD testing serves a dual purpose, to minimise both the cumulative number of PUVA treatments and the incidence of adverse effects. It also establishes that sufficient psoralen is present in the patient's skin. If the extent of disease precludes MPD testing, the initial dose is based on skin phototype.

The traditional method of assessing MPD is cumbersome and time consuming for both patients and staff and requires a separate source of UVA. In our unit, this used to take 15– 20 min. The difficulties (due to time required, equipment and training) of performing MPD testing discourage its widespread adoption. Potential errors of the traditional method of assessing MPD using an open panel of UVA lamps including UV source nonuniformity due to curvature of the test site, patient movement and exposure timing errors may be resolved. An easier, safer method of establishing the MPD may encourage more centres to perform this important check.

A device that overcomes many of these difficulties is the MED tester used for UVB. This uses a compact fluorescence tube (CFL) in a handheld housing as the source and a UVB opaque template with 10 x 1-cm-diameter apertures. The output of nine of these apertures is successively attenuated by a factor of 1.25 by steel shaver-type foils. A small handheld MED tester, being convenient and reliable, could be made available for MPD testing by replacing the UVB tube with a CFL TL-10 tube. The nearest equivalent CFL to a PUVA lamp is the Philips

CHAPTER FIVE

Discussion

TL-10 CFL, which has a narrower spectrum centred around a longer wavelength (370nm). As PUVA photochemotherapy uses only psoralen as the sensitiser and only PUVA-designated lamps, it may be possible to establish a fixed factor to convert observed MPD using the TL-10 CFL to a PUVA-equivalent MPD.

The modified handheld MPD tester was calibrated for UV output using a Bentham DM150 spectroradiometer. The DM150 was calibrated against a tungsten lamp which had a calibration from 250nm – 800nm traceable to the National Physical Laboratory. The hand-held MPD tester required a 2 minute warm-up and 15 minute cool down between successive MPD tests. Successive doses of UVA were delivered within a maximum time of 3 minutes 25 seconds. MPD testing using the modified hand-held tester was safer and easier for both patients and staff to use.

When comparing the handheld MPD results to the traditional PUVA panel MPDs, there was a close linear relation to the PUVA panel MPD results (Pearson's correlation Coefficient = 0.82). However, the difference in MPD between the PUVA lamp and the modified handheld MPD tester (CFL TL-10 lamp) was much less than predicted from the PUVA action spectrum[37]. The erythemal effectiveness of the TL-10 lamp, calculated using the PUVA erythema action spectrum of Cripps *et al*[38], is 2·48, compared with the PUVA lamp effectiveness of 16·33 (arbitrary units). Thus PUVA MPDs should be 0·15 of the TL-10 MPDs.

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This suggested that formal re-evaluation of the erythema action spectrum for PUVA was warranted.

Published research on topical psoralen ultraviolet A (PUVA) erythemal action spectrum used methods that do not reflect current clinical practice for psoralen sensitization. The study by Cripps *et al.*[38] used 8-methoxy psoralen at 1% dissolved in acetone and then in ethanol and applied (via pipette) directly to the skin of the lower dorsum trunk of 6 Caucasian males. This was then followed by irradiation with various wavelengths of UVA. No details were provided for the time between application of psoralen and UVA irradiation. MPDs were read at 72 hours. Their findings were a peak sensitivity between 330-335nm for 8-MOP, 6 times more effective than 365nm. In the study by Buck *et al.*[34] there was a delay of between 1½ - 2 hrs between application of 1% 8-MOP solution in chloroform and illumination with UVA.

This scenario differs greatly from present clinical practice in the UK, where the skin is immersed in an aqueous solution of 8-methoxypsoralen at 37ºC[39] for 15 minutes, followed by UVA irradiation within 30 minutes. The study by Schempp *et al*.[40] showed there was a marked, significant reduction in erythema after 60 minutes delay between soaking in an 8-MOP bath and irradiation and no erythema was detected after 180 and 360 minute delay. Man *et al.*[57] showed that time to develop topical 8-MOP induced erythema had a broad peak at 120 hours. However, MPD assessment during or beyond 120 hours is

best avoided due to confounding effects of the development of pigmentation. Their recommendation was that topical 8-MOP MPD should be read four days (96 hours) after exposure.

We therefore re-evaluated the PUVA erythema_action spectrum using aqueous psoralen at 2.6mg/L concentration as is used routinely in current clinical practice in the UK and assessed MPDs at 96 hours. We then used our action spectrum to estimate the "PUVA equivalent" output of a range of UVA sources. This study has established the erythemal action spectrum for bath or soak PUVA therapy for the first time, using an aqueous application of psoralen as is used in routine clinical practice. In all volunteers, the action spectrum for 8-MOP induced erythema has its maximum activity (peak sensitivity) at 325nm. All volunteers showed a similar trend across the wavelengths studied irrespective of skin type. The PUVA induced clearance of psoriasis study by Farr *et al.*[165] involving 24 patients with psoriasis, found that lamps with peak emission at 325nm were significantly superior to lamps with peak emission at 352nm or 370nm for clearance of psoriasis over a 6-week period. Equally erythmogenic doses from each of the lamps were used. They concluded that the therapeutic action spectrum for PUVA is not the same as the action spectrum for PUVA erythema. However, our topical PUVA action spectrum would more closely agree with their psoriasis clearance action spectrum.

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Discussion

The output of lamps conventionally used in PUVA whole-body units, have peak emissions at around 365 nm. A lamp with peak emission at 325nm, would enable clearance of psoriasis with a lower cumulative UV dose over a shorter time period and would improve the efficacy and efficiency of PUVA. Our measured action spectrum for topical 8-MOP PUVA-induced erythema differs from previously published erythema action spectra[34,38].

This is most probably due to the use of strong solvents to deliver the psoralen in different concentration, and differences in timings in application of psoralen and reading of erythema in previous studies. Our study was designed to test sensitisation of skin as would be experienced after topical (bath) 8-MOP psoralen sensitisation as performed in routine clinical practice today. Our action spectrum was confirmed by the results of our previous study on MPD values established from PUVA lamps and TL-10 cfl lamps (see Table 3.3 PUVA effective ratio of typical PUVA sources used in clinical practice – Chapter 3).

The table gives PUVA efficiency of the 2-ft fluorescent tube as 0.48, and that of the TL-10 UVA1 cfl lamp as 0.236. The ratio of these gives our prediction of the relative erythemal efficacy of the UVA1 lamp compared to the PUVA lamp. This value (0.236/0.48) is 0.49, which is almost exactly the value (0.48) that we measured from the MPD results

from our volunteer patients. This gives strong evidence of the validity of the action spectrum measured in this study.

Regarding palmo-plantar dermatoses, just over two-thirds of respondents used topical 8-MOP rather than Psoralen gel.

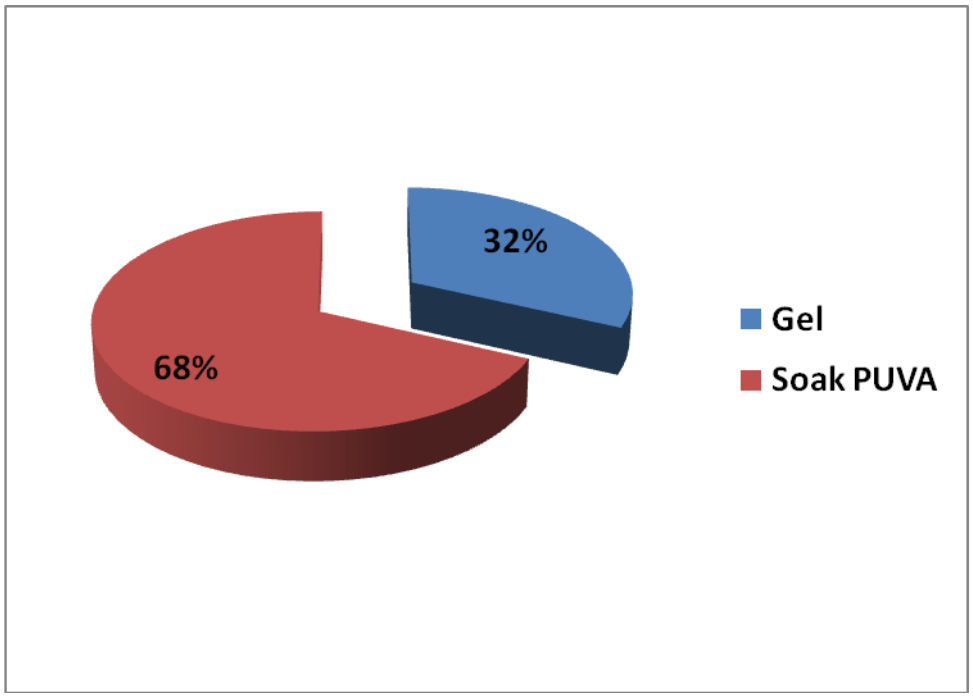

Figure 5.1Results of Questionnaire Survey

Proportion of topical 8-MOP use compared to psoralen gel

CHAPTER FIVE

Discussion

Despite BPG Guidelines[52] advocating a 30 minute wait following psoralen application and irradiation with UVA, results of the survey confirmed that there is a great deal of heterogeneity regarding time between immersion of acral surfaces in aqueous 8-MOP or application of psoralen gel to the areas and irradiation with UVA see figure 5.2.

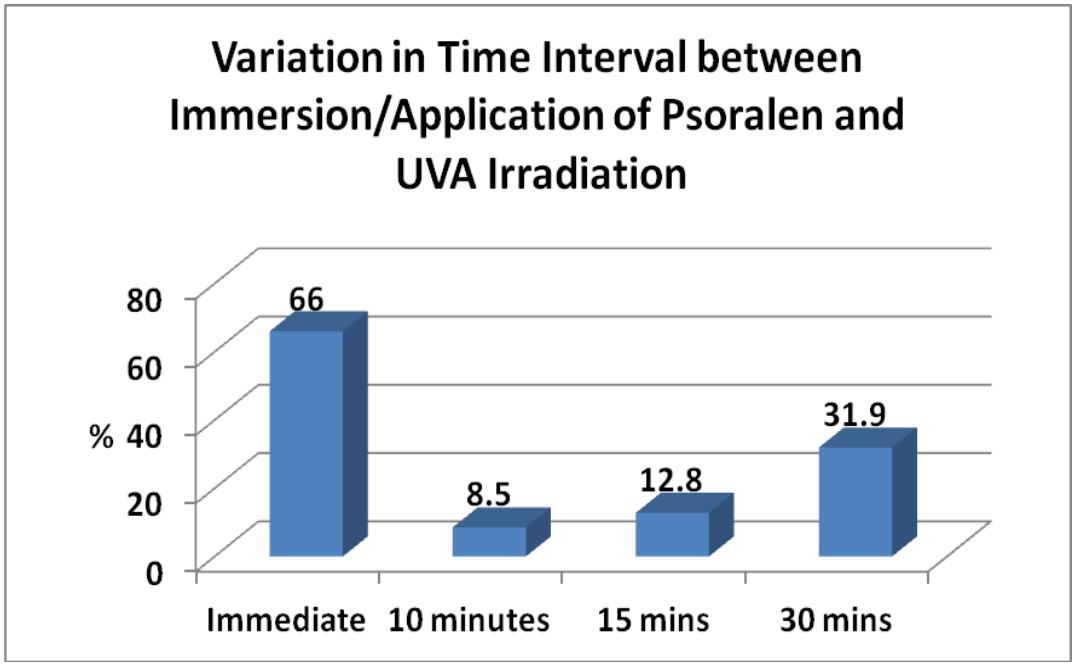

Figure 5.2. Variation in Time Interval between Immersion/Application of Psoralen and UVA Irradiation

The principal reasons for this variation in clinical practise, as highlighted by the responders of this survey include preconceptions (based on personal opinion instead of evidence) by some clinical staff that PUVA is ineffective in the treatment of hand foot dermatoses. Another reason mentioned is the time required to wait for half an hour prior to exposing the limb to UVA, which is perceived as inconvenient by patients and

staff equally. Competing demands on clinical time to provide timely services to the patients has also been quoted as one of the basis for the varied practise. These are also some of the reasons which adversely affected patient recruitment in this study as highlighted below.

Although the numbers of patients included in the trial results (Chapter 4) are too small to draw firm conclusions from, they seem to suggest that patients with both hand/foot eczema and psoriasis improved during the course of treatment with regards to the Total Score (Erythema, Thickness, Scaliness, Fissures, Pruritus/Pain, Vesiculation and Oedema) and Physician's Global Assessment. In fact, there was a statistically significant reduction in Physician's Global Assessment and Total score as length of treatment progressed. One patient with hyperkeratotic psoriasis affecting the soles of his feet showed a definite improvement after waiting for 30 minutes, in keeping with results from an earlier study[174].

Patient recruitment was challenging in this study. Potential reasons for the difficulty in recruitment of patients into this study include the time-commitments essential for patients to attend their phototherapy sessions for extended periods (to accommodate for the delayed illumination of the control limb 30 minutes post Psoralen immersion) and the resulting impact on their other commitments. Furthermore, if a patient previously had been treated with topical PUVA and achieved a satisfactory response to immediate UVA treatment following a soak in

psoralen, they declined participation in the trial as there was little incentive for them to try the delayed exposure method. Hence, lack of patient commitment with regards to time and trying out a new approach contributed significantly to the sub-satisfactory participant numbers in this study. Simultaneously, lack of nursing staff to deliver this time intensive approach contributed to the recruitment difficulties. The availability of more convenient alternative systemic treatment options for patients including oral Alitretinoin may also be a factor in patients declining participation in this study.

This study also impacted on the phototherapy staff nurses who are required to deliver safe and effective treatment to an increasing patient population. A delay of 30 minutes prior to treatment may have been a contributing factor to poor recruitment as mentioned above.

The decline of psoralen ultraviolet A (PUVA) as treatment for chronic hand eczema (CHE) ignores the existing evidence and may deny some patients a useful treatment option.

The licensing of alitretinoin for treatment-resistant CHE has greatly improved the outlook for patients with this disabling variant of eczema. The evidence for the efficacy of this drug is robust, with two multinational randomised controlled trials published, although their design would have been improved by inclusion of quality-of-life (QOL) outcomes.[182] In the first study, 319 subjects were treated over a 12-week period, and a significant dose-dependent improvement in disease

status was reported. However, 3 months after discontinuation of treatment, the rate of relapse was 26%, independent of dose.[183] In the subsequent study, 1032 subjects were treated over a 24-week period; 47.7% of subjects had clear or almost clear skin by week 24of treatment with 30 mg alitretinoin, compared with 16.6% for placebo ($P < 0.001$). A confounding factor was the discontinuation of treatment halfway through the study in a subgroup of responders.[183] Median time to relapse was 5–6 months.[184] The main adverse events (AEs) reported in these two studies were headache, dry mouth and erythema. In addition, increases in cholesterol and triglycerides occurred, as did asymptomatic changes in levels of thyroid-stimulating hormone. AEs were generally dose dependent and reversible. It is clear from these studies that alitretinoin is not effective in all cases of CHE, that many patients relapse after withdrawal of treatment, and that 10% of patients receiving 30 mg withdrew from the trial because of AEs. [182,183,184]

What alternative treatments are available for this group of alitretinoin non-responders and for women of child-bearing age, for whom systemic retinoids are contraindicated? Topical PUVA is one option for treatment-resistant CHE. Unlike topically applied PUVA in the form of a gel, lotion or cream preparation, soak PUVA allows a more uniform cutaneous absorption of 8-methoxypsoralen (8-MOP); the macerated stratum corneum of CHE facilitates penetration of 8-MOP, and carries a lower risk of phototoxic reactions and persistent hyperpigmentation than

topically applied psoralens.[185] Furthermore, patients with CHE do not have several courses of topical PUVA; the cumulative doses are usually low, and there is no evidence for a skin cancer risk after topical hand / foot soak PUVA.

In a prospective trial of 38 subjects with CHE treated with PUVA three times per week, 53% patients were disease-free after an average of 19 sessions (range 8–42) with patients receiving treatment,[186] and 29% of patients had improved after an average of 12 sessions (range 1–22 weeks). Maintenance was given once a week for most patients and one patient had maintenance twice a week.[186] Disease-free patients remained in remission for a median period of 10 months.[186] When relapse occurred in these subjects it was reported to be more benign than previously.[186]

Grattan et al. reported a double-blind randomised within-patient trial on 15 subjects, comparing topical PUVA against UVA for the treatment of vesicular CHE. There was improvement in both hands during the 8-week treatment period ($P < 0.05$), and they remained subjectively and objectively better during the 8-week follow-up, with no significant difference between treatment methods at any stage. At follow-up 18 months later, four patients reported that their eczema was healed. The authors concluded that UVA alone may be beneficial for CHE.[187]

In a further study, narrow-band UVB was compared with paint PUVA in a 9-week prospective, left–right comparison study of 15 patients with

the dry and dyshidrotic types of CHE. Both groups showed clinical improvement, with little difference between treatment methods.[188]

A retrospective study on localised topical and systemic photochemotherapy for chronic hand and foot dermatoses of 40 patients noted no difference in efficacy between treatment methods. However, the study population was mixed, and included patients with psoriasis, palmoplantar pustulosis and CHE. This more recent study included QOL measurements, unlike the earlier studies.[170] A recent open-label RCT compared the efficacy of home-administered oral PUVA with hospital-delivered bath PUVA for CHE in 150 patients. Both groups responded well, and there was no difference between treatment groups after 10 weeks and at follow-up 8 weeks later.[189] There still remains a role for other systemic immunosuppressant treatments including azathioprine, ciclosporin, methotrexate and mycophenolate mofetil in the management of refractory cases of hand eczema. Although one study[190] demonstrated prolonged remission for one year in 74% of patients treated with a 6-week course of ciclosporin 3mg/kg/day, other studies showed high relapse rates shortly following discontinuation of ciclosporin[191,192]

Methotrexate, at doses between 15 – 22.5mg/week, was shown to be effective in 5 patients with severe recalcitrant dyshidrotic eczema when used as adjunctive therapy. Patients were able to reduce or discontinue systemic steroid use.[193]

CHAPTER FIVE

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Mycophenolate mofetil 2 – 3 grams/day has been successfully used to treat a 39 year-old male with severe dyshidrotic eczema. Long-term remission was achieved and maintained after one year of treatment.[194]

Although unlicensed, clobetasol propionate cream 60% mixed with the penetrant propylene glycol 40% under polythene occlusion to the palms overnight for two or three nights until clear and at the first sign of recurrence introduced by Dr. Gerald Levene at St. John's Hospital, London is extremely effective. It leads rapidly to complete remission without adverse effects and if used very early during the expected recurrence after a week or so clears again with usually only one night's use, leading eventually to longer and longer remissions.(Personal communication John Hawk).

The paucity of data regarding the most clinically effective treatment for severe hand eczema following suboptimal response to potent topical steroid ointments prompted the calls for the ALPHA study. This prospective UK RCT directly compares Alitretinoin 30mg (once daily) to immersion PUVA (twice weekly) to establish which of these two treatments is the most effective in the management of particular types of hand eczema. Prior to commencing treatment, patients will be tested for fillagrin mutations. The ALPHA study will examine both the short term and longer term effectiveness of each treatment modality in terms of remission of hand eczema and subsequent flares.

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Discussion

PUVA remains an important treatment option for those patients who have a contraindication to retinoids and for those who fail to respond or are intolerant to alitretinoin, or who relapse early after alitretinoin treatment. The efficacy of a retinoid + PUVA compared with alitretinoin should now be examined in patients who fail to respond to either therapy given alone.

Recommendations

- The semi-automated MPD tester was shown to be safe, convenient and reliable compared to the traditional ‘open-panel’ method of UVA lamps. This may be used in a larger cohort of patients undergoing topical PUVA treatment for other dermatoses, for example atopic dermatitis.

- Re-evaluation of the erythema action spectrum of topical psoralen sensitised skin has shown that peak sensitisation occurred at 325nm. Treatment of patients with 325nm lamps need to be explored as this has shown in controlled study environments to be

more efficacious than the standard UVA phototherapy cabins emitting longer wavelengths.

- Further studies are needed to evaluate the topical regime used in hand/foot dermatoses (eczema or psoriasis), particularly in patients with hyperkeratotic dermatoses. It is possible that a delay of 30 minutes following immersion in topical psoralen followed by UVA illumination may be more successful for such patients. However, completion of the current study is necessary to formally investigate this hypothesis.

CHAPTER SIX

PUBLICATIONS

Clinical study to validate Minimal Phototoxic Dose (MPD) measurements using a semi-automated MPD tester

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Introduction

The traditional method of assessing MPD in patients prior to commencing photochemotherapy (PUVA) is inconvenient, time-consuming and associated with numerous errors.

A Durham Minimal Erythema Dose (MED) tester was modified by fitting TL-10 UVA compact fluorescence lamps (CFL).

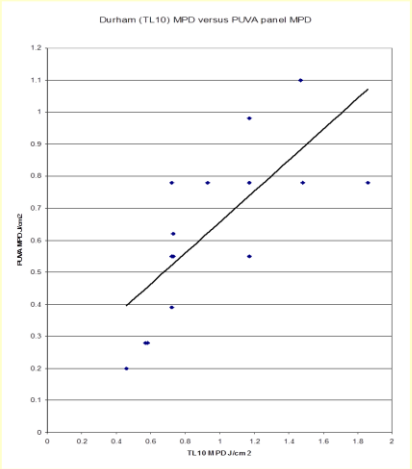
This study's objectives were to assess:
• If MPD testing is possible with a modified Durham MPD light source
• Whether a fixed factor to convert observed MPD with this device : PUVA-equivalent MPD may be calculated.

Methodology

• Patients due to commence PUVA phototherapy had both MPD tests performed on symmetrical, contra-lateral sites of the lower back

• MPD test results from a panel of PUVA lamps were compared to MPD from the modified Durham MPD tester

• Erythema was assessed at 72 hours (oral PUVA) or 96 hours later (bath PUVA).



Results

• 31 patients (13 Females, 18 Males)

• Aged 18 -65 years

Skin Type	No. Patients
I	4
II	11
III	12
IV	4

Linear relationship between Durham MPD to the PUVA panel MPD:

PUVA MPD = 0.48 x Durham MPD + 0.17 J/cm2

• Measured PUVA MPD was 0.48 of the Durham MPD not 0.15 as predicted by the published PUVA action spectrum[1].

Conclusion

• The modified Durham MPD tester is a convenient and reliable method for PUVA MPD testing.

• The difference in MPD between the PUVA lamps and the TL-10 lamp was lower than predicted from published PUVA action spectrum studies.

• This uncertainty about results from the original studies from 1982 suggests that formal re-evaluation of the erythema action spectrum for PUVA is now needed.

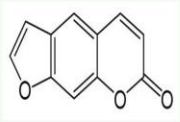
References

1. Cripps DJ, Lowe NJ, Lerner AB. Action spectra of topical psoralens: a re-evaluation. Br J Dermatol 1982; 107: 77-82

CHAPTER SIX

PUBLICATIONS

PUVA THROUGH THE AGES
Ibn al-Bitar to El-Mofty



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Psoralens and ultraviolet light have been used in the treatment of cutaneous disease since antiquity.

- The "Ebers Papyrus", (fig.1) an ancient Egyptian papyrus, (circa 1550 B.C.) is the oldest preserved medical document[1]
- 110-pages contain >700 remedies for various ailments
- Psoralea corylifolia,(family Leguminosa), seeds were used to treat vitiligo.
- Physicians and herb specialists formulated preparations - either applied topically as a paste or ingested two hours prior to sun exposure.

Fig. 1 Part of Ebers Papyrus. Stored at the University of Leipzig library, Germany[2]

- Source of the papyrus is unknown, allegedly found between the legs of a mummy in the Assassif district of the Theban necropolis[2]
- 1872 George Ebers, a German Egyptologist, purchased the papyrus in Luxor (Thebes) [2]

Psoralea corylifolia

Middle Ages were the dark period of phototherapies, pale skin represented wealth and beauty, phototherapy floundered

IBN al-BAITAR[3]

- One of the greatest scientists of Al-Andalus(Andalucia)
- Highly regarded botanist and pharmacist of the Middle Ages.
- Systematically observed, analyzed and classified materia medica
- Greatest botanical compilations in history, and botanical authority for centuries.

Ibn al-Baitar
1197-1248

- Wrote Kitab al-Adwiya al-Mufrada[3] (fig. 2) pharmaceutical-encyclopaedia:
- 1,400 medicinal plants and vegetables, of which 200 plants were not known earlier
- Describes "cure" for leukoderma using powdered seeds of Aatrillal,(*Ammi majus* linnaeus) and sunlight

Fig. 2 Kitab Al-Adwiya Al-Mufrada[3]

Fig. 3 Aatrilal (*Ammi majus*)

- Aatrilal (fig. 3)
Still used by Egyptian herbalists today as treatment for vitiligo

3 millenia later.....

- 1947 – Fahmy[4], an Egyptian pharmacologist and his student Abu-Shady, isolated psoralen compounds from Ammi majus
- 1948 – El-Mofty[5], an Egyptian dermatologist, first reported the successful use of crystalline 8-methoxypsoralen plus sunlight achieving repigmentation of vitiliginous macules

References
1.Pathak MA, Fitzpatrick TB. The evolution of photochemotherapy with psoralens and UVA(PUVA): 2000BC to 1992AD. *J Photochem, Photobiol B Biol* 1992;**14**:3-22
2.http://www.galter.northwestern.edu/news/index.cfm/2007/10/3Milestones-in-Dermatology-15721808-Selected-Treasures-in-the-Galter-Librarys-Special-Collections
3.www.wn.com/Ibn_al-Baitar#
4.Fahmy IR and Abu-Shady H. Ammi Majus Linn: pharmacological study and isolation of a crystalline constituent, ammoidin. Q. J. Pharm. Pharmacol. 1947; **20**: 281-291
5.El-Mofty AM. A preliminary clinical trial report on the treatment of leukoderma with *Ammi Majus* linn. *J.R.Egypt Med Assn* 1948; **21**:651-65

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Viewpoints in dermatology • Invited clinical opinion

Invited clinical opinion

Is there still a role for psoralen ultraviolet A in the treatment of chronic hand eczema?

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The obituary for psoralen ultraviolet A (PUVA) as treatment for chronic hand eczema (CHE) ignores the existing evidence and may deny some patients a useful treatment option.

The licensing of alitretinoin for treatment-resistant CHE has greatly improved the outlook for patients with this disabling variant of eczema. The evidence for the efficacy of this drug is robust, with two multinational randomized controlled trials published, although their design would have been improved by inclusion of quality-of-life (QOL) outcomes.[1] In the first study, 319 subjects were treated over a 12-week period, and a significant dose-dependent improvement in disease status was reported. However, 3 months after discontinuation of treatment, the rate of relapse was 26%, independent of dose.[2] In the subsequent study, 1032 subjects were treated over a 24-week period; 47.7% of subjects had clear or almost clear skin by week 24 of treatment with 30 mg alitretinoin, compared with 16.6% for placebo ($P < 0.001$). A confounding factor was the discontinuation of treatment halfway through the study in a subgroup of responders.[1] Median time to relapse was 5–6 months.[3] The main adverse events (AEs) reported in these two studies were headache, dry mouth and erythema. In addition, increases in cholesterol and triglycerides occurred, as did asymptomatic changes in levels of thyroid-stimulating hormone. AEs were generally dose-dependent and reversible.

It is clear from these studies that alitretinoin is not effective in all cases of CHE, that many patients relapse after withdrawal of treatment, and that 10% of patients receiving 30 mg withdrew from the trial because of AEs.[1–3] What alternative treatments are available for this group of alitretinoin nonresponders and for women of child-bearing age, for whom systemic retinoids are contraindicated?

Topical PUVA is one option for treatment-resistant CHE. Unlike topically applied PUVA in the form of a gel, lotion or cream preparation, soak PUVA allows a more uniform cutaneous absorption of 8-methoxypsoralen (8-MOP); the macerated stratum corneum of CHE facilitates penetration of 8-MOP, and carries a lower risk of phototoxic reactions and persistent hyperpigmentation than topically applied psoralens.[4] Furthermore, patients with CHE do not have several courses of topical PUVA; the cumulative doses are usually low, and there is no evidence for a skin cancer risk after topical hand / foot soak PUVA.

In a prospective trial of 38 subjects with CHE treated with PUVA three times / week, 53% patients were disease-free after an average of 19 sessions (range 8–42) with patients receiving treatment,[5] and 29% of patients had improved after an average of 12 sessions (range 1–22 weeks). Maintenance was given once a week for most patients, and one patient had maintenance twice a week.[5] 'Disease-free' patients remained in remission for a median period of 10 months.[5] When relapse occurred in these subjects it was reported to be more benign than previously.[5]

Grattan et al. reported a double-blind randomized within-patient trial on 15 subjects, comparing topical PUVA against UVA for the treatment of vesicular CHE. There was improvement in both hands during the 8-week treatment period ($P < 0.05$), and they remained subjectively and objectively better during the 8-week follow-up, with no significant difference between treatment methods at any stage. At follow-up 18 months later, four patients reported that their eczema was healed. The authors concluded that UVA alone may be beneficial for CHE.[6]

In a further study, narrow-band UVB was compared with paint PUVA in a 9-week prospective, left–right comparison study of 15 patients with the dry and dyshidrotic types of CHE. Both groups showed clinical improvement, with little difference between treatment methods.[7]

A retrospective study on localized topical and systemic photochemotherapy for chronic hand and foot dermatoses of 40 patients noted no difference in efficacy between treatment methods. However, the study population was mixed, and included patients with psoriasis, palmoplantar pustulosis and CHE. This more recent study included QOL measurements, unlike the earlier studies.[8] A recent open-label RCT compared the efficacy of home-administered oral PUVA with hospital-delivered bath PUVA for CHE in 150 patients. Both groups responded well, and there was no difference between treatment groups after 10 weeks and at follow-up 8 weeks later.[9]

In conclusion, alitretinoin has undoubtedly improved our ability to treat resistant CHE. However, PUVA remains an important treatment option for those patients who have a contraindication to retinoids and for those who fail to

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respond or are intolerant to alitretinoin, or who relapse early after alitretinoin treatment. The efficacy of a retinoid + PUVA compared with alitretinoin should now be examined in patients who fail to respond to either therapy given alone. We therefore respectfully suggest that the demise of PUVA as a treatment option for CHE has been exaggerated.

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References

1 Ingram J, Batchelor JM, Williams HC. Alitretinoin as a potential advance in the management of severe chronic hand eczema. Arch Dermatol 2009; 145: 314–5.
2 Ruzicka T, Larsen FG, Galewicz D et al. Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy results of a randomized, double-blind, placebo-controlled, multicenter trial. Arch Dermatol 2004; 140: 1453–9.
3 Bissonnette R, Worm M, Gerlach B et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. Br J Dermatol 2010; 162: 420–6.
4 Schempp CM, Muller H, Czech W et al. Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. J Am Acad Dermatol 1997; 36: 733–7.
5 Tegner E, Thelin I. PUVA treatment of chronic eczematous dermatitis of the palms and soles. Acta Dermato Venereologica 1985; 65: 451–3.
6 Grattan CEH, Carmichael AJ, Shuttleworth GJ et al. Comparison of topical PUVA with UVA for chronic vesicular hand eczema. Acta Derm Venereol 1991; 71: 118–22.
7 Sezer E, Etikan I. Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema. Photodermatol Photoimmunol Photomed 2007; 23: 10–4.
8 Hawk JL, Grice PL. The Efficacy of localized PUVA therapy for chronic hand and foot dermatoses. Clin Exp Dermatol 1994; 19: 479–82.
9 van Coevorden AM, Kamphof WG, van Sonderen E et al. Comparison of oral psoralen-UV-A with a portable tanning unit at home vs hospital-administered bath psoralen-UV-A in patients with chronic hand eczema: an open-label randomized controlled trial of efficacy. Arch Dermatol 2004; 140: 1463–6.

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CONCISE COMMUNICATION

BJD
British Journal of Dermatology

Minimal phototoxic dose (MPD) measurements for topical photochemotherapy using a semiautomated MPD tester

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Summary

Background The traditional method of assessing minimal phototoxic dose (MPD) prior to photochemotherapy with psoralen–ultraviolet A (PUVA) is inconvenient and cannot directly determine PUVA start doses. A handheld minimal erythema dose UVB tester can be modified by fitting a TL-10 UVA compact fluorescence lamp (CFL).

Objectives To determine whether MPD testing is possible with a CFL and to calculate a fixed factor to convert observed MPD to PUVA-equivalent MPD.

Methods Patients had two sets of MPD tests performed on symmetrical, contralateral sites on the lower back. MPD test results from a panel of PUVA lamps were compared with MPD from the modified handheld tester. Additionally, a questionnaire survey was completed by 43 U.K. phototherapy units to assess routine practice concerning MPD testing prior to PUVA therapy.

Results Thirty-seven patients with psoriasis were recruited. Boston phototypes in the 31 with conclusive MPD reactions were: I, four; II, 11; III, 12; and IV, four. The handheld MPD results were linearly related to the PUVA panel MPD results as follows: PUVA MPD = 0·48 ϴ handheld MPD + 0·17 J cm^{-2}. The measured PUVA MPD was 0·48 of the handheld MPD, not 0·15 as predicted by the published PUVA action spectrum.

Conclusions The modified MPD tester is a convenient and safe method for PUVA MPD testing, overcoming many problems of the 'traditional method'. The difference between the PUVA and TL-10 lamps was lower than predicted from published studies. This suggests that formal re-evaluation of the erythema action spectrum for PUVA is now needed.

What's already known about this topic?

- Minimal phototoxic dose (MPD) tests prior to commencing psoralen–ultraviolet A (PUVA) therapy optimize therapeutic potential.
- Few units perform MPD testing despite recommendations from published PUVA guidelines.

What does this study add?

- A modified handheld MPD tester provides a safe and convenient method for MPD assessment.
- A PUVA-equivalent dose may be calculated from the MPD induced by the compact fluorescence lamp TL-10 tube.
- Formal re-evaluation of the erythema action spectrum for PUVA is now needed.

Psoralen–ultraviolet A (PUVA) phototherapy has an important therapeutic role in cases of dermatoses recalcitrant to conventional narrowband UVB phototherapy, and is still used in psoriasis, atopic eczema and mycosis fungoides.[1] Initial treatment doses are limited by the sensitivity of unaffected, normal skin. To optimize PUVA phototherapy, it is important to

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establish the lowest dose of UV radiation that causes a just-perceptible erythema – the minimal phototoxic dose (MPD). The British Photodermatology Group guidelines[2] also recommend subsequent dose increments based on a percentage (20–40%) of the previous dose. This serves a dual purpose, to minimize both the cumulative number of PUVA treatments and the incidence of adverse effects. It also establishes that sufficient psoralen is present in the patient's skin. If the extent of disease precludes MPD testing, the initial dose is based on skin phototype.

The traditional method of assessing MPD is cumbersome and time consuming for both patients and staff and requires a separate source of UVA. In our unit, this used to take 15–20 min. Several small areas of skin are exposed to increasing doses of UVA from a panel of UVA lamps.

This 'open' source is associated with the potential for errors, including UV source nonuniformity due to curvature of the test site, patient movement and exposure timing errors. A device that overcomes many of these difficulties is the minimal erythema dose (MED) tester used for UVB.[3] This uses a compact fluorescence tube (CFL) in a handheld housing as the source and a UVB opaque template with 10 9 1-cm-diameter apertures. The output of nine of these apertures is successively attenuated by a factor of 1·25 by steel shaver-type foils. Our previous study established that the test–retest reliability of this method was high. The kappa measure of agreement was calculated for the comparison of two MED tests prepared on the same patient at the same time, and for two MED tests on the same patient but administered 24 h later. Both scenarios gave agreement of 0·8 or higher, indicating excellent agreement.[3] Differences in photosensitivity results using different magnitudes of irradiance (testing 'reciprocity') have been checked by our group using a high-intensity UVA-1 light-emitting diode source. We found no differences in MED using 100 mW cm^{-2} and 200 mW cm^{-2} intensities. This indicates that there are unlikely to be significant differences between our two MPD methods, which differed in applied UVA-1 irradiance by a factor of 2 (approximately 8 mW cm^{-2} for PUVA panel vs. approximately 16 mW cm^{-2} for modified UVA MPD tester).

CFLs with the same UVA spectrum as phototherapy lamps (Philips Cleo series lamps; Philips, Amsterdam, the Netherlands) are not available. As industrial, consumer and medical users of UVA require larger irradiation areas, this has been achieved using traditional 6-foot (180-cm) and 2-foot (60-cm) fluorescent tubes. Manufacturers have little commercial incentive to choose UVA CFL spectra that are exactly the same as the larger tube lamps. The nearest equivalent CFL to a PUVA lamp is the Philips TL-10 CFL, which has a narrower spectrum centred around a longer wavelength.

As PUVA photochemotherapy uses only psoralen as the sensitizer and only PUVA-designated lamps, it may be possible to establish a fixed factor to convert observed MPD using the TL-10 CFL to a PUVA-equivalent MPD. This would be convenient and repeatable, ameliorating many of the disadvantages of the traditional method.

Materials and methods

This study was approved by the South East Wales Local Research Ethics Committee. A prospective randomized left–right comparison study was carried out on 31 patients with psoriasis due to commence PUVA phototherapy. All patients soaked in 30 mL 1·2% 8-methoxypsoralen bath lotion (Puvasoralen; Crawford Pharmaceuticals, Knutsford, U.K.), in 140 L water (2·6 mg L^{-1} psoralen) for 10 min at 37 °C. All patients recruited had a template with 8 9 1-cm or 10 9 1-cm square apertures with removable covers applied to an uninvolved area of skin of the lower back. The remainder of the patient's skin was fully protected from UV exposure. A panel of UVA lamps was positioned 20 cm from the patient and was used to illuminate the test site after a warm-up period of 10 min. The covers were removed sequentially at specific intervals enabling a graduated decrement of UVA dose by a factor of 1·41 between successive sites. The modified handheld MPD tester was used on a symmetrical contralateral site on the lower back. For a calibration with a margin of 8% uncertainty, the compact MPD tester requires 2 min warm-up and 15 min cool down between successive MPD tests. MPD test results from a panel of PUVA lamps were compared with MPD from the modified Durham MPD tester (10 apertures with 1·26 factor between doses). Erythema was assessed 96 h later (bath PUVA). Phototherapy nurses assessed MPD reactions according to usual practice. They were not blinded to the test method allocation.

A questionnaire survey was sent to 78 phototherapy units around the U.K. to gauge current practice concerning usage of MPD testing in phototherapy treatment protocols (see Supporting Information Data file S1). Responses from 43 phototherapy units were obtained. The survey comprised five questions. It was estimated that accurate completion of the questionnaire would take no more than 3 min.

Results

Thirty-seven patients with psoriasis (17 women and 20 men) aged 18–65 years were recruited. Six had inconclusive MPD reactions and were excluded from the studies. The phototypes of the remaining 31 patients included four with skin type I, 11 with skin type II, 12 with skin type III and four with skin type IV. The handheld MPD results were linearly related to the PUVA panel MPD results as follows:

$$\text{PUVA MPD} = 0 \cdot 48 \times \text{handheld MPD} + 0{:}17\ \text{J cm}^{-2}$$

The linear regression was performed on logarithmically transformed data, as a geometric dose series was used (Fig. 1).

The measured PUVA MPD was 0·48 times the handheld MPD, not 0·15 as predicted by the published PUVA action spectrum.[4] The ratios of PUVA MPD to handheld MPD ranged from 0·43 to 1·08. The PUVA-equivalent MPD differed by a maximum of 0·28 J cm^{-2} higher and 0·26 J cm^{-2} lower than the panel MPD; in 90% of cases the difference was one or fewer MPD categories.

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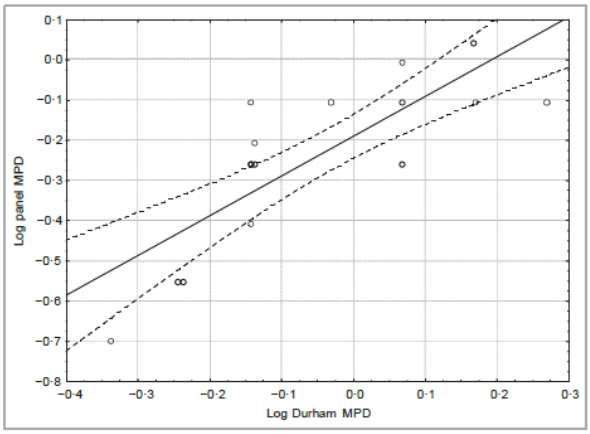

Fig 1. Relationship between the logarithmic transformed minimal phototoxic dose (MPD) values determined by the handheld MPD tester and from a panel of psoralen–ultraviolet A lamps. Pearson's correlation coefficient, $r = 0{\cdot}82$, $P < 0{\cdot}001$, $r^2 = 0{\cdot}67$. Dotted lines represent the 95% confidence intervals about the line of best fit. Overlapping data points are not shown.

Furthermore, only six of 43 phototherapy centres (14%) that responded to our survey routinely performed MPD testing. The remainder found the practice was time consuming, and commenced treatment based on Fitzpatrick skin type.

Discussion

The handheld MPD results are linearly related to the PUVA panel MPD results. However, the difference in MPD between the PUVA lamp and the modified handheld MPD tester (CFL TL-10 lamp) was much less than predicted from the PUVA action spectrum. The erythemal effectiveness of the TL-10 lamp, calculated using the PUVA erythema action spectrum, is 2·48, compared with the PUVA lamp effectiveness of 16·33 (arbitrary units). Thus PUVA MPDs should be 0·15 of the TL-10 MPDs. This suggests that formal re-evaluation of the erythema action spectrum for PUVA is now needed. Furthermore, only 14% of phototherapy centres surveyed routinely assess MPD prior to photochemotherapy, the principle reason being that it is too time consuming. We conclude that the small handheld MED tester, being convenient and reliable, could be made available for MPD testing by replacing the UVB tube with a CFL TL-10 tube. The MPD dose is then adjusted according to our results to indicate a PUVA-equivalent dose.

References

1 Stern RS. Psoralen and ultraviolet A light therapy for psoriasis. N Engl J Med 2007; 357:682–90.
2 Halpern SM, Anstey AV, Dawe RS et al. Guidelines for topical PUVA: a report of the workshop of the British Photodermatology Group. Br J Dermatol 2000; 142:22–31.
3 Otman SG, Edwards C, Gambles B, Anstey AV. Validation of a semi-automated method of minimal erythema dose testing for narrow-band B phototherapy. Br J Dermatol 2006; 155:416–21.
4 Cripps DJ, Lowe NJ, Lerner AB. Action spectra of topical psoralens: a re-evaluation. Br J Dermatol 1982; 107:77–82.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Data S1. PUVA questionnaire.

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TRANSLATIONAL RESEARCH

BJD
British Journal of Dermatology

Erythema action spectrum of topical 8-methoxypsoralen-sensitized skin re-evaluated: implications for routine clinical practice

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Summary

Background Published methodology used to determine psoralen plus ultraviolet A (PUVA) erythemal action spectrum does not reflect current clinical practice for psoralen sensitization. We re-evaluated the PUVA action spectrum using aqueous 8-methoxypsoralen (8-MOP) 2·6 mg L^{-1} as used routinely in current clinical practice.

Objectives To determine the UVA erythema action spectrum of topical 8-MOP-sensitized normal skin.

Methods Twenty healthy volunteers with skin phototypes I–V were recruited. Forearms were psoralen-sensitized at 37 °C for 10 min. Six UVA irradiations at 10-nm intervals between 325 and 375 nm were randomly allocated to forearm sites and were applied using a 10-nm bandwidth irradiation monochromator. The visual minimal phototoxic dose (MPD) was recorded on each site at 96 h.

Results Volunteer Boston phototypes were: I, n = 2; II, n = 6; III, n = 6; IV, n = 5 and V, n = 1. The mean MPD (J cm^{-2}) for all subjects at each wavelength was as follows: 325 nm, 0·64 (SD 0·37); 335 nm, 0·80 (SD 0·58); 345 nm, 0·96 (SD 0·55); 355 nm, 1·50 (SD 0·85); 365 nm, 2·19 (SD 0·90); and 375 nm, 2·89 (SD 1·06). Therefore, the relative sensitization at each wavelength (erythemal action spectrum) was: 1, 0·83, 0·67, 0·43, 0·29 and 0·22. There were significant differences between the PUVA erythemal effectiveness at different wavelengths but none between skin types.

Conclusions This study has established the erythemal action spectrum for bath/soak PUVA therapy as is currently performed. In all volunteers, the peak sensitivity was at 325 nm. All volunteers showed a similar trend across the wavelengths studied irrespective of skin type. The determination of the action spectrum for PUVA-induced erythema is important as it permits reliable estimates of erythemal efficacy of any UVA source where the emission spectrum of the lamp is known or can be measured.

What's already known about this topic?

- Previously published studies on topical psoralen plus ultraviolet A (PUVA) action spectrum do not reflect current practice.
- Published studies failed to predict the erythemal effectiveness of a nonstandard UVA lamp.

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What does this study add?

- This study has established the erythemal action spectrum for bath/soak PUVA therapy as is currently performed.
- The therapeutic action spectrum for topical PUVA appears to be similar to the action spectrum of topical PUVA erythema, with peak senstivity at 325 nm.
- This study allows reliable estimates of erythemal efficacy of any UVA source where the emission spectrum of the lamp is known or can be measured.

Published research on topical psoralen ultraviolet A (PUVA) erythemal action spectrum has used methods that do not reflect current clinical practice for psoralen sensitization. The study by Cripps et al.[1] used 8-methoxypsoralen (8-MOP) at 1% dissolved in acetone and then in ethanol and applied (via pipette) directly to the skin of the lower dorsum trunk of six white male subjects. This was then followed by irradiation with various wavelengths of UVA. No details were provided for the time between application of psoralen and UVA irradiation. Minimal phototoxic doses (MPDs) were read at 72 h. These findings showed a peak sensitivity between 330 and 335 nm for 8-MOP, six times more effective than 365 nm. In the study by Buck et al.[2] there was a delay of between 1.5 and 2 h between application of 1% 8-MOP solution in chloroform and illumination with UVA.

This scenario differs greatly from present clinical practice in the U.K., where the skin is immersed in an aqueous solution of 8-MOP at 37 °C for 15 min,[3] followed by UVA irradiation within 30 min. The study by Schempp et al.[4] showed that there was a marked, significant reduction in erythema after a 60-min delay between soaking in an 8-MOP bath and irradiation and no erythema was detected after 180-min and 360-min delays. Man et al.[5] showed that time to develop topical 8-MOP-induced erythema had a broad peak at 120 h. However, MPD assessment during or beyond 120 h is best avoided due to confounding effects of the development of pigmentation. Their recommendation was that topical 8-MOP MPD should be read 4 days (96 h) after exposure.[5,6] Therefore, we re-evaluated the PUVA erythema action spectrum using aqueous psoralen at 2·6 mg L^{-1} concentration as is used routinely in current clinical practice in the U.K. and assessed MPDs at 96 h.

Materials and methods

This study was approved by the South East Wales Local Research Ethics Committee. A prospective randomized single-blinded study was carried out on 20 healthy volunteers with skin phototypes I–V. A randomization table was produced using the random number function in Microsoft Excel to determine the location of each wavelength to either right or left forearm. The position of each wavelength test area was not blinded to the assessors. The Boston classification of skin phototype was determined in all volunteers.[7] Their forearms were soaked in 2·5 mL 1·2% 8-MOP bath lotion (Puvasoralen; Crawford Pharmaceuticals, Knutsford, U.K.) in 10 L water (2·6 mg L^{-1} psoralen) for 10 min at 37 °C. After drying the area, a template made from opaque Fablon (sticky-backed plastic) with 18 holes (6-mm diameter) in a grid pattern was applied to the volar forearms 2 cm from the antecubital fossae to facilitate accurate irradiation of the test sites, and again at the time of reading to help identify the previously irradiated sites. UVA irradiation was then applied. Six UVA irradiations at 10-nm intervals with centre wavelengths between 325 and 375 nm were tested on volunteers' volar forearm skin (three wavelengths per forearm) using a 1-Kw Xenon arc irradiation monochromator (components from Newport Oriel, Irvine, CA, U.S.A.) with a full width at half maximum bandwidth of 10 nm. A water filter removed infrared radiation. A Schott WG320 filter was used to reduce the UVB content. The UVB content at each wavelength was checked from their measured spectra. The 325-nm spectrum contained less than 0·1% UVB, while all other wavelengths used contained less than 0·01% UVB.

For each volunteer at each wavelength the irradiance at the application face of the light guide was measured using a calibrated radiometer. This was used to calculate the times (minutes:seconds) required to apply the dose sequence for that wavelength to the volunteer's skin. Measured irradiances at each centre wavelength ranged as follows: 325 nm, 24·2–36·6 mW cm^{-2}; 335 nm, 33·6–49·6 mW cm^{-2}; 345 nm, 39·8–59·5 mW cm^{-2}; 355 nm, 48·9–66·6 mW cm^{-2}; 365 nm, 52·5–71·8 mW cm^{-2} and 375 nm, 58·0–75·2 mW cm^{-2}. Each site was irradiated with a sequence of geometrically increasing (40% increment) doses via a liquid light guide with a circular area of 5-mm diameter. Erythema was measured using an erythema/melanin meter (Mexameter, Courage + Khazaka Electronic GmbH, Cologne, Germany) at each of the six sites. One measurement of nonirradiated skin at each of the six sites was also recorded. Visual assessments of erythema were agreed by two observers and recorded for each site at 96 h. At each wavelength the dose required to elicit a barely perceptible erythema was designated as the MPD for that particular wavelength.

Results

Boston phototypes in the 20 volunteers (14 women, six men) with mean age 44·5 years (range 23–67 years) were as

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follows: type I, n = 2; type II, n = 6; type III, n = 6; type IV, n = 5 and type V, n = 1.

The mean MPD (J cm^{-2}) for all subjects at each wavelength was as follows: 325 nm, 0·64 (SD 0·37); 335 nm, 0·80 (SD 0·58); 345 nm, 0·96 (SD 0·55); 355 nm, 1·50 (SD 0·85); 365 nm, 2·19 (SD 0·90) and 375 nm, 2·89 (SD 1·06) (Fig. 1).

PUVA erythemal effectiveness was determined by wavelengths (ANOVA, $P < 0·05$). There were no significant differences between the PUVA erythema action spectrum and skin types (Fig. 2).

The mean MPD values can be used to calculate the relative sensitization at each wavelength (the erythemal action spectrum). The action spectrum for topical PUVA erythema at 10-nm intervals between 325 and 375 nm was: 1, 0·83, 0·67, 0·43, 0·29 and 0·22.

With small numbers of data (n = 20) and all results from a geometric series, data distribution may not conform to a normal distribution. To check for possible non-normality errors, the calculation of the action spectrum was repeated using the geometric means at each wavelength. The resulting action spectrum sequence was 1, 0·89, 0·68, 0·44, 0·285 and 0·215. These figures did not materially differ from those calculated using the mean values, so the means were retained for the action spectrum calculation.

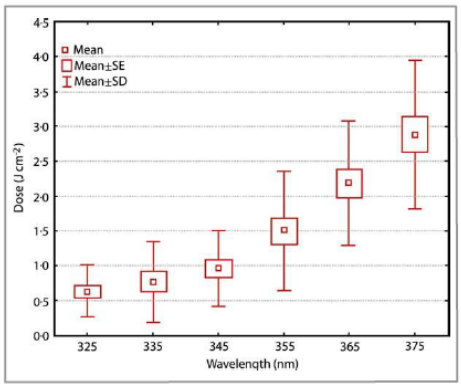

Fig 1. Minimal phototoxic dose of all volunteers at each wavelength.

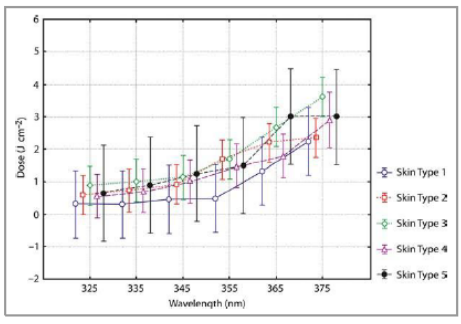

Fig 2. Minimal phototoxic dose by skin type at each wavelength. Vertical bars denote 95% confidence intervals.

Using Microsoft Excel a linear least squares best fit was applied to these values. The best fit equation was:

$$Y = -0.016x + 6.33$$

with $R^2 = 0·98$

The equation was used to interpolate values of the action spectrum at 1-nm intervals between 320 and 400 nm. All calculated values of the action spectrum were constrained to lie between 0 and 1, as values outside these limits are not possible (Fig. 3).

Discussion

It has been shown that the action spectrum of oral 8-MOP PUVA for clearance of psoriasis follows the PUVA erythema action spectrum.[8] If we assume that this will also be the case for topical PUVA this topical PUVA action spectrum can be used to assess the relative efficacy, or efficiency, of any lamps used for topical PUVA phototherapy. For example, typical fluorescent lamps that are used for whole-body and extremities PUVA can be compared with newer UVA sources. Applying the PUVA action spectrum relative sensitivities to each wavelength measured in any UVA lamp spectrum allows the calculation of the 'PUVA equivalent' output from that lamp. The ratio of this 'PUVA equivalent UVA' to the measured unweighted UVA irradiance gives a ratio that can be used to describe the 'PUVA efficiency' of any UVA lamp. Table 1 shows the PUVA effective ratio of typical PUVA sources used in clinical practice and other UVA lamps that may also be used for PUVA phototherapy.

In a previous study[9] we used the action spectrum published by Cripps et al.[1] to predict the PUVA erythemal efficacy of a Philips TL10 UVA1 compact fluorescent tube lamp compared with our standard PUVA lamps used to establish the MPD of patients in our phototherapy unit. We predicted that the TL10 lamp should be 0·15 as effective as the PUVA lamp. However, when we performed MPD assessments using each of these lamps in 37 of our patients we found that the TL10 lamp was in fact 0·48 as effective. We concluded that the published action spectrum was unreliable, and should be reassessed. We can now examine the effectiveness of these same lamps calculated using the action spectrum we have established in this study. Table 1 gives PUVA efficiency of the 2-ft fluorescent tube as 0·480, and that of the TL10 UVA1 compact fluorescent lamp as 0·236. The ratio of these gives our prediction of the relative erythemal efficacy of the UVA1 lamp compared with the PUVA lamp. This value (0·236/0·480) is 0·49, which is almost exactly the value (0·48) that we measured from the MPD results from our volunteer patients. This gives strong evidence of the validity of the action spectrum measured in this study.

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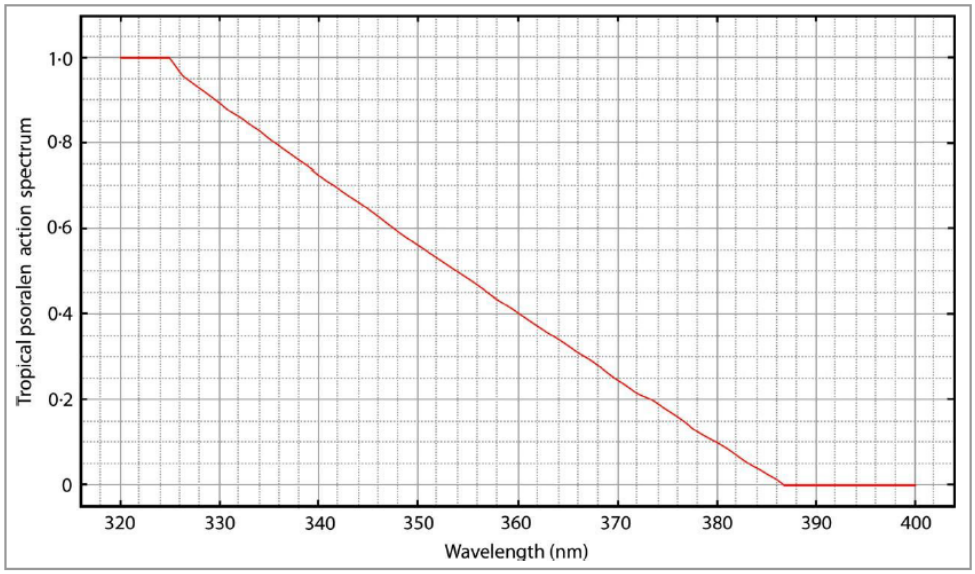

Fig 3. Topical psoralen plus ultraviolet A erythema action spectrum.

Table 1 PUVA effective ratio of typical PUVA sources used in clinical practice.

Lamp	Irradiance/PUVA erythemal irradiance	PUVA effective ratio
UV800K 2-ft fluorescent lamp	2·145/4·465	0·48
Philips cleo PUVA 6-ft fluorescent lamp	7·43/16·29	0·456
UVA1 LED	0·754/6·23	0·12
Blacklight compact fluorescent lamp	1·196/2·565	0·466
PhilipsTL10 compact fluorescent lamp	3·929/16·62	0·236
PUVA 180 UVA compact fluorescent lamp	2·956/7·461	0·396
TP4 UVA compact fluorescent lamp	10·64/22·25	0·478
Enfis UNO light engine 365 nm LED	12·44/55·93	0·22

LED, light-emitting diode; PUVA, psoralen plus ultraviolet A.

The therapeutic action spectrum of 8-MOP differs markedly from its absorption spectrum.[10] Potential reasons for this are that psoralen and 8-MOP undergo chemical changes on their incorporation into the skin. Exposure to UVA and the action spectra within the skin will differ according to the absorption spectra of the chromophores they target. The UV absorption spectra for psoralen and 8-MOP compounds have been reported by Fowlks[11] as having maxima in their absorption spectra at approximately 220, 245 and 295 nm (with a shoulder at 330 nm) for psoralen and 220, 250 and 310 nm for 8-MOP.

This study has established the erythemal action spectrum for bath or soak PUVA therapy for the first time, using an aqueous application of psoralen as is used in routine clinical practice. In all volunteers, the action spectrum for 8-MOP-induced erythema has its maximum activity (peak sensitivity) at 325 nm. All volunteers showed a similar trend across the wavelengths studied irrespective of skin type. The PUVA-induced clearance of psoriasis study by Farr et al.,[8] involving 24 patients with psoriasis, found that lamps with peak emission at 325 nm were significantly superior to lamps with peak emission at 352 nm or 370 nm for clearance of psoriasis over a 6-week period. Equally erythemogenic doses from each of the lamps were used. They concluded that the therapeutic action spectrum for PUVA is not the same as the action spectrum for PUVA erythema. However, our topical PUVA action spectrum would more closely agree with their psoriasis clearance action spectrum. The output of lamps conventionally used in PUVA whole-body units have peak emissions at around 365 nm. A lamp with a peak emission at 325 nm would enable clearance of psoriasis with a lower cumulative UV dose over a shorter time period and would improve the efficacy and efficiency of PUVA.

Our measured action spectrum for topical 8-MOP PUVA-induced erythema differs from previously published erythema action spectra.[1,2] This is most probably due to the use of

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strong solvents to deliver the psoralen in a different concentration, and differences in timings in application of psoralen and reading of erythema in previous studies. Our study was designed to test sensitization of skin as would be experienced after topical (bath) 8-MOP-sensitization as performed in routine clinical practice today. Our action spectrum was confirmed by the results of our previous study on MPD values established from PUVA lamps and TL10 compact fluorescent lamps. As such, our action spectrum is most relevant in establishing the potential effectiveness of novel lamps for PUVA phototherapies.

This enables accurate assessment of new UVA lamps, such as light-emitting diodes or plasma screen sources, which may be used for PUVA in the future. Larger studies are required to assess differences in the PUVA erythema action spectrum between skin types.

References

1 Cripps DJ, Lowe NJ, Lerner AB. Action spectra of topical psoralens: a re-evaluation. Br J Dermatol 1982; 107:77–82.
2 Buck HW, Magnus IA, Porter AD. The action spectrum of 8-methoxypsoralen for erythema in human skin. Preliminary studies with a monochromator. Br J Dermatol 1960; 72:249–55.
3 Gruss C, Behrens S, von Kobyletzki G et al. Effects of water temperature on photosensitisation in bath-PUVA therapy with 8-methoxypsoralen. Photodermatol Photoimmunol Photomed 1998; 14:145–7.
4 Schempp CM, Schopf E, Simon JC. Phototesting in bath PUVA: marked reduction of 8-MOP activity within one hour after an 8-MOP bath. Photodermatol Photoimmunol Photomed 1996; 12:100–2.
5 Man I, Dawe RS, Ferguson J et al. The optimal time to determine the minimal phototoxic dose in skin photosensitized by topical 8 methoxypsoralen. Br J Dermatol 2004; 151:179–82.
6 Halpern SM, Anstey AV, Dawe RS et al. Guidelines for topical PUVA: a report of the workshop of the British Photodermatology Group. Br J Dermatol 2000; 142:22–31.
7 Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988; 124:869–71.
8 Farr PM, Diffey BL, Higgins EM et al. The action spectrum between 320 and 400 nm for clearance of psoriasis by psoralen photochemotherapy. Br J Dermatol 1991; 124:443–8.
9 Al-Ismail D, Edwards C, Al-Ofi O, Anstey AV. Minimal phototoxic dose (MPD) measurements for topical photochemotherapy using a semiautomated MPD tester. Br J Dermatol 2013; 169:687–9.
10 Lerner AB, Denton CR, Fitzpatrick TB. Clinical and experimental studies with 8-methoxypsoralen in vitiligo. J Invest Dermatol 1953; 20:299–314.
11 Fowlks WL. The chemistry of the psoralens. J Invest Dermatol 1959; 32:249–54.

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1. http://www.galter.northwestern.edu/news/index.cfm/2007/10/3Milestones-in-Dermatology-15721808-Selected-Treasures-in-the-Galter-Librarys-Special-Collections

2. Bendl BJ. PUVA photochemotherapy. *Canadian Medical Association Journal* 1978; **118**: 11:1348-50

3. Pathak MA, Fitzpatrick TB. The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. *Journal of Photochemistry and Photobiology B: Biol.,* 1992; **14:** 3-22

4. www.wn.com/Ibn_al-Baitar#

5. Fitzpatrick TB, Pathak MA. Historical aspects of methoxsalen and other furocoumarins. *Journal of Investigative Dermatology* 1959; **32(S)**:229-31

6. Kuske H. Experimentelle Untersuchungen zur Photosensibilisierung der Haut durch pflanzliche Wirkstoffe . Lichtensensibilisierung durch furocoumarine als Ursache verschiedener phytogener Dermatosen. *Archives of Dermatology Syph*ilol. 1938;**178**:112-123.

7. Fahmy IR and Abu-Shady H. Ammi Majus Linn: pharmacological study and isolation of a crystalline constituent, ammoidin. Q. J. Pharm. Pharmacol. 1947; **20**: 281-291

8. El-Mofty AM A preliminary clinical report on the treatment of leukoderma with *Ammi majus* Linn, *J.R. Egypt Med Assoc* 1948; *31*:651-65

9. Parrish JA, Fitzpatrick TB, Pathak MA *et al.* Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. *New England Journal Medicine* 1974; **291:** 1207-1211

10. Hönigsmann H, Jaschke E, Gschnait F *et al.* 5 – methoxypsoralen (bergapten) in photochemotherapy of psoriasis. *British Journal of Dermatology* 1978; **101:** 369-378

11. Berg M, Ros AM. Treatment of Psoriasis with Ultraviolet-A. A double-blind comparison of 8-methoxypsoralen and 5-methoxypsoralen. *Photodermatology, Photoimmumology and Photomedicine* 1994; **10(5):** 217-220

12. Melski JW, Tanenbaum L, Parrish JA *et al.* Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. *Journal of Investigative Dermatology* 1977; **68**:328-35

13. Henselar T, Wolff K, Hönigsmann H, *et al.* Oral 8-methoxypsoralen photochemotherapy of psoriasis. The European PUVA study: a cooperative study among 18 centres. *Lancet* 1981; **1**:853-7

14. Fritsch RO, Hönigsmann H, Jaschke E *et al.* Augmentation of oral methoxsalen-photochemotherapy with an oral retinoic acid derivative.*Journal of Investigative Dermatology* 1978; **70**:178-182

15. Edelson R, Berger C, Gasparro F *et al.* Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. *New England Journal of Medicine* 1987;**316:**297-303

16. McKenna KE, Whittaker S, Rhodes LE, et al. Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *British Journal of Dermatol*ogy 2006;154(1):7-20.

17. Knobler RM, French LE, Kim Y, et al. A randomised, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. *Journal of the American Academy of Dermatol*ogy May 2006;54(5):793-9.

18. Neustadter JH, Samarin F, Carlson KR, Girardi M. Extracorporeal photochemotherapy for generalised deep morphea. *Archives of Dermatol*ogy Feb 2009;145(2):127-30.

19. Mathur K, Morris S, Deighan C, Green R, Douglas KW. Extracorporeal photopheresis improves nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis: three case reports and review of literature. *Journal of Clinical Apher*esis 2008;23(4):144-50.

20. Stern R, Nichols TK, Väkevä LH. Malignant Melanoma in Patients Treated for Psoriasis with Methoxsalen (Psoralen) and Ultraviolet A Radiation (PUVA). *New England Journal of Med*icine 1997;**336**:1041-1045

21. Stern R. The risk of melanoma in association with long-term exposure to PUVA Follow-up Study. *Journal of the American Academy of Dermatology* 2001;**44(5):**755-61

22. Scheinfeld N and Deleo V. A review of studies that have utilised different combinations of psoralen and ultraviolet B phototherapy and ultraviolet A phototherapy . *Dermatology Online Journal* 2003; **9**: (5)7

23. Bethea D, Fullmer B, Syed S *et al.* Review Article Psoralen photobiology and photochemotherapy: 50 years of science and medicine. *Journal of Dermatological Science* 1999; **19**: 78-88

24. Aboul-Enein HY, Kladna A, Kruk I, Lichszteld K, Michalska T. Effect of psoralens on Fenton-like reaction generating reactive oxygen species. *Biopolymers*. 2003; **72:** 59-68.

25. Trosko JE, Isoun M. Photosensitizing effect of trisoralen on DNA synthesis in human cells grown in vitro. *International Journal of Radiation Biology and Related Studies in Physics Chemistry and Med*icine 1971; **19:** 87-92.

26. Yurkow EJ, Laskin JD. Mechanism of action of psoralens: isobologram analysis reveals that ultraviolet light potentiation of psoralen action is not additive but synergistic. *Cancer Chemotherapy and Pharmacology*. 1991; **27**: 315-9.

27. Johnson R, Staiano-Coico L, Austin L *et al.* PUVA treatment selectively induces a cell cycle block and subsequent apoptosis in human T-lymphocytes. *Photochemistry Photobiology* 1996;63: 566-71

28. Coven TR, Walters IB, Cardinale I, Krueger JG. PUVA-induced lymphocyte apoptosis: Mechanism of action in psoriasis. *Photodermatology Photoimmunology & Photomedicine* 1999; **15**: 22-27.

29. Beijersbergen van Henegouwen GMJ, Wijn ET, Schoonderwoerd SA *et al.* Method for the determination of the in vivo irreversible binding of 8-methoxypsoralen (8-MOP) to epidermal lipids, proteins and DNA/RNA of rats after PUVA treatment. *Journal of Photochemistry Photobiology B: Biol* 1989; **3**: 631-5

30. Schmitt IM, Chimenti S, Gasparro FP. Psoralen-protein photochemistry – a forgotten field. *Journal of Photochemistry Photobiology B Biol* 1995; **27**: 101-7

31. Lerner AB, Denton CR and Fitzpatrick TB. Clinical and experimental studies with 8-methoxypsoralen in vitiligo. *The Journal of Investigative Dermatology* 1953; **20**: 299

32. Fowlks, W. L. The chemistry of the psoralens. *Journal of Investigative Dermatology* 1959; **32**: 249-254

33. Stegmaier OC. The use of methoxsalen in sun tanning. *The Journal of Investigative Dermatology,*1995; **32:** 345-349

34. Buck HW, Magnus IA and Porter AD. The action spectrum of 8-methoxypsoralen for erythema in human skin. Preliminary studies with a monochromator. *British Journal of Dermatology,* 1960; **72**: 249- 255

35. Pathak, MA. Mechanism of psoralen photosensitization in vivo biological action spectrum of 8-methoxypsoralen. *Journal of Investigative Dermatology* 1961; **37**, 397-407

36. Owens DW, Glicksman JM, Freeman RG *et al*. Biological action spectrum of 8-methoxypsoralen determined by monochromatic light. *Journal of Investigative Dermatology* 1968; **51**: 435 - 40.

37.Nakayama L, Morikawa F, Mukada M. *et al.* (1974) Action spectra of psoralen compounds. In: *Sunlight and Man* (Ed, by T.B, Fitzpatrick, M, A, Pathak, L .C Harber, M. Seiji and A, Kukita), p.599, University of Tokyo Press.

38. Cripps DJ, Lowe NJ, Lerner AB. Action spectra of topical psoralens: a re-evaluation. *British Journal of Dermatology* 1982; **107**: 77-82.

39. Gruss C, Behrens S, von Kobyletzki G *et al.* Effects of water temperature on photosensitisation in bath-PUVA therapy with 8-methoxypsoralen. *Photodermatology, Photoimmunology, & Photomedicine* 1998; **14**: 145-147

40. Schempp CM, Schopf E, Simon JC. Phototesting in bath PUVA: marked reduction of 8-MOP activity within one hour after an 8-MOP bath. *Photodermatology, Photoimmunology, & Photomedicine* 1996: **12**; 100-102

41. Artuc M, Stuetgetten G, Schalla W *et al.* Reversible binding of 5- and 8-methoxypsoralen to human serum proteins (albumin) and to epidermis in vitro. *British Journal of Dermatology* 1979; **101:**669-677

42. Roelandts R, Van Boven M, Deheyn T *et al.* Dietary influences on 8-MOP plasma levels in PUVA patients with psoriasis. *British Journal of Dermatology* 1981; **105:** 569-572

43. Herfst MJ, De Wolff FA. Intraindividual and interindividual variability in 8-methoxypsoralen kinetics and effect in psoriatic patients. *Clinical Pharmacology & Therapeutics* 1983; **34:**117-124

44. Hönigsmann H, Schwarz T. Photochemotherapy with Psoralens (PUVA). In Dermatology Third Edition. Bolognia J, Jorizzo JL, Schaffer JV. Elsevier Saunders 2012. Vol 2, p 2225

45. Brickl R, Schmid J, Koss FW. Clinical pharmacology of oral psoralen drugs. *Photodermatology* 1984; **1:**174-86

46. Weber G. Combined 8-methoxypsoraien and black light therapy of psoriasis. *British Journal of Dermatology* 1974: **90**: 317-25 .

47. Lakshmipathi T, Gould PW. Mackenzie LA *et al,* Photochemotherapy in the treatment of psoriasis. *British Journal of Dermatology* 1977;**96:** 587-94.

48. Abel EA. Goldberg I,H. Parber EM. Treatment of palmoplantar psoriasis with topical methoxsalen plus long-wave ultraviolet light. *Archives of Dermatology* 1980; **116:** 1257-61.

49. Layton AM. Sheehan-Dare R, Cunliffe W. A double-blind, placebo-controlled trial of topical PUVA in persistent palmoplantar pustuiosis. *British Journal of Dermatology* 1991; **124**: 581-4.

50. Konya J, Diffey BL, Hindson TC. Time course of activity of topical 8-methoxypsoralen on palmoplantar skin. *British Journal of Dermatology* 1992;**127:** 654-5.

51. Gazith J, Scballa W, Bauer E and Schaefer H. 8-methoxypsoralen (8-MOP) in human skin: penetration kinetics. *Journal of Investigative Dermatology* 1978; **71**: 126-30.

52. Halpern SM, Anstey AV, Dawe RS *et al.* Guidelines for topical PUVA: a report of the workshop of the British Photodermatology Group. *British Journal of Dermatology* 2000; **142**: 22-31

53. Fitzpatrick TB, Hopkins CE, Blickenstaff DD, Swift S. Augmented pigmentation and other responses of normal human skin to solar radiation following oral administration of 8-methoxypsoralen. *Journal of Investigative Dermatology* 1955; **25**: 187–90.

54. Frain-Bell W. Treatment. In: Cutaneous Photobiology. Oxford: Oxford University Press, 1985: 170-202.

55. Parrish JA. Methoxsalen-UV-A therapy of psoriasis. *Journal of Investigative Dermatology* 1976; **67**: 669–71.

56. Ibbotson SH, Farr PM. The time-course of psoralen ultraviolet A (PUVA) erythema. *Journal of Investigative Dermatology* 1999; **113**: 346–50

57. Man I, Dawe RS, Ferguson J *et al.* The optimal time to determine the minimal phototoxic dose in skin photosensitised by topical 8 methoxypsoralen. *British Journal of Dermatology* 2004; **151**: 179–182.

58. Fitzpatrick T.B. The validity and practicality of sun-reactive skin types I through VI. *Archives of Dermatology* 1988; **124** (6):869-71

59. Schiener R, Behrens-Williams SC, Pillekamp H *et al.* Does the minimal phototoxic dose after 8-methoxypsoralen baths correlate with the individual's skin phototype? *Photodermatology Photoimmunology & Photomedicine* 2001 Aug;**17**(4):156-8.

60. Kraemer CK, Menegon DB, Cestari TF. Determination of the minimal phototoxic dose and colorimetry in psoralen plus ultraviolet A radiation therapy**.** *Photodermatology Photoimmunology & Photomedicine*. 2005 Oct;**21**(5):242-8.

61. Hönigsmann H Psoralen photochemotherapy, mechanisms,drugs, toxicity. *Current Problems in Dermatology.* 1986;**15:** 52-66

62. Morison WL, Marwaha S, Beck L. PUVA-induced phototoxicity: incidence and causes. *Journal of the American Academy of Dermatology* 1997; **36:**183-5

63. Tegner E. Severe skin pain after PUVA treatment. *Acta Dermato Venereologica* 1979;**59:**467-70

64. Zamiri M, Bisland D. Treatment of bath PUVA-induced skin pain with gabapentin. *British Journal of Dermatology* 2004;**151:**516-517

65. Kumakiri M, Hashimoto K, Willis I. Biological changes of human cutaneous nerves caused by ultraviolet irradiation: an ultrastructural study. *British Journal of Dermatology* 1978;**99:**65-75

66. Ledbetter LS, Hsu S. Melanonychia associated with PUVA therapy. *Journal of the American Academy of Dermatology* 2003;**48:**S31-2

67. Gilchrest BA. Skin aging and photoaging: an overview. *Journal of the American Academy of Dermatology* 1989; **21:** 610–613.

68. Griffiths CE, Wang TS, Hamilton TA, *et al*. A photonumeric scale for the assessment of cutaneous photodamage. *Archives of Dermatology* 1992; **128:** 347–351

69. Chung J H. Photoageing in Asians. *Photodermatology, Photoimmunology & Photomedicine* 2003; **19**(3):109-121

70. Stern RS, Laird N for the Photochemotherapy Follow-Up Study. The carcinogenic risk of treatments for severe psoriasis. *Cancer.* 1994;73:2759-2764

71. Stern RS. Genital tumours among men with psoriasis exposed to psoralen and ultraviolet A-treated patients (PUVA) and ultraviolet B radiation. *New England Journal of Medicine* 1990;**322:**1093-7

72. Aubin F, Puzenat E, Arveux P, *et al.* Genital squamous cell carcinoma in men treated by photochemotherapy. A cancer registry-based study from 1978 to 1998. *British Journal of Dermatology.* 2001; **144:** 1204-6

73. Stern R, Nichols TK, Väkevä LH. Malignant Melanoma in Patients Treated for Psoriasis with Methoxsalen (Psoralen) and Ultraviolet A Radiation (PUVA). *New England Journal of Med*icine 1997;**336**:1041-1045

74. Hannuksela-Svahn A, Sirgurgeirsson B, Pukkala E, *et al.* Trioxsalen bath PUVA did not increase the risk of squamous cell carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis. *British Journal of Dermatology* 1999; **141**:497-501

75. Hannuksela-Svahn A, Pukkala E, Koulu L, *et al.* Cancer incidence among Finnish psoriasis patients treated with 8-methoxypsoralen bath PUVA. *Journal of the American Academy of Dermatology* 1999; **40**: 694-6

76. Malanos D, Stern RS. Psoralen plus ultraviolet A does not increase the risk of cataracts. A 25-year prospective study. *Journal of the American Academy of Dermatology* 2007; **57**: 231-7

77. Hönigsmann H. Psoralen photochemotherapy-mechanisms, drugs, toxicity. *Current Problems in Dermatology*. 1986; 15:52-66

78. Henseler T, Wolff K, Hönigsmann H, *et al.* Oral 8-methoxypsoralen photochemotherapy of psoriasis. The European PUVA study: a cooperative study among 18 centres. *Lancet* 1981; **1**:853-7

79. Calzavara-Pinton PG, Franceschini F, Rastrelli M, *et al.* Antinuclear Antibodies are not induced by PUVA treatment in uncomplicated psoriasis. *Journal of the American Academy of Dermatology* 1994; **30:** 955-8.

80. Stern RS. Psoralen and Ultraviolet A Light Therapy for Psoriasis. *New England Journal of Medicine* 2007; **357:** 682-90

81. Hönigsmann H, Schwarz T. Ultraviolet therapy. In: *Bolognia: Dermatology 2nd Edition*. Elsevier Inc., Amsterdam, The Netherlands (2008).

82. Tauscher AE, Fleischer AB Jr, Phelps KC *et al.* Psoriasis and pregnancy. *Journal of Cutaneous Medicine and Surgery* 2002;**6:**561-70.

83. Griffiths CE, Clark CM, Chalmers RJ *et al.* A systematic review of treatments for severe psoriasis. *Health Technology Assessment* 2000;**4:**1-125.

84. Gordon PM, Diffey BL, Matthews JNS, *et al*. A randomised comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *Journal of the American Academy of Dermatology* 1999; **41(5):** 728-732

85. Yones SS, Palmer RA, Garibaldinos TT, Hawk JL. Randomised double-blind trial of the treatment of chronic plaque psoriasis: efficacy of psoralen-UV-A therapy vs narrowband UV-B therapy. *Archives of Dermatology* 2006; **142:** 836-42.

86. Van Weelden H, De la Faille HB, Young E. *et al.* Comparison of narrowband UVB phototherapy and PUVA photochemotherapy in the treatment of psoriasis. *Acta Dermato Venereologica.*1990;**70**:212- 215

87. Tanew A, Radakovic-Fijan S, Schemper M *et al.* Narrowband UV-B phototherapy vs photochemotherapy in the treatment of chronic plaque psoriasis. *Archives of Dermatology.*1999;**135**:519- 524

88. Markham T, Rogers S, Collins P. Narrowband UV-B (TL-01) phototherapy versus oral 8-methoxypsoralen psoralen–UVA for the treatment of chronic plaque psoriasis. *Archives of Dermatology.* 2003;**139(3**):325-328

89. Brazzelli V, Barbagallo T, Trevisan V, *et al.* The duration of clinical remission of photochemotherapy and narrow-band UV-B phototherapy in the treatment of psoriasis: A retrospective study. *International Journal of Immunopathology and pharmacology* 2008; **21(2):** 481-484

90. Schmoll M, Henseler T, Christophers E. Evaluation of PUVA, topical corticosteroids and the combination of both in the treatment of psoriasis. *British Journal of Dermatology* 1978; **99:**693-702.

91. Morison WL, Parrish JA, Fitzpatrick TB. Controlled study of PUVA and adjunctive topical therapy in the management of psoriasis. *British Journal of Dermatology* 1978; **98:** 125-32.

92. Torras H, Aliaga A, Lopez-Estebaranz JL, *et al*. A combination therapy of calcipotriol cream and PUVA reduces the UVA dose and improves the response of psoriasis vulgaris. *Journal of Dermatological Treatment* 2004;**15:**98-103.

93. Nijsten TE, Stern RS. Oral retinoid use reduces cutaneous squamous cell carcinoma risk in patients with psoriasis treated with psoralen-UVA: a nested cohort study. *Journal of the American Academy of Dermatology* 2003;**49:**644-50

94. Anstey AV, Hawk JL. Isotretinoin-PUVA in women with psoriasis. *British Journal of Dermatology* 1997; **136:** 798-9

95. Özdemir M, Engin B, Baysal I, *et al*. A Randomised Comparison of Acitretin-narrow-band TL-01 Phototherapy and Acitretin-Psoralen plus Ultraviolet A for Psoriasis. *Acta Dermato-Venereologica* 2008; **8(6):**589-593

96. Lowe NJ, Weingarten D, Bourget T *et al.* PUVA therapy for psoriasis: a comparison of oral and bath-water delivery of 8-methoxypsoralen. *Journal of the American Academy of Dermatology* 1986; **14:**754-60

97. Collins P, Rogers S. Bath-water compared with oral delivery of 8-methoxypsoralen PUVA therapy for chronic plaque psoriasis. *British Journal of Dermatology* 1992;**127:** 392-5

98. Murray D, Corbett MF, Warin AP. A controlled trial of photochemotherapy for persistent palmoplantar pustulosis. *British Journal of Dermatology* 1980; **102:** 659-63

99. Rosen K, Mobacken H, Swanbeck G. PUVA, etretinate, and PUVA-etretinate therapy for pustulosis palmoplantaris. *Archives of Dermatology* 1987;**123**:885–9.

100. Layton AM, Sheehan-Dare R, Cunliffe WJ. A double blind, placebo-controlled trial of topical PUVA in persistent palmoplantar pustulosis. *British Journal of Dermatology* 1991;**124**:581–4.

101. Matsunami E, Takashima A, Mizuno N *et al.* Topical PUVA, etretinate, and combined PUVA and etretinate for palmoplantar pustulosis: comparison of therapeutic efficacy and the influences of tonsillar and dental focal infections. *Journal of Dermatology* 1990;**17**(2):92–6.

102. Lassus A, Lauharanta J, Eskelinen A. The effect of etretinate compared with different regimens of PUVA in the treatment of persistent palmoplantar pustulosis. *British Journal of Dermatology* 1985;**112**:455–9.

103.Nielsen PG, Madsen SM. Occlusive treatment of palmoplantar pustular psoriasis with clobetasol propionate ointment succeeded by short-term PUVA. *Journal of Dermatological Treatment* 1995;**6**:77–9.

104. Marsland AM, Chalmers RJG, Hollis S, *et al.* Interventions for chronic palmoplantar pustulosis. *Cochrane database of systematic reviews (Online)* 2006; **1:**1-51

105. Atherton DJ, Carabott F, Glover MT *et al.* The role of psoralen photochemotherapy (PUVA) in the treatment of severe atopic eczema in adolescents. *British Journal of Dermatology* 1988; **118:** 791-5

106. Sheehan MP, Atherton DJ, Norris P *et al.* Oral psoralen photochemotherapy in severe childhood atopic eczema: an update. *British Journal of Dermatology* 1993; **129:** 431-6

107. De Kort WJ, van Weelden H. Bath psoralen-ultraviolet A therapy in atopic eczema. *Journal of the European Academy of Dermatology and and Venereology* 2000; **14:** 172-4

108. Reynolds NJ, Franklin V, Gray JC *et al.* Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *Lancet* 2001 **357(9273):**2012-6.

109. Garritsen FM, Brouwer MW, Limpens J *et al.* Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *British Journal of Dermatology.* 2014; 170(3):501-13.

110. Krutmann J, Morita A. Therapeutic photomedicine: phototherapy. In: *Fitzpatrick Dermatology in General Medicine.* McGraw-Hill Inc., New York, NY, USA, 2243–2249 (2008).

111. Krutmann J, Diepgen TL, Luger TA *et al.* High-dose UVA1 therapy for atopic dermatitis: results of a multicentre trial. *Journal of the American Academy of Dermatology.* 1998; **38(4):** 589–593

112. Olsen E, Vonderheid E, Pimpinelli N, *et al*, and the ISCL/EORTC. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. Sep 15 2007;**110(6):**1713-22.

113. Gilchrest BA, Parrish JA, Tanenbaum L, Haynes HA, Fitzpatrick TB. Oral methoxsalen photochemotherapy of mycosis fungoides. *Cancer* 1976;**38(2):** 683–689

114. Herrmann JJ, Roenigk HH Jr, Hönigsmann H. Ultraviolet radiation for treatment of cutaneous T-cell lymphoma. *Hematology Oncology Clinics of North America* 1995; **9:** 1077–1088

115. Querfeld C, Rosen ST, Kuzel TM, et al. Long-term follow-up of patients with early-stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy. *Archives of Dermatology* 2005; **141**: 305–311.

116. Carter J, Zug KA. Phototherapy for cutaneous T-cell lymphoma: online survey and literature review*. Journal of the American Academy of Dermatology* 2009; **60:** 39–50

117. Rautinger F. Phototherapy of mycosis fungoides. *Photodermatology, Photoimmumology & Photomedicine* 2011; **27(2):** 68-74

118. Ortel B, Tanew A, Höningsmann H. Vitiligo treatment*. Current Problems in Dermatology* 1986; **15**: 256–271

119. Kwok YKC, Anstey AV, Hawk JLM. Psoralen photochemotherapy (PUVA) is only moderately effective in widespread vitiligo: a 10-year retrospective study. *Clinical Experimental Dermatology* 2002; **27:** 104–110.

120. Ortel B, Tanew A, Hönigsmann H. Treatment of vitiligo with khellin and ultraviolet A*. Journal of the American Academy of Dermatology* 1988; **18**: 693–701.

121. Pacifico A, Leone G. Photo(chemo)therapy for vitiligo. *Photodermatology, Photoimmumology & Photomedicine* 2011; **27(5):** 261-277

122. Westerhof W, Nieuweboer-Krotbova L. Treatment of vitiligo with UV-B radiation vs. topical psoralen plus UV-A. *Archives of Dermatology* 1997;**133:**1525-8

123. El Mofty M*,* Mostafa W*,* Esmat S*, et al.* Narrow band ultraviolet B 311 nm in the treatment of vitiligo*:* two right-left comparison studies*. Photodermatology, Photoimmunology & Photomedicine* 2006*;* **22***:* 6–11

124. Parsad D, Kanwar AJ, Kumar B. Psoralen-ultraviolet A vs. narrow-band ultraviolet B phototherapy for the treatment of vitiligo. *Journal of the European Academy of Dermatology and Venereology* 2006; **20**: 175–177.

125. Bhatnagar A*,* Kanwar AJ*,* Parsad D*,* . Comparison of systemic PUVA and NB-UVB in the treatment of vitiligo*:* an open prospective study*. Journal of the European Academy of Dermatology and Venereology* 2007*;* **21*:*** 638–642*.*

126. Yones SS, Palmer RA, Garibaldinos TM, Hawk JL. Randomised double-blind trial of treatment of vitiligo: efficacy of psoralen-UVA therapy vs narrowband UV-B therapy. *Archives of Dermatology* 2007; **143:** 578–584

127. Gonzalez E, Momtaz TK, Freedman SJ. Bilateral comparison of generalised lichen planus treated with psoralens and ultraviolet A. *Journal of the American Academy of Dermatology* 1984;**10:**958-61

128. Helander I, Jansen CT, Meurman L. Long-term efficacy of PUVA treatment in lichen planus: comparison of oral and external methoxsalen regimens. *Photodermatology* 1987; **4:**265-8

129. Flowers ME, Parker PM, Johnston LJ, *et al*. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomised trial. *Blood* 2002;**100**:415–419

130. Zecca M, Prete A, Rondelli R, *et al*. Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. *Blood* 2002;**100**:1192–1200

131. Volc-Platzer B, Hönigsman H, Hinterberger W, *et al.* Photochemotherapy improves chronic cutaneous graft versus host disease. *Journal of the American Academy of Dermatology* 1990;**23:**220-8

132. Reinauer S, Lehmann P, Plewig G, *et al.* Photochemotherapie (PUVA) for Acute Graft Versus Host Disease. *Hautarzt* 1993;**44(11):**708-712

133. Kunz M, Wilhelm S, Freund M, *et al.* Treatment of severe erythrodermic acute graft versus host disease with photochemotherapy. *British Journal of Dermatology* 2001;**144:**901-2

134. Vaatainen N, Hannuksela M, Karvonen J. Local photochemotherapy in nodular prurigo. *Acta Dermato Venereologica* 1979;**59:**544-7

135. Hans SK, Cho MY, Park YK. UV treatment of generalised prurigo nodularis. *Journal of the American Academy of Dermatology* 1990; **29:**436-7

136. Hammes S, Hermann J, S. Roos S, *et al.* UVB 308-nm excimer light and bath PUVA: combination therapy is very effective in the treatment of prurigo nodularis. *Journal of the European Academy of Dermatology and Venereology*. 2011;**25(7)**:799-803

137. Méni C, Bruneau J, Georgin-Lavialle S *et al.* Paediatric mastocytosis: a systematic review of 1747 cases. *British Journal of Dermatology.* 2015 **172(3):**642-51

138. Godt O, Proksch E, Streit V, *et al.* Short- and long-term effectiveness of oral and bath PUVA therapy in urticaria pigmentosa and systemic mastocytosis. *Dermatology* 1997;**195:** 35-9

139 Hindson TC, Spiro JG, Cochrane H. PUVA therapy of diffuse granuloma annulare. *Clinical Experimental Dermatology* 1988; **13:** 26-27

140. Browne F, Turner D, Goulden V. Psoralen and ultraviolet A in the treatment of granuloma annulare *Photodermatology Photoimmunology & Photomedicine* 2011; **27(2):**81-84

141. Kerscher M, Volkenandt M, Gruss C. *et al.* Treatment of localised scleroderma with PUVA bath photochemotherapy. *Lancet* 1994;**343(8907):**1233

142. Kerscher M, Meurer M, Sander C. PUVA bath photochemotherapy for localised scleroderma. Evaluation of 17 consecutive patients. *Archives of Dermatology* 1996;**132(11):**1280-82

143. Pasic A, Ceovic R, Lipozencic J, *et al.* Phototherapy in paediatric patients. *Paediatric Dermatology* 2003;**20(1):**71-77

144. Farnaghi F, Seirafi H, Ehsani AH. *et al.* Comparison of the therapeutic effects of narrow band UVB vs. PUVA in patients with pityriasis lichenoides. *Journal of the European Academy of Dermatology and Venereology* 2011; **25(8**):913-916

145. Wantzin GL, Thompsen K. PUVA-treatment in lymphomatoid papulosis. *British Journal of Dermatology* 1982;**107**:687-90

146. Lan Ma, H, Metze D, Luger TA. *et al.* Successful treatment of generalised eruptive histiocytoma with PUVA. *Journal of the German Society of Dermatology*. 2007;5(2):131-4

147. Kwon OS, Cho KH, Song KY. Primary cutaneous Langerhans cell histiocytosis treated with photochemotherapy. *Journal of Dermatology* (Tokyo) 1997; **24**(1):54-56

148. Sakai H, Ibe M, Takahashi H, *et al.* Satisfactory remission achieved by PUVA therapy in Langerhans cell hisiocytosis in an elderly patient. *Journal of Dermato*logy Jan 1996;**23**(1):42-6.

149. Wong WK, Ratnam KV. A report of two cases of pigmented purpuric dermatoses treated with PUVA therapy. *ActaDermato Venereologica*. 1991;**71(1**):68-70

150. Seckin D, Yazici Z, Senol A, Demircay Z. A case of Schamberg's disease responding dramatically to PUVA treatment. *Photodermatology Photoimmunology & Photomedicine*. Apr 2008;**24**(2):95-6.

151. Lotti T*,* Ghersetich I*,* Panconesi E. Why should we use PUVA treatment in pigmented purpuric lichenoid dermatitis? *Journal of the American Academy of Dermatology* 1994*;* **30***:* 145*.*

152. Kaskel P, Grundmann-Kollmann M, Schiller PI *et al.* Bath PUVA as a treatment for pityriasis rubra pilaris provoked by ultraviolet B*. British Journal of Dermatology* 1999; **140**: 769–70

153. Honig B, Morison WL, Karp D. Photochemotherapy beyond psoriasis, *Journal of the American Academy of Dermatology* 1994;**31**:775-90

154. Murphy GM, Logan RA, Lovell CR et al. Prophylactic PUVA and UVB therapy in polymorphic light eruption—a controlled trial. *British Journal of Dermatology* 1987; **116(4)**:531-538

155. Bilsland D, George SA, Gibbs NK, *et al.* A comparison of narrow band phototherapy (TL-01) and photochemotherapy (PUVA) in the management of polymorphic light eruption. *British Journal of Dermatology*; 1993;**129**:708–712

156. Roelandts R. Pre-PUVA UVA desensitization for solar urticaria. *Photodermatology* 1985*;* **2***:* 174–6*.*

157. Farr PM. Solar Urticaria. *British Journal of Dermatology* 2000; **142**:4-5

158. Duchini G, Bäumler W, Bircher AJ. *et al.* Failure of omalizumab (Xolair®) in the treatment of a case of solar urticaria caused by ultraviolet A and visible light. *Photodermatol Photoimmunol Photomed* 2011; **27**: 336–337.

159. Baliu-Pique C, Aguilera Peiro P. Three cases of solar urticaria successfully treated with omalizumab. *Journal of the European Academy of Dermatology and Venerology* 2016:**30**: 704-705

160. Hindson C, Spiro J, Downey A. PUVA therapy of chronic actinic dermatitis. *British Journal of Dermatology* 1985; **113**:157-60

161.Jaschke E, Hönigsmann H. Aktionsspektrum. *Hautarzt* 1981;**32**:350-3

162. Sonnex TS, Hawk JLM. Hydroa vacciniforme: a review of 10 cases. *British Journal of Dermatology* 1988; **118:** 101-8

163. Roelandts R. Photo(chemo)therapy and general management of erythropoietic protoporphyria. *Dermatology* 1995;**190**:330-

[164]. Otman SG, Edwards C, Gambles B, Anstey AV. Validation of a semiautomated method of minimal erythema dose testing for narrowband B phototherapy. *British Journal of Dermatology 2006*; **155**:416–21.

165. Farr PM, Diffey BL, Higgins EM *et al.* The action spectrum between 320 and 400nm for clearance of psoriasis by psoralen photochemotherapy. *British Journal of Dermatology* 1991; **124(5):**443-8

166. Al-Ismail D, Edwards C, Al-Ofi O, Anstey AV. Minimal phototoxic dose (MPD) measurements for topical photochemotherapy using a semiautomated MPD tester. *British Journal of Dermatology 2013*; **169**:687–689

167. Shephard SE, Schregenberger N, Dummer R *et al.* Comparison of 8-MOP Aqueous Bath and 8-MOP Ethanolic Lotion (Meladinine®) in Local PUVA Therapy. *Dermatology* 1998;**197**: 25-30

168. Grundmann-Kollmann M, Behrens S, Peter RU *et al.* Treatment of severe recalcitrant dermatoses of the palms and soles with PUVA-bath versus PUVA-cream therapy. *Photodermatology, Photoimmunology &, Photomedicine* 1999:**15:**87-89

169. Schiener R, Gottlöber P, Müller B *et al.* PUVA-gel vs. PUVA-bath therapy for severe recalcitrant palmoplantar dermatoses. A randomised, single-blinded prospective study. *Photodermatology Photoimmunology &, Photomedicine* 2005;**21:**62-67

170. Hawk JL, Grice PL. The efficacy of localised PUVA therapy for chronic hand and foot dermatoses. *Clinical Experimental Dermatology* 1994; **19(6):**479-82

171. Hofer A, Fink-Puches R, Keri H *et al.* Paired comparison of bathwater versus oral delivery of 8-methoxypsoralen in psoralen plus ultraviolet A therapy for chronic palmoplantar psoriasis. *Photodermatology, Photoimmunology & Photomedicine* 2006;**22(1):**1-5

172. Redon E, Bursztejn AC, Loos C *et al.* A retrospective efficacy and safety study of UVB-TL01 phototherapy and PVA therapy in palmoplantar psoriasis. *Annales de Dermatologie et de Venereologie* 2010;**137(10):**597-603

173. Sezer E, Erbil AH, Kurumlu Z *et al.* Comparison of the efficacy of local narrowband ultraviolet B (NB-UVB) phototherapy versus psoralen plus ultraviolet A (PUVA) paint for palmoplantar psoriasis. *Journal of Dermatology* 2007;**34(7):435-440**

174. Desai S, Halpern S. Optimal timing for hand and foot photochemotherapy following local immersion. *British Journal of Dermatology* 2007; **157** (**S1**): 134

175 L.F. Eichenfield, A.W. Lucky, M. Boguniewicz, *et al.* Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic

dermatitis in children and adolescents. *Journal of the American Academy of Dermatology* 2002; **46**:495–504

176 Bollag W, Ott F. Successful treatment of chronic hand eczema with oral 9-cis-retinoic acid. *Dermatology* 1999; **199:**308–12.

177 Ruzicka T, Larsen FG, Galewicz D, Horva´th A, Coenraads PJ, Thestrup-Pedersen K et al. Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomised, double-blind, placebocontrolled, multicentre trial. *Archives of Dermatology* 2004; **140:**1453–9.

178. Inzinger M, Heschl B, Weger W *et al.* Efficacy of psoralen plus ultraviolet A therapy vs. Biologics in moderate to severe chronic plaque psoriasis: retrospective data analysis of a patient registry. *British Journal of Dermatology* 2011; **165:** 640-5

179.Hönigsmann H. Comparison of psoralen plus ultraviolet A therapy and biologics in moderate to severe chronic plaque psoriasis. . *British Journal of Dermatology* 2011; **165:** 455-6

180. Julien D, Prinz C, Nestle FO. Immunogenicity of biotherapy used in psoriasis: the science behind the scenes. *Journal of Investigative Dermatology* 2015; **135:** 31-8

181. Legat FJ, Hofer A, Quensberger F *et al.* Reduction of treatment frequency and UVA dose does not substantially compromise the antipsoriatic effect of oral psoralen-UVA. *Journal of the American Academy of Dermatology* 2004; **51:**746-54.

182 Ingram J, Batchelor JM, Williams HC. Alitretinoin as a potential advance in the management of severe chronic hand eczema. *Archives of Dermatology* 2009; **145:** 314-5

183. Ruzicka T, Larsen FG, Galewicz D et al. Oral alitretinoin(9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy results of a randomised, double-blind, placebo-controlled, multicentre trial. *Archives of Dermatology* 2004; **140**: 1453–9.

184. Bissonnette R, Worm M, Gerlach B et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *British Journal of Dermatology* 2010; **162**: 420–6.

185. Schempp CM, Muller H, Czech W et al. Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. *Journal of the American Academy of Dermatology* 1997; **36**: 733–7.

186.Tegner E, Thelin I. PUVA treatment of chronic eczematous dermatitis of the palms and soles. *Acta Dermato-Venereologica* 1985; **65**: 451–3.

187.Grattan CEH, Carmichael AJ, Shuttleworth GJ et al. Comparison of topical PUVA with UVA for chronic vesicular hand eczema. *Acta Dermato- Venereologica* 1991; **71**: 118–22.

188. Sezer E, Etikan I. Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema. *Photodermatology Photoimmunology & Photomedicine* 2007; **23**: 10–4.

189. van Coevorden AM, Kamphof WG, van Sonderen E *et al.* Comparison of oral psoralen-UV-A with a portable tanning unit at home vs hospital-administered bath psoralen-UV-A in patients with chronic hand eczema: an open-label randomised controlled trial of efficacy. *Archives of Dermatology* 2004; **140**: 1463–6.

190 Granlund H, Erkko P, Reitamo S. Long-term follow-up of eczema patients treated with cyclosporine. *Acta Dermato- Venereoogical* 1998; **78(1):**40-3

191 Granlund H, Erkko P, Eriksson E, *et al.* Comparison of cyclosporine and topical betamethasone-17, 21-dipropionate in the treatment of severe chronic hand eczema. *Acta Dermato-Venereologica* 1996; **76(5)**:371-6

192 Petersen CS, Menné T. Cyclosporine A responsive chronic severe vesicular hand eczema. *Acta Dermato- Venereologica* 1992;**72(6):**436-7

193 Egan CA, Rallis TM, Meadows KP, *et al.* Low-dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. *Journal of the American Academy of Dermatology* 1999; **40(4):**612-4

194 Pickenäcker A, Luger TA, Schwartz T. Dyshidrotic eczema treated with mycophenolate mofetil. *Archives of Dermatology* 1998; **134(3):** 378-9