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What's New In Phototherapy? Old Dogs, New Tricks

Dr Wong Su-Ni*

Introduction

Phototherapy is the science and art of using light sources to treat various ailments. To the non-dermatologist, phototherapy invokes images of newborn babies being treated with blue light for neonatal jaundice. To the dermatologist, phototherapy involves treatment of various skin conditions with non-ionising radiation, such as ultraviolet A, ultraviolet B, and light in the visible light spectrum (e.g. blue light, red light). The combined use of chemicals “activated” by exposure to radiant energy and irradiation, e.g. psoralen and UVA (PUVA), is known as photochemotherapy.

Old dogs?

Phototherapy using artificial light sources began in 1895 when Niels Finsen used a carbon arc source to treat lupus vulgaris. Broadband UVB (BBUVB) in combination with coal tar was introduced by Goekerman in 1923 for the treatment of psoriasis, and Ingram introduced BBUVB with dithranol for psoriasis in 1953. BBUVB was later found, in the 1970s, to be efficacious as monotherapy in various dermatoses. PUVA was introduced in 1974 using 8-methoxypsoralen (8-MOP) and UVA, and was shown in multicentre studies to be very effective in psoriasis. Its use became widespread in the next decade, but has declined since the introduction of narrowband UVB (NBUVB), as well as reports of non-melanoma skin cancer and melanoma with prolonged use.

The action spectrum for psoriasis was defined in 1976, with a peak at 313nm. Narrowband UVB, with a peak spectrum at 311nm, was introduced in 1984, and has proven to be more effective than BBUVB in psoriasis with less side effects. It has also proven to be useful in atopic eczema and vitiligo, and has increasingly overtaken the use of BBUVB. The combination of UVA and BBUVB (UVAB) was introduced in 1985, and found to be more efficacious than BBUVB for the treatment of atopic dermatitis.

Extracorporeal photopheresis — an extension of PUVA where lymphocytes are extracted from patients by leucopheresis, treated with 8-MOP and UVA in an extracorporeal irradiation device, then reinfused into the patient — was first used successfully in leukaemic cutaneous T-cell lymphoma in 1987 and is the first line treatment in Sezary Syndrome.

In 1992, UVA1 (340-400nm), a subset of UVA (320-400nm), was introduced for atomic dermatitis. Longer wavelength UVA penetrates deeper and is thus able to reach the dermis, with less side effects of erythema or burning which is associated with shorter wavelengths. In 1997, the excimer laser, a high-energy source emitting ultraviolet B radiation at the wavelength of 308nm, was introduced for use in psoriasis. It is more efficacious than NBUVB, with sparing of unaffected areas during irradiation, but is limited by the small treatment field of the laser machine and the need for administration by a trained doctor in this part of the world.

Discovered at the beginning of the 20th century but taking off only in the last 10 years with more convenient drugs and light sources, photodynamic therapy is the latest form of photochemotherapy developed initially for the treatment of cancers. Our centre will be acquiring the necessary equipment in the near future, and this therapy will be covered in greater detail in another invited article.

The most recent and promising new light source on the phototherapy scene is the ultraviolet-free irradiation device Dermodyne®, a novel laser-like photonic partial body irradiation device with emission spectrum in the visible light range (400-500nm). It has resulted in significant improvement in atopic hand and/or foot eczema when compared with sham-irradiation in a single blinded study. Visible light, according to current knowledge, does not cause skin cancer, and the development of UV-free phototherapy would be an important milestone in the development of safer therapeutic options for children and young adults.

As the development of each new light source requires years to even decades of research and clinical testing, it is inevitable that dermatologists continue to use the “old dogs”, and constantly try to develop “new tricks” for them.

New Tricks

With the slow pace of development of new lights, new regimens or modifications to existing protocols, or combination therapies using existing modalities, have been introduced in attempts to enhance efficacy, and improve safety. Existing modalities have also been tried on other dermatoses, sometimes rather empirically, expanding the list of newer indications for phototherapy. As understanding of the mechanisms of action of each modality improves, more rational experimentation may become possible.

a. Enhancing efficacy

This may be achieved by combination therapy, or by optimizing phototherapy regimens or dosimetry.

A ready example from history is the addition of retinoids to PUVA (rePUVA) which dramatically improves the efficacy of PUVA in the treatment of psoriasis. Addition of retinoids to UVB (reUVB) also results in more rapid & more effective clearing, with lower doses of retinoids than
required in monotherapy\textsuperscript{11}. Addition of MTX to UVB results in more rapid response, less treatments required and lower cumulative doses of both UV and MTX\textsuperscript{12}.

In combination with topical therapy, addition of calcipotriol to UVB results in slightly more clearing of psoriasis than UVB alone\textsuperscript{13}, while its addition to PUVA has been associated with faster clearing and lower UVA doses\textsuperscript{14}. The addition of tazarotene to UVB also results in faster and more effective clearing of psoriasis\textsuperscript{15}. However, the calcipotriol-NBUVB combination has not been shown to be more effective than NBUVB alone in vitiligo in a recent right-left comparison study\textsuperscript{16}. Combination therapy with NBUVB and cream PUVA for treatment-resistant psoriatic plaques has been employed recently with good results\textsuperscript{17}.

Modifications of existing protocols have been introduced to optimize efficacy. More aggressive PUVA treatment protocols such as the European regimen, which employs erythemogenic starting doses, individualized dose increments and more frequent treatments compared to the American regimen, are able to clear psoriasis with less exposures and lower cumulative dose\textsuperscript{18}. Another aggressive PUVA schedule optimizes UVA irradiations by repeated determination of phototoxic doses during the course of therapy, with increased efficacy and lower cumulative doses\textsuperscript{19}. Goeckerman's regimen and Ingram's regimen have also been modified, using modern light sources such as NBUVB and combinations, with excellent results in psoriasis\textsuperscript{20,21}.

b. Improving safety/ reducing side effects

As oral PUVA was associated with systemic side effects such as nausea, prolonged photosensitivity and cataract formation, topical and bath PUVA were used as early as 1976 to avoid systemic side effects. Topical psoralsens plus PUVA is effective in clearing psoriasis, but the phototoxic erythema reaction is less predictable than with oral PUVA and may result in blistering\textsuperscript{22}. Bath PUVA, which involves soaking for 20 minutes in a bath of diluted psoralsens solution, followed by drying and immediate exposure to UVA, has been as effective as oral PUVA in psoriasis, with, to date, no excess of skin cancers reported\textsuperscript{23}. Soak PUVA, or local bath-PUVA, useful for palmo-plantar psoriasis or eczema, is similar in principle to bath PUVA, but only the affected area is soaked and irradiated\textsuperscript{24}. Cream-PUVA or gel-PUVA have been subsequently successfully employed in palmar-plantar dermatoses with similar efficacy to soak PUVA with the advantage of less organizational effort and time spent in the phototherapy unit\textsuperscript{25,26}.

In a continuing quest for new psoralsens with reduced side effects, 5-MOP was developed. It is associated with lower gastrointestinal side effects than 8-MOP, and less clinical phototoxicity\textsuperscript{27}.

Modalities that limit delivery of radiation only to affected areas have been developed to decrease adverse effects. Localised UVB phototherapy is available for limited psoriasis or vitiligo with broad-band UVB delivered via a handpiece. Excimer laser is also only employed at the affected sites.

More aggressive phototherapy protocols have been introduced in Europe, enabling faster clearance with less cumulative doses of UVA. The addition of retinoids (e.g. etretinate, acitretin) to oral PUVA in psoriasis, apart from halving the total cumulative UVA dose, and reducing the number of exposures by one-third\textsuperscript{28}, may also provide chemoprophylaxis against non-melanoma skin cancers\textsuperscript{29}.

c. Expansion of therapeutic indications

Phototherapy is widely used for psoriasis, vitiligo, and eczema, where there exists much data to support its use.

As phototherapy induces T-cell apoptosis, among other effects, broadband UVB, NBUVB, oral PUVA and more recently UVA-1\textsuperscript{30} have all been shown to be effective in early-stage mycosis fungoides (MF). As UVA is able to penetrate deeper, oral PUVA is the current treatment of choice for plaque stage MF. The newer long wavelength UVA-1 has shown great promise, with efficacy similar to oral PUVA in early MF in a small trial\textsuperscript{31}, as well as proving effective even for more advanced stages of MF\textsuperscript{32}.

As clinicians experiment with phototherapy in various therapy-resistant dermatoses, case reports and small case series emerge, with newer therapeutic indications that have not yet been substantiated in large controlled trials. Some of these are summarized here:

1. Lichen planus

Oral PUVA, and more recently bath PUVA, is effective in generalized lichen planus, but requiring more treatment sessions and higher cumulative doses than in psoriasis, with possibility of early relapse\textsuperscript{33}.

2. Pityriasis lichenoides

Pityriasis lichenoides chronica responds well to UVB, while pityriasis lichenoides acuta does not, but the latter responds to PUVA\textsuperscript{34,35}.

3. Localised scleroderma (morphoea)

There have been case reports of remission with bath or oral PUVA. More recently, UVA-1 therapy was shown to result in remission or significant reduction in thickness/increase in elasticity of sclerotic skin in case series as well as case reports, with high-dose regimen (130J/cm\textsuperscript{2}) superior to low-dose (20J/cm\textsuperscript{2})\textsuperscript{36}. The effects are likely secondary to induction of collagenase I mRNA expression.

4. Systemic sclerosis

Medium dose (60J/cm\textsuperscript{2}) UVA-1 therapy was associated with softening of skin lesions, increase in passive joint mobility, skin temperature and cutaneous elasticity in a small series of patients with systemic sclerosis\textsuperscript{37}. In a more recent open study of 18 patients, low-dose UVA1 therapy was associated with significant decrease in hand score and softening of former stiffness\textsuperscript{38}.
5. Lichen sclerosus (LS)

As lichen sclerosus shows similar clinical and histological features as morphea, low-dose UVA-1 (20J/cm²) has been tried in extra-genital LS with significant improvement in clinical scores, and decrease in ultrasonographically measured skin thickness, and repigmentation. Similarly, UVA-1 has also been reported to be effective in sclerotic graft-versus-host disease.

6. Generalised granuloma annulare

PUVA (oral, bath, topical) has been reported to be effective. High dose or medium dose UVA-1 was also shown in a recent open study involving 20 patients to result in substantial improvement or near complete clearance in 50% of cases. The mechanism of action remains unknown.

7. Urticaria pigmentosa (cutaneous mastocytosis)

PUVA results in marked improvement of pruritus and Darier's sign, although hyperpigmentation is unaffected, and early relapse is usual. High-dose (130J/cm²) UVA-1 therapy, in a small case series, is associated with faster response, after only 3 sessions, and longer remission of 10-23 months. More recently, medium-dose UVA-1 (60J/cm²) was shown to be as effective as high-dose UVA-1 (130J/cm²) in urticaria pigmentosa, with reduction of mast cells in lesional skin, improvement in both pruritus and systemic symptoms, and prolonged remission in both groups.

8. Pruritus

UVB therapy can be beneficial in pruritus, particularly those associated with diabetes and liver disorders, and the efficacy of UVB and UVA has been demonstrated in uremic pruritus. PUVA also has been successfully used in aquagenic pruritus and pruritus of polycythemia rubra vera. The mechanism of action is not known but thought to be related to decreased cutaneous histamine reactivity.

9. Transplant rejection

Photopheresis has been demonstrated in small trials to be a valuable adjunct in the control and prevention of heart transplant rejection, and has also been used successfully in renal and lung transplantation. With its immunomodulatory effect on T-cells, photopheresis holds promise in the management of other T-cell mediated diseases, and has been shown in small trials or case series to be effective in graft-versus-host disease, therapy-resistant pemphigus vulgaris, and systemic lupus erythematosus.

There remains, however, many gaps in our knowledge of how UV radiation works, and why some inflammatory diseases respond while other do not – only when these are filled then we may look forward to a more rational approach to phototherapy.

References


Photodynamic therapy (PDT) is an exciting new treatment for skin disorders and the indications for its use in dermatology have been increasing over the years.

What is photodynamic therapy?

PDT, like PUVA treatment, is a form of phototheraputry. There are 3 key components in PDT – an activating light source, a photosensitizer and oxygen. The photosensitizer itself is pharmacologically inert. However, in the target tissue, it is activated by an appropriate wavelength of light. This activated photosensitizer passes on the light energy it has absorbed to molecular oxygen and results in the generation of singlet oxygen. This results in its cytotoxic effect and damage of the target tissue.

Photosensitizers

The photosensitizers should ideally be highly selective for the target tissue. They should be activated by an activating light source, preferably one with a longer wavelength for deeper penetration. They should have a high photodynamic yield and should have a short half-life and be quickly cleared from normal tissue.

The first generation photosensitizers are the haematoporphyrins. An example is photofrin. It is administered by intravenous injection and accumulates in tumour tissue. Its main disadvantage is that it is cleared slowly from the skin and the patient may be photosensitive for 6 to 10 weeks following treatment. Second generation photosensitizers have the benefit of faster clearance from tissues but still require strict avoidance of light for a considerable period of time.

It was with the development of endogenous photosensitizers that PDT gained increase popularity in its use in cutaneous disease. Endogenous photosensitizers like 5-amino-laevulinic acid (5-ALA) are prodrugs which, as themselves, are not photosensitizers. However, after application, they are converted in the target tissue, through the haem biosynthesis pathway, to protoporphyrin IX. In this pathway, there are 2 rate-limiting enzymes, ALA synthetase and ferrochelatase. The ALA administered bypasses the 1st rate-limiting step and results in accumulation of protoporphyrin IX. This is completely metabolised in 24 to 48 hours and leaves no residual photosensitivity. Newer topical PDT agents such as the methyl-ALA, are more lipophilic and have better penetration in the target tissue.

Topical ALA has been shown to preferentially accumulate in abnormal tissue. This results in minimal damage to the surrounding normal tissue and results in minimal scarring.

The photosensitizer accumulates in the mitochondria and it activation leads to membrane damage and cell death. In addition, it causes apoptosis of the target tissue. As the singlet oxygen is generated in the mitochondria, there is little DNA damage and the risk of carcinogenicity is minimal.

Clinical Indications

The role of topical photodynamic therapy in dermatology has been expanding. It is used in dermatology to treat cancerous and pre-cancerous lesions as well as other benign diseases.

1. Cancers and Precancerous lesions

Actinic keratosis has been shown to be effectively treated with PDT and PDT is FDA approved for the treatment of actinic keratosis. Other cancers that have been shown to have good outcome include Bowen's disease and superficial basal cell carcinoma. In Bowen's disease, an analysis of 13 open and 3 randomised comparative studies showed complete response rates, following 1 and 2 PDT treatments of 86% and 93% respectively. The recurrence rate was reported to be between 0 to 40% during a follow up period of 3 to 36 months. However, for the treatment of squamous cell carcinoma, PDT is not regarded as an effective treatment in view of the recurrence rate and metastatic potential of squamous cell carcinoma.

For basal cell carcinoma, from a review of 12 open studies, the complete response rate was 87% for superficial basal cell carcinoma and 53% for nodular basal cell carcinoma. The response of morphoeic and pigmented basal cell carcinoma was noted to be poor. However, there is a current lack of 5-year follow up data. More recent studies have shown better results using methyl-ALA PDT in the treatment of nodular basal cell carcinomas.

PDT may be a useful adjuvant in the treatment of cutaneous T-cell lymphoma. A few case reports and case series on the use of PDT in the treatment of mycosis fungoides (MF) have been published. Elstrom et al reported the treatment of 9 plaques of MF and 2 tumour lesions from 10 MF patients. The lesions were treated with 5-ALA and red light at 630 nm. In 7 of the 9 plaques, complete clinical clearance was observed, while none of the tumour lesions cleared with treatment. Histological regression was confirmed on the biopsy. Therefore PDT appears to have good clinical and histological effect in treating local plaques of MF.
2. Non-oncologic indications

The rationale for using PDT to treat viral warts is that these are benign proliferative disorders in which the photosensitizers have been shown to accumulate. There have been 2 adequately designed studies demonstrating the efficacy of PDT in treatment of viral warts. However, pain can be a limiting side effect. Fabbrocini et al. reported the treatment of 64 plantar warts with 20% ALA and red light, with 57 warts (controls) treated with only vehicles. The clearance rate was 75% (48 of 64) in the PDT group versus 22.8% (13 of 57) in the control group.

The rationale for treating acne vulgaris is that *P. acnes* contain endogenous porphyrins and PDT is effective in destroying the *P. acnes in vitro*. Hongcharu et al. conducted an open study of ALA-PDT in 22 patients with acne on their back. 20% ALA was applied with irradiation of red light and the acne was found to improve significantly, together with a reduction in sebum secretion. Kimura et al reported over 90% improvement, with 60.8% reporting marked improvement in acne, following 2 treatments with oral delta-ALA and polychromatic visible light from a metal halide lamp. Therefore, PDT appears to be a promising treatment in acne but more work is required to optimise therapy.

Other conditions that have been reported to improve with PDT treatment include actinic cheilitis, Erythrophasia of Queyrat, vulval lichen sclerosus and localized scleroderma. The use of PDT in facial rejuvenation is also increasingly being studied.

How is topical ALA PDT applied?

Topical PDT is a simple procedure that can be done in the clinics. The lesion for treatment must first be identified and prepared. This involves removing the overlying scale to allow for better penetration of the topical ALA. After preparation, the topical ALA is applied directly onto the lesion and occluded for 3 to 4 hours. Following this, the ALA is cleaned off and the lesion irradiated with the activating light source (Fig. 1). The duration of the irradiation is commonly between 8 to 20 minutes. Following treatment, the lesion is kept protected from sunlight for 2 days.

In the treatment of actinic keratosis, a single treatment may be all that is required. In Bowen’s disease and superficial basal cell carcinoma, often 2 treatments of PDT may be all that is required. In Bowen’s disease and superficial basal cell carcinoma is also higher compared with conventional surgery. Currently, the cost of PDT is relatively high.

In conclusion, topical PDT treatment is an exciting new treatment modality in dermatology. As more research is being carried out in this area, we will certainly see an increase in conditions treated with PDT and more optimal treatment protocols developed.

Advantages

Topical PDT is a simple, non-invasive procedure that can be used in an outpatient setting. There is no generalized photosensitivity compared with systemic administration of photosensitizers. A main advantage is that lesions treated heal very well, with minimal scarring and excellent cosmetic outcome has been consistently observed. Furthermore, sub-clinical lesions can be treated. It can also be used in treatment of recurrent disease as repeated treatments can be given, as there is no evidence of cumulative toxicity.

Disadvantages

Pain and burning during treatment is common, necessitating the administration of local anaesthesia in some cases. The risk of recurrence in Bowen’s disease and superficial basal cell carcinoma is also higher compared with conventional surgery. Currently, the cost of PDT is relatively high.

References


Ultraviolet Light-induced Immunosuppression – How Does It Occur?

Dr Chong Wei Sheng*

Introduction

Ultraviolet (UV) light is an important environmental factor affecting human health. In fact, the primary cause of non-melanoma skin cancer is the UV light in sunlight. UVB exposure induces skin tumour formation through 2 mechanisms: a direct effect of UVB on DNA, causing specific gene mutations, and an indirect effect on the immune system impairing the ability to generate an immune response against tumour antigen. In addition, UVB exposure has been shown to suppress immune responses to various antigens, including microorganisms, leading to exacerbation of infectious diseases, such as herpes simplex infection. All these UVB-induced consequences are relevant for human health since they occur during normal occupational and recreational exposure.

Experimental models

It has been shown experimentally in murine models that UVB induces immunosuppression. UVB-induced skin tumours are immunogenic and are rejected after transplantation into normal syngeneic mice. However, when the recipient mice are UVB-irradiated, the UVB-induced skin tumours grow progressively. In addition, UVB exposure can stimulate the in vivo growth of murine melanoma cells by impairing the local immune efferent response.

Low-dose UVB irradiation induces inhibition of the local sensitisation phase of the contact hypersensitivity response to a hapten applied to previously irradiated skin. High-dose UVB irradiation induces inhibition of the systemic sensitisation phase of the contact hypersensitivity reaction to the hapten and the delayed hypersensitivity reaction to the alloantigen when antigen is applied or injected into distant non-irradiated skin respectively. Both low and systemic immunosuppression are genetically restricted. It has also been demonstrated that polymorphisms in the TNF region confer susceptibility to UVB-induced impairment of contact hypersensitivity reaction induction in mice and humans. Both low-dose and high-dose models are associated with the production of transferable hapten-specific T regulatory cells and with the induction of tolerance.

Chromophores

Urocanic acid (UCA) is generated in the metabolic pathway of histidine, and accumulates in the stratum corneum as keratinocytes lack enzymes to further catabolise UCA. It exists in both isomeric forms, trans and cis. Trans-UCA is the predominant form in non-irradiated epidermis, and upon UVB irradiation, UCA is photoisomerised from trans- to cis-UCA. It absorbs UV light in the range of 305-341 nm (UVA & UVB) with a peak absorption spectrum of 290-310 nm (UVB). Cis-UCA inhibits the immune response, impairs the antigen-presenting function of Langerhans cells and stimulates prostaglandin E2 (PGE2) production.

In DNA, purine and pyrimidine bases absorb UV light in the range of 230-300 nm (UVB & UVC) with the formation of photoadducts, the most important of which are the cyclobutyl pyrimidine dimers, which can lead to DNA damage. Repair mechanisms are important to repair the DNA damage and block induction of immune suppression of the contact hypersensitivity reaction. It has been shown that the T4N5 bacteriophage excision repair enzyme reduces the number of pyrimidine dimers, antagonises the inhibition of systemic and local contact hypersensitivity or delayed hypersensitivity responses. It also blocks the induction of T regulatory cells and secretion of IL-10 and TNFα. Thus, DNA damage plays a major role in UVB-induced immunosuppression.

UVB may also affect cytoplasmic and membrane targets, including the lipid membrane. Membrane lipid peroxidation induced by UVB leads to the formation of free radicals which contribute to platelet-activating factor (PAF) activation. This leads to cytokine synthesis. Furthermore, UVB can also directly trigger surface receptors and activate the Src tyrosine kinase. This results in the activation of various signal transduction proteins, which then further lead to immunosuppression.

Figure 1 summarises the signalling pathways induced by the effects of UVB on lipid membrane peroxidation.

![Figure 1. Signaling pathways induced by the effects of UVB on lipid membrane peroxidation (adapted from Aubin F1).](image-url)
UVB-induced immune suppressive mediators

Upon UVB irradiation, keratinocytes secrete various cytokines such as IL-1, IL-6, IL-8, TNFα and PGE2. TNFα has been suggested as an important mediator in local UVB-induced immunosuppression. It alters the antigen-presenting function of Langerhans cells and depletes them. UVB exposure also causes a shift in the activation of T cells from a Th1- to a Th2-type immune response. UVB alters the antigen-presenting function of Langerhans cells by blocking its antigen presentation to Th1 cells, but not interfering with antigen presentation to Th2 cells. PGE2 appears to have a critical role in UVB-induced systemic immunosuppression, and UVB exposure can directly activate PGE2 synthesis in irradiated keratinocytes via the induction of cyclooxygenase-2 (COX-2). PGE2 stimulates IL-4 and IL-10 secretion, which in turn leads to systemic suppression of the antigen-presenting function of the Langerhans cells. Moreover, UVB-irradiated keratinocytes are able to secrete PAF, which in turn upregulates their COX-2 gene expression and PGE2 secretion.

Effects of UVB on the immune response

UVB radiation induces numerical, morphological and functional alterations of Langerhans cells, with destruction of their dendritic network. In addition, UVB suppresses the expression of surface molecules such as ATPase activity, MHC class II, ICAM-1 and B7. All these alterations result in depletion of the Langerhans cells with subsequent reduction of surface molecule expression and apoptosis. Furthermore, whereas normal Langerhans cells present antigens equally well to Th1 and Th2 cells, UVB-irradiated Langerhans cells efficiently present antigen to Th2, but do not stimulate Th1 cell clones. UVB exposure can sequentially activate PGE2 synthesis in irradiated keratinocytes via the induction of cyclooxygenase-2 (COX-2). PGE2 stimulates IL-4 and IL-10 secretion, which in turn leads to systemic suppression of the antigen-presenting function of the Langerhans cells. Moreover, UVB-irradiated keratinocytes are able to secrete PAF, which in turn upregulates their COX-2 gene expression and PGE2 secretion.

IL-12 produced by Langerhans cells and macrophages is the major cytokine in the activation of Th1 cells. It overcomes UV-induced immunosuppression and tolerance, with suppression of IL-10 production. As PGE2 is a potent inhibitor of IL-12 production, UVB therefore suppresses IL-12 secretion and leads to failure of the Langerhans cells to present antigen to Th1 cells. UVB stimulates macrophages to produce IL-10 but suppresses their IL-12 production, and thus contributes to UV-induced immunosuppression as well. Furthermore, UVB irradiation induces a strong expression of IL-4 mRNA in CD15+ neutrophils and leads to immunosuppression. Mast cells are activated by PAF, UCA and neuropeptides such as the calcitonin-gene related peptide (CGRP), and may secrete immunoregulatory cytokines such as IL-10. Histamine induces PGE2 production by keratinocytes, suppresses IL-12 and stimulates IL-10 production by monocytes.

What about UVA?

The role of UVA (which constitutes 95% of ambient UV light) has been less widely studied. Some results have been contradictory but recent studies highlighted the role of UVA in immunosuppression. For instance, it was shown experimentally that UVA-2 suppressed the delayed
Conclusion

Immune modulation following UV exposure may be desirable under many circumstances. Of course, UV-induced immunosuppression is not desirable in the case of skin cancers or infections, whereby the development of tumour cells or infectious agents is facilitated by the escape from immune surveillance. On the other hand, the mechanisms underlying UV-induced immunosuppression may explain the efficiency of phototherapy in the treatment of various T-cell mediated dermatoses such as psoriasis.

References


Ciclosporin In The Treatment Of Psoriasis -
Our Experience At The National Skin Centre

Dr Colin Theng Thiam Seng*, Dr Lawrence Khoo Shih Wee **

Abstract

**aim:** The aim of this study is to determine the profile of psoriasis patients treated with ciclosporin at the National Skin Centre, Singapore and to determine the response to treatment and frequency of side effects, in particular, the renal and hypertensive side effects. **Methodology:** This is a retrospective study of all psoriasis patients treated with ciclosporin for more than one month from 1999 to 2001 at the National Skin Centre. **Results:** There were 18 patients, 14 males and 4 females, on ciclosporin, with a mean age of 45 years. There were 13 Chinese, 2 Indian, 1 Malay and 2 patients of other ethnicity. Best response was noted after 4.7 months of treatment. Thirteen (72.2%) patients had excellent response, 1 (5.6%) had good response and 4 (22.3%) patients had poor response to treatment. In 5 patients, the serum creatinine levels exceeded 30 percent of the baseline level while on treatment. Two of the patients required discontinuation of treatment. Two patients had hypertension on ciclosporin treatment, which was controlled with oral calcium channel blockers. **Conclusion:** Ciclosporin is effective in the treatment of psoriasis. It has a good safety profile with close monitoring of serum creatinine and blood pressure.

Introduction

Ciclosporin is known to be a highly effective treatment in psoriasis. However, its side effects include renal toxicity and hypertension, which may lead to serious, irreversible morbidity. Its efficacy was shown in a recent meta-analysis of 579 patients with severe psoriasis treated with ciclosporin, etretinate or placebo. Ciclosporin was significantly superior to etretinate and ciclosporin at 1.25 mg/kg/day was more effective than placebo. An increase in serum creatinine that required intervention was noted in 3.4% of ciclosporin treated patients. Ciclosporin, although effective, is only palliative as relapses often occur on discontinuation of treatment. A study by Jan V et al showed that in patients with severe chronic plaque psoriasis treated with ciclosporin for 278 weeks, there was an overall efficacy of 72%. Relapses were noted in 53% of the patients at 16 weeks after discontinuation of treatment.

The purpose of this study is to determine the profile of psoriasis patients started on ciclosporin treatment at the National Skin Centre, Singapore. The duration of treatment, frequency of side effects, in particular renal and hypertensive side effects, response to treatment and relapses post-treatment were also examined.

Methodology

This is a retrospective study of all cases of psoriasis treated with ciclosporin from 1999 to 2001 at the National Skin Centre, Singapore. The cases of psoriasis were diagnosed clinically. The case notes of the patients were retrieved and their biodata, dose and duration of ciclosporin treatment and treatment responses were collated. Only patients who had completed more than 1 month of ciclosporin were included in the study.

Baseline blood pressure and serum creatinine, and highest creatinine and blood pressure while on treatment were recorded. The extent of disease pre and post-treatment as reflected by the percentage of body surface area (BSA) involved was noted. Clearance was defined as the complete disappearance of all the skin lesions. Excellent response was defined as more than 75% improvement. Good response and moderate response were defined as improvement of between 50-75% and 25-50% respectively. Poor response was defined as less than 25% improvement or worsening of psoriasis while on treatment.

Results

Biodata

There were 22 patients who were on ciclosporin treatment. Eighteen patients had received ciclosporin for more than 4 weeks and were included in the study. There were 14 males and 4 females. The mean age was 45 years (range 21 to 80 years). There were 13 Chinese, 1 Malay, 2 Indian and 2 patients of other ethnicity. The mean duration of disease was 14 years (range 5 to 21 years). Two patients had a history of diabetes mellitus, and 1 patient had hypertension controlled on oral calcium channel blockers. Five of the patients had psoriatic arthropathy.

Previous treatments

All patients were previously on topical treatments. Seventeen patients were previously on phototherapy, either PUVA or UVB treatment. Fifteen patients were previously treated with methotrexate and 10 were previously on acitretin.
The mean body surface area (BSA) pre-treatment was 55% (10 to 100%) (Table 1).

### Table 1.

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<th>Pre-treatment BSA involvement</th>
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<tbody>
<tr>
<td>No of patients</td>
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<tr>
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<td>8</td>
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<tr>
<td>5</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body Surface Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24%</td>
</tr>
<tr>
<td>25-49%</td>
</tr>
<tr>
<td>50-74%</td>
</tr>
<tr>
<td>75-100%</td>
</tr>
</tbody>
</table>

### Side effects of treatment

Five (27.7%) patients on treatment had elevation of serum creatinine of greater than 30% above baseline. Of the five patients, 2 (11.1%) had to discontinue treatment because of persistently elevated serum creatinine following dose reduction. The creatinine levels normalized within 2 months of discontinuation. In both cases, the highest ciclosporin dosage used was 3.6 mg/kg. The total duration of treatment was 10 months in one case and 17 months in the other. In the remaining 3 patients, the highest ciclosporin dosages used were 4.3 mg/kg/day, 3.5 mg/kg/day and 3.2 mg/kg/day. Serum creatinine normalized after dose reduction and the patients were continued on ciclosporin treatment.

Significant elevation of blood pressure of greater than 30 mmHg above baseline was noted in 2 (11.1%) patients. They were started on oral calcium channel blockers with good control of the blood pressure. The highest doses of ciclosporin used in the 2 cases were 2.9 mg/kg and 3.2 mg/kg. On discontinuation of ciclosporin, one patient was subsequently noted to have hypertension and was continued on the anti-hypertensive medication. The other patient defaulted on follow-up after discontinuing ciclosporin treatment.

### Outcome of patients

Two patients defaulted on their follow-up. Four patients did not relapse after discontinuation of ciclosporin. Of the 4 patients, 2 patients were on acitretin with no relapse after 4 and 8 months of follow-up. In the remaining 2 patients, the psoriasis remained clear after 3 months of follow-up while on topical treatment.

Twelve patients relapsed on discontinuation of ciclosporin. The mean duration to relapse was 2.7 months (range 1-6 months). Five patients were on acitretin treatment, one on narrow band UVB, one on narrow band UVB with methotrexate, one on azathioprine and one on sulphasalazine and 3 patients were on topical treatment only at the time of relapse.

### Discussion

Ciclosporin is an immunomodulator that has been in use for over 15 years, with its initial experience gained from treatment of renal transplant patients. It is now used increasingly in dermatology, and conditions like psoriasis, atopic dermatitis, pyoderma gangrenosum, alopecia areata, are some examples of the many ciclosporin-responsive dermatoses.
Psoriasis is a common skin condition, which presents classically with thick erythematous plaques with silvery scales. It can be extensive in some cases, requiring systemic treatment for control of the disease. Commonly used systemic treatments in psoriasis include phototherapy, methotrexate and oral retinoids. Ciclosporin has been shown in several studies to have impressive results in the treatment of psoriasis^4,5. More recently, there has been increasing interest in the use of biologic agents in the treatment of psoriasis.

The results of this study show that ciclosporin is effective in the treatment of psoriasis, with 77.8% of the patients showing good to excellent response to treatment. Most of the patients had long-standing psoriasis and were previously tried on at least one form of systemic therapy. The effect of ciclosporin on improvement in psoriasis was fairly rapid, with marked improvement noted as early as 1 month from the start of treatment, with an average of 4 months of treatment for best response to be achieved.

Most cases relapsed after discontinuation of treatment. The relatively quick onset of improvement but relapse on discontinuation of treatment makes ciclosporin ideal for use as a bridge therapy.

With regard to the safety of ciclosporin, about a quarter of our cases had elevation of serum creatinine, but all cases responded to discontinuation or decrease in the dose of ciclosporin. In all 4 cases, the highest dose of ciclosporin used was greater than 3 mg/kg/day. The renal toxic effect of ciclosporin is dose related and is more likely to be seen with dosages above 5 mg/kg/day. Clinical data from a recent review^6 showed that elevation of creatinine was rarely noted in patients treated with low-dose ciclosporin of below 3mg/kg daily. It was suggested that in patients on ciclosporin greater than 3 mg/kg/day, monitoring of trough levels may be indicated. This may be important, particularly in patients who are on medications that may interact with ciclosporin.

Significant elevation of blood pressure was noted in 2 (11.1%) cases, and the blood pressure was controlled on anti-hypertensive medication. However, one patient had persistent hypertension on discontinuing treatment. This may have been a result of ciclosporin unmasking an underlying hypertension.

An international consensus statement on the use of ciclosporin in psoriasis was recently published^7. The recommended starting dose of ciclosporin is 2.5 - 5.0 mg/kg/day. The baseline blood pressure and 2 baseline serum creatinine levels on separate occasions should be taken before starting ciclosporin. The blood pressure and serum creatinine should be monitored at every visit. Initial follow-ups should be done every 2 weeks for the first 2 months. If the serum creatinine level rises to above 30% of the baseline, the level should be rechecked again in 2 weeks. If the level remains elevated, the dose of creatinine should be reduced by at least 1 mg/kg/day for 1 month and rechecked. If the serum creatinine remains elevated despite the dose reduction, ciclosporin should be discontinued and levels rechecked after one month. If the serum creatinine returns to baseline, ciclosporin may be continued at the reduced dosage.

In conclusion, in our experience, ciclosporin is an effective treatment for moderate to severe psoriasis. It has a good safety profile with close monitoring of the blood pressure and serum creatinine. However, alternative treatments should be considered on discontinuing treatment as relapses occur frequently after discontinuation of treatment.

Reference
The Use Of Narrow-band UVB In The Treatment Of Uraemic Pruritus: A Preliminary Report

Dr Melvin Ee*, Dr Gil Yosipovitch**, Dr Wong Su-Ni***

Abstract

Aim: This study aims to evaluate the treatment of uraemic pruritus with narrow band ultraviolet B (NBUVB) in patients with chronic renal failure. Methodology: This is a prospective analysis of 4 patients with renal pruritus seen at the National Skin Centre. Results: 3 of the 4 patients had hypertensive renal disease. Their mean age was 64.3 years (range 55-70). Their mean haemodialysis duration was 338 weeks and a past history of pruritus with a mean duration of 192 weeks. All patients had disturbed sleep. 3 of the 4 patients had improved sleep after 16 sessions of NBUVB treatment and they remained free of pruritus for the 6-month period of follow-up. The major aggravating factors included lying down, sitting still, specific fabrics, dryness, heat and sweat while alleviating factors are the use of hot/cold water, cold and sleep. Conclusion: NBUVB can provide long lasting relief of renal pruritus in the majority of patients with chronic renal failure. Here, the use of 2 treatment sessions per week for 8 weeks seems to be a reasonable therapeutic schedule. However a larger study would be required to confirm this initial observation.

Introduction

Uraemic pruritus is a common and bothersome symptom in patients on chronic dialysis. Conventional therapy with antihistamines, topical corticosteroids and emollients has proved to be disappointing. For many years, sun exposure has been known to improve the pruritus associated with several unrelated dermatosis. Studies in the 1970-80’s have demonstrated the failure of UVA1 but showed success of UVB as a modality of treatment in uraemic pruritus.2-5 Documented evidence showed improvement in pruritus within 6-8 treatments and remission averaging 2-3 months, but sometimes lasting longer than 2 years.2,5 Narrow-band UVB (NBUVB) has gained popularity as it induces a longer remission in other dermatosis (e.g. psoriasis) than broad-band UVB, and is associated with a lower risk of burns or carcinogenesis.

To date, there is a paucity of documented studies to show the efficacy of this modality in the treatment of renal pruritus although many have benefited from it at our phototherapy unit. In this preliminary report, we compare the effects of renal pruritus before and after NBUVB treatment on sleep, daily activities and habits. At the time of publication, we are in the process of collating data involving quality of life issues and a verbal descriptor scale of itch sensation.

Methodology

Subjects. This case series consisted of 4 patients who were recruited prospectively from the general dermatological clinics within a tertiary dermatological setting. The inclusion criteria included patients undergoing haemodialysis with pruritus for more than one month. All were ambulant and had no history of syncope or tendency to postural hypotension. None of the patients included had any medical cause for pruritus (e.g., iron deficiency anaemia, thyroid dysfunction, secondary hyperparathyrodism etc) or any dermatological disorders antedating the renal failure. A normal blood test including FBC, serum iron, ferritin, liver function test, thyroid function, calcium, phosphate and parathyroid hormones was required. None of the patients had a positive serum ANA. None had a history of any photosensitive dermatosis, non-melanoma skin cancers, melanoma or pre-malignant skin lesions. All their concurrent medications were continued throughout the study period. Prior to the study, approval was granted from the hospital ethics committee and informed consent was obtained from all subjects.

Treatment protocol. The patients were treated with NBUVB phototherapy twice a week for 2 months and treatment was then stopped. They were subsequently followed up monthly for 6 months. Treatment could be restarted during the follow-up phase if pruritus relapsed.

Light sources. NBUVB was provided by 48 Phillips TL-01 fluorescent tubes in parallel arrays, lining a Daavlin hexagonal cabin, providing an irradiance of average 15mW per square meter. The same NBUVB machine was used for all patients.

Study design. Treatment was given on non-dialysis days. All patients disrobed completely. Male patients protected their genitalia with appropriate clothing. The face was shielded with a hood. Each patient’s minimal erythema dose (MED), the ultraviolet exposure necessary to produce just perceptible erythema, was estimated according to the patient’s history of sunburn and ability to tan. Initial treatment
times were calculated to achieve 70% of the estimated MED. Before each treatment, patients were examined for erythema and tanning, and were questioned regarding severity of itch and sensation of sunburn from the last treatment session. A 20% dose increment was given if there was no erythema from the last treatment. This stepwise increment was limited to a maximum dose of 3000-4000mJ/cm² for the body and 500mJ/cm² for the face. The dose modification for missed or cancelled treatment, and the occurrence of adverse effects of phototherapy, are stipulated in Table 1 and 2 respectively. No alterations were made to their current medications. Standard symptomatic treatment with antihistamines, 0.025% betametasone cream, and aqueous cream were allowed.

### Table 1. Dose modification for missed or cancelled treatment

<table>
<thead>
<tr>
<th>Number of treatments missed</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 treatment</td>
<td>repeat previous dose</td>
</tr>
<tr>
<td>2 treatments</td>
<td>reduce dose by 25%</td>
</tr>
<tr>
<td>3-4 treatments</td>
<td>reduce dose by 50%</td>
</tr>
<tr>
<td>5-6 treatments</td>
<td>reduce dose by 75%</td>
</tr>
<tr>
<td>&gt;6 treatments</td>
<td>restart treatment from</td>
</tr>
<tr>
<td></td>
<td>starting dose or see doctor</td>
</tr>
</tbody>
</table>

### Table 2. Adverse effects and procedure for dose adjustments

- **Grade I erythema (mild)** – barely perceptible erythema: Repeat previous dose and reduce to 10% increments thereafter.
- **Grade II erythema (moderate)** – well defined non-symptomatic erythema: Postpone 1 treatment and repeat previous dose at next visit with 10% increments thereafter.
- **Grade III (severe)** – symptomatic erythema and/or bulla. No treatment. When erythema has completely settled, treat with penultimate dose and increase subsequently with 10% increments.

**Assessment of response.** The patients were assessed by the same investigator (Wong Su-Ni) at each treatment session, and any adverse effects or change in therapy dosing were recorded. During the treatment phase, a validated itch questionnaire for the assessment of pruritus was administered at every alternate treatment session, while during the follow-up phase, it was administered monthly. In total, 4 responses were derived during the treatment phase and another 6 during the follow-up phase. A short description of the parameters used in the questionnaire is summarized in Table 3.

### Results

Demographics. Of the 4 patients (2 men and 2 women) analysed, 3 had hypertensive renal disease while one had idiopathic renal failure. Their mean age was 64.3 years (range 55-70) and their mean haemodialysis duration was 338 weeks (range 312-364 weeks). They had a past history of pruritus of 156 to 208 weeks (mean 192 weeks). All the patients suffered daily pruritus. No circumstances of the initiation of pruritus, and its cessation, as well as accompanying symptoms were recorded.

### Table 3. Pruritus questionnaire.1

1. Personal data: This section includes personal data, past history and medical history.
2. Pruritus history: The history of pruritus contains the following items:
   a. Does the patient suffer from pruritus at present (during the last 5 months) or did he/she suffer from it previously?
   b. When does it appear? (daily, weekly, fortnightly or monthly)
   c. What is its duration?
   d. Open questions regarding the circumstances of the initiation of pruritus, and its cessation, as well as accompanying symptoms, such as pain, sweating, headache, heat sensation and cold sensation. Circadian changes in the appearance and pattern of pruritus.
3. Current antipruritic medications: The various medications were documented and their efficacy was marked as follows: 1= no effect, 2= short-term effect (less than 24 h), and 3= long term effect.
4. Effect on sleep: Patients were asked to rank the effect of pruritus on sleep with 3 descriptors (almost always, sometimes, never) in the following categories: difficulty in falling asleep, disturbance of sleep by pruritus, and the requirements of soporifics.
5. Effect of pruritus on daily activities and habits: Patients were asked to evaluate the effect of the daily activities and physical conditions on their symptoms; whether it caused an increase in the intensity, did not affect, or relieved their itch.
6. Coping with pruritus, and quality-of-life measures: The patients were questioned regarding the effect of pruritus on mood, behavior, ability to concentrate, change in appetite and sexual desire and function.
7. Verbal descriptor scale of itch sensation and affective dimension: A set of words, which were used by more than 80 historical cases of patients suffering from generalized pruritus to characterize their itch sensation, was selected as descriptors. The following 6 words were most commonly used to describe the sensation: tickling, stinging, crawling like ants, stabbing, pinching, burning. Another set of 4 words, which were most commonly mentioned by patients suffering from pruritus, was used to characterize the affective dimension of the itch: bothersome, annoying, unbearable, and/or worrisome. Each descriptor could be ranked on an intensity scale of 0= none, 1= mild, 2= moderate, and 3= severe. For the 6 parameters describing sensation, an index of sensation was calculated as the sum of all parameters divided by the maximum possible number 18. For the 4 affective parameters, an index of affect was similarly calculated. The questions regarding sensory and affective dimensions referred to pruritus during the last half year.
8. Severity of pruritus: The severity of pruritus was assessed by a visual analogue scale (VAS) for 4 different temporal states; at present, i.e. at the time when the patient was being examined, at the time of the worst pruritus, at the time when the condition was in the best state, and at the time of the strongest itch after a mosquito bite. A VAS was constructed consisting of a 10 cm line anchored at one end by a label ‘no itch’ and at the opposite end by a label ‘very strong itch, as bad as could possibly be’. The subject was asked to mark the intensity of the itch in the aforementioned situations.
9. Area of itch: The patient was asked to mark the areas where he or she usually itches on a body diagram so that the percentage of area of skin affected by pruritus could be calculated using the rule of nines, which divides the body surface into areas of 9%, and is used clinically to assess the severity of burns.
Current antipruritic medication. All 4 patients received antihistamines (1 had chlorpheniramine 4mg three times a day, 3 had hydroxyzine 25mg twice a day), topical steroids (all 0.025% betametasone cream) and emollients (aqueous cream) for more than 2 months. They derived only short-term benefit from the medications (less than 24 hours of relief from pruritus).

Effect on sleeping. In all patients, pruritus was aggravated during the night and they had difficulty falling asleep. All patients were awakened by the pruritus and sometimes required the use of sleeping medications. After the treatment period (16 courses of NBUVB), 3 of the 4 patients responded promptly and remained free of pruritus during the 6-month follow-up period. These patients had no difficulty falling asleep, were not awakened by pruritus and did not require the use of sleeping medications. 1 patient continued to suffer from pruritus affecting his sleep but did not require sleeping medications after the 2-month treatment.

Effect on daily activities. The major aggravating factors include lying down, sitting still, specific fabrics, dryness, heat and sweat, while alleviating factors are the use of hot/cold water, cold and sleep (Table 4). These remained similar throughout the entire study.

Effect of dialysis. Prior to the start of the study, the number of patients who felt that pruritus was more pronounced pre-dialysis, during dialysis, post-dialysis and of no correlation to dialysis was 2, 1, 0 and 1 respectively. At the end of treatment, 1 patient felt that the pruritus had no correlation to dialysis as he remained symptom-free. At the last follow-up session, 3 of the 4 patients felt that the pruritus had no correlation to the effects of dialysis as they remained symptom-free.

### Discussion
Renal itch associated with chronic uraemia was recognized in the early 1900’s. This may be generalized or localized, affecting patients with chronic renal failure where there is no primary skin disease. The prevalence of uraemic pruritus varies widely, and the occurrence of renal itch is independent of age, sex, race and aetiology of renal failure. The incidence of itch increases with deteriorating renal function, and is independent of the duration of dialysis. In our cohort, all patients suffered from end-stage renal failure requiring haemodialysis. They appear to have developed pruritus only after being on dialysis for a protracted period (mean 146 weeks).

This current study demonstrated that uraemic pruritus causes significant suffering and disturbs the quality of life. Despite using medications for symptomatic control, which includes the use of oral antihistamines and topical corticosteroids, only short-term benefits were derived. Even so, all patients had difficulty sleeping and disturbed sleep requiring the use of tranquillisers. With NBUVB treatment, 75% of the patients had impressive symptomatic control with no requirements for oral medications. The number of treatments required to achieve such a response was in contrast to studies performed in Caucasian patients. Our cohort required 16 treatment sessions (vs. 6-8 in Caucasian patients) for full symptomatic control. This delay can be explained by the darker skin type in our cohort, and "epidermal hardening" as our patients are exposed to perennial intense sunlight in the tropics.

The remission of uraemic pruritus produced by NBUVB, as in previous studies, was long lasting, and there were no major side effects.

### Table 4. Effect on daily activities

<table>
<thead>
<tr>
<th>Increases Pruritus</th>
<th>Does not affect</th>
<th>Relieves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Pre/2months treatment and follow up</td>
<td>0/0/1</td>
<td>1/3/2</td>
</tr>
<tr>
<td>Rest Pre/2months treatment and follow up</td>
<td>2/2/2</td>
<td>2/2/2</td>
</tr>
<tr>
<td>Activity Pre/2months treatment and follow up</td>
<td>0/0/1</td>
<td>3/2/2</td>
</tr>
<tr>
<td>Lying Down Pre/2months treatment and follow up</td>
<td>3/1/3</td>
<td>1/3/1</td>
</tr>
<tr>
<td>Sitting Pre/2months treatment and follow up</td>
<td>3/2/3</td>
<td>0/2/1</td>
</tr>
<tr>
<td>Stress Pre/2months treatment and follow up</td>
<td>3/1/2</td>
<td>0/3/2</td>
</tr>
<tr>
<td>Fatigue Pre/2months treatment and follow up</td>
<td>1/0/0</td>
<td>2/4/3</td>
</tr>
<tr>
<td>Eating Pre/2months treatment and follow up</td>
<td>1/0/1</td>
<td>3/4/3</td>
</tr>
<tr>
<td>Physical Effort Pre/2months treatment and follow up</td>
<td>2/2/0</td>
<td>1/1/3</td>
</tr>
<tr>
<td>Specific Fabrics Pre/2months treatment and follow up</td>
<td>3/2/4</td>
<td>1/2/0</td>
</tr>
<tr>
<td>Hot Water Pre/2months treatment and follow up</td>
<td>0/1/3</td>
<td>1/2/0</td>
</tr>
<tr>
<td>Cold Water Pre/2months treatment and follow up</td>
<td>1/0/0</td>
<td>1/0/0</td>
</tr>
<tr>
<td>Dryness Pre/2months treatment and follow up</td>
<td>3/3/3</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Sweat Pre/2months treatment and follow up</td>
<td>3/2/2</td>
<td>1/2/2</td>
</tr>
<tr>
<td>Cold Pre/2months treatment and follow up</td>
<td>2/0/0</td>
<td>0/1/0</td>
</tr>
<tr>
<td>Heat Pre/2months treatment and follow up</td>
<td>2/3/4</td>
<td>2/1/0</td>
</tr>
</tbody>
</table>
Several interesting aspects of uraemic pruritus were disclosed during the course of the study. The major aggravating factors include lying down, sitting still, specific fabrics, dryness, heat and sweat, while alleviating factors are the use of hot/cold water, cold and sleep. Of interest is the finding that although heat aggravated itch, hot water alleviated it. This finding was reiterated in an earlier study performed by Yosipovitch et al. A possible explanation suggested by this group was that the flow of water causes relief in itch, as is the case with cold water. However, different temperature ranges have different effects on itch; moderately warm temperatures (as in hot ambient temperature) increases it, while temperatures around 40°C (hot shower) relieve it by stimulating pain fibres, thus creating a block effect as explained by the gate theory.

A delayed effect on pruritus is also evident in the use of NBUVB. While 75% of the patients described felt that the pruritus was pronounced pre/peri dialysis, 25% and 75% were symptom-free at the end of the 2-month treatment period, increasing to 75% at the end of the 6-month follow-up period. The mechanism for this delayed and prolonged effect is not fully understood. In fact, the mechanism of action of UVB and UVA in the relief of various forms of pruritus is still not well understood, and is thought to be related to effects on mast cell degranulation, cutaneous histamine reactivity, and neural sensitivity threshold.

Uraemic pruritus is a distressing symptom and can be a considerable cause of morbidity. Although dermatologists should adopt a multi-disciplinary approach with nephrologists and consider renal transplantation as the definitive treatment, NBUVB provides the first opportunity for dermatologist to intervene. The optimal NBUVB doses, role of maintenance treatment and predictive factors for success are yet to be determined. Nevertheless, NBUVB can provide long lasting relief of uraemic pruritus in the majority patients with chronic renal failure. Here, the use of 2 treatment sessions per week for 8 weeks seems to be a reasonable therapeutic schedule. However a larger study would be required to confirm this initial observation.

References
Solar Urticaria: How Common Is It In Singapore?

Dr Chong Wei Sheng*, Dr Lawrence Khoo Shih-Wee**

Abstract

**Aim:** To examine the photobiological characteristics of solar urticaria in the heterogeneous group of Singaporean patients. **Methodology:** The photobiological features of all patients treated for solar urticaria at the National Skin Centre over a 10-year period were retrospectively examined. **Results:** A total of 19 patients were diagnosed to have solar urticaria from 1993 to 2002. The mean age at diagnosis was 26 years, with a racial distribution of 17 (90%) Chinese, 1 (5%) Malay and 1 (5%) Indian. Fifteen (79%) patients were males and 4 (21%) were females. The face/neck (47%) and arms/forearms (58%) were most often affected. Six (32%) patients had a history of atopy and 2 (11%) had dermographism. Fifteen (79%) patients had Fitzpatrick skin type IV, 3 (16%) had skin type III and 1 (5%) patient had skin type V. The mean exposure time to wheal formation was 23 minutes. The action spectra of solar urticaria were visible light for 12 (63%) patients, ultraviolet (UV) A for 1 (5%), visible light and UVA for 5 (27%), and natural sunlight for 1 (5%) patient. All patients reported partial improvement with a combination of antihistamines and sunscreens as the main modality of treatment. **Conclusion:** Our data suggest that solar urticaria is an uncommon photodermatosis and a rare form of urticaria. Wheals were mostly elicited by visible light and/or UVA. A combination of antihistamines and sunscreens provided a useful form of therapy for patients with solar urticaria.

Introduction

Solar urticaria is an uncommon photodermatosis characterised by the appearance of wheals after sun exposure. The wheals are transient, usually appearing within 30 minutes of sun exposure and disappearing within 24 hours. However, this condition can be chronic, causing variable amount of distress to patients, especially those young and active ones who spend a considerable amount of time participating in outdoor sports activities under the sun. The action spectrum is most often that of visible light, though ultraviolet (UV) A and UVB have been implicated as well. Hence, phototesting is a useful tool for confirming the diagnosis of solar urticaria and determining the exact action spectrum.

In this study, we report the data concerning 19 cases of solar urticaria who were studied at the National Skin Centre from 1993 to 2002, with emphasis on the demographic characteristics, action spectrum and treatment.

Materials and Methods

A retrospective analysis was conducted of the records of all patients phototested at NSC, and subsequently diagnosed to have solar urticaria from 1 January 1993 to 31 December 2002. The biodata, duration between onset of symptoms and diagnosis, history of atopy, duration between sun exposure and onset of urticaria, results of phototesting, treatment and response of each case were recorded for further analysis.

The diagnosis of solar urticaria was made by the induction of urticaria using the following light sources: a Kindermann slide projector equipped with a 150 W light bulb (Ochsenfurt, Germany) for visible light, a Supuvasun Mutzhas 3000 high-pressure metal-halide source (spectral output 350-450 nm, peak 370-385 nm) (Munich, Germany) for UVA, and a Dermaray M-DMR-100 bank of 7 fluorescent bulbs (FL20S E-30/DMR 305 nm, emission spectrum 290-390 nm, peak 305 nm) (Eisai, Japan) for UVB. The patients' buttocks were exposed to increasing doses of UV radiation. For UVA, radiation doses ranged in geometric progression from 25 J/cm^2^ to 100 J/cm^2^ (irradiance 24 mW/cm^2^ at 21 cm distance) and for UVB, 30 mJ/cm^2^ to 200 mJ/cm^2^ (irradiance 1 mW/cm^2^ at 30 cm distance). The patients' inner forearms were exposed to visible light emitted from the slide projector placed at a distance of 10 cm. The presence of wheals elicited by visible light, UVA or UVB would then be checked 20 minutes later and recorded. The minimal erythema dose (MED) responses for UVA and UVB were also documented. Monochromatic phototesting was not available.

Results

Of a total of 19 patients diagnosed to have solar urticaria from 1 January 1993 to 31 December 2002, 15 (79%) were males and 4 (21%) were females. The mean age of presentation of symptoms was 26 years (range 7 - 46 years). Seventeen (90%) patients were Chinese, 1 (5%) was Malay and 1 (5%) patient was Indian. Six (32%) patients had a history of atopy (atopic eczema, bronchial asthma and/or allergic rhinitis) whereas 13 (68%) were not atopic. Two (11%) patients had associated physical dermographism. None of the 19 patients had systemic symptoms such as dizziness or syncope.

The location of solar urticaria varied. In our series, 9 (47%) patients had lesions on the face and the V of the
Solar Urticaria

neck, 2 (11%) on the trunk, 11 (58%) on the arms and forearms, and 5 (27%) patients on the lower limbs. Thus, the most common sites of involvement were the arms/forearms and the face/neck.

The mean duration of the disease at presentation was 21.8 months, ranging from 2 to 96 months. The median duration was 12 months. The length of sun exposure required for the induction of solar urticaria symptoms and signs ranged from 5 to 60 minutes, with a mean of 23 minutes.

An analysis of the skin types according to Fitzpatrick revealed the following: 3 patients (16%) were of skin type III, 15 (79%) were of skin type IV, and 1 (5%) patient was of skin type V.

None of the patients had a history of oral ingestion of or had contact with a phototoxic or photoallergic drug, or chemical.

Laboratory tests were done in all patients diagnosed to have solar urticaria to exclude underlying or associated photosensitive disorders. In all 19 patients, full blood count (FBC) and erythrocyte sedimentation rate (ESR) tests were normal, and the antinuclear antibody (ANA) and serum/urine porphyrin tests all showed negative results.

The action spectrum was determined in all patients presenting with solar urticaria. A phototest was taken as positive when a wheal reaction was detected (Figure 1). Twelve (63%) patients were sensitive only to visible light, 1 (5%) to UVA, 5 (27%) to visible light and UVA, and 1 (5%) patient showed a response only after exposure to natural sunlight. None of the patients tested positive to UVB.

All patients with solar urticaria were treated with a combination of sunscreens and H1-receptor antihistamines, including chlorpheniramine, hydroxyzine, buclizine, cetirizine and loratadine. In our study, the mean follow-up period was 15.6 months (range: 1 to 72 months). Such therapy was able to reduce the intensity of wheals in all 19 patients, achieving a partial improvement in symptoms. No complete remission was observed in our patients. None of the patients required the usage of phototherapy or photochemotherapy in the control of the urticarial symptoms and signs.

Discussion

At NSC over a 10-year period (from 1993 to 2002), solar urticaria represented an uncommon form of photodermatosis, as well as an unusual form of urticaria. Solar urticaria constituted 7% of all forms of photodermatoses seen in our centre. Of a total of 21974 new cases of urticaria (all types) seen in the last 10 years, 19 cases were diagnosed to have solar urticaria. Therefore, the incidence of solar urticaria was estimated to be 8.6 per 10,000 cases of urticaria diagnosed. These 19 patients also represented 2% of all patients who underwent phototesting during this study period. The diagnosis of solar urticaria can be difficult at times based on clinical grounds alone as the lesions persist for a short period of time and most patients do not exhibit any sign at all when consulting a doctor. Thus, the diagnosis of solar urticaria can only be made with certainty after confirming with phototesting. Such phototests are necessary to determine the action spectrum, such as visible light, UVA or UVB1.

Demographically, our series showed a male preponderance of 79%. In contrast, series by Horio2 and Monfrecola et al3 revealed a female preponderance of 59% and 56% respectively. Chinese patients (90%) dominated the racial distribution in our series and this approximately conformed to our own Singaporean racial distribution with Chinese constituting the majority (76.8%). Six (32%) patients had a history of atopy (atopic eczema, bronchial asthma and/or allergic rhinitis). In contrast, in a series by Ryckaert et al1, nearly half (48%) of the patients had atopy.

The action spectra in solar urticaria differ among cases. In our series, 12 (63%) patients were sensitive to visible light alone, 1 (5%) to UVA alone, and 5 (27%) patients to both visible light and UVA. Thus, the most common action spectrum was visible light. It is interesting to note that 1 patient developed wheals only when tested to natural sunlight4. None of our patients were sensitive to UVB. In a Japanese series by Horio5 of 42 patients, 24 (57%) patients were sensitive to visible light alone, and 5 (27%) patients both to visible light and UVA. Thus, the most common action spectrum was visible light. It is interesting to note that 1 patient developed wheals only when tested to natural sunlight4. None of our patients were sensitive to UVB. In a Japanese series by Horio5 of 42 patients, 24 (57%) patients were sensitive to visible light, and this finding was similar to ours. In contrast, the European series seemed to reveal less frequent involvement by visible light, and UV radiation was the more common eliciting spectrum. Ryckaert et al1, in a Belgian series of 25 cases, reported 20% of patients being sensitive to visible light alone. The Frain-Bell’s Scottish series had 19% of patients being responsive to visible light alone5. In contrast, an Italian series by Monfrecola of 57 cases, 66.7% of patients had a positive reaction to visible light and 3 patients had a positive response to natural sunlight6. Hence, whether geographical or ethnic factors play a role in the different action spectra is still a question unanswered6.

Fig 1. A positive wheal reaction elicited 15 minutes after irradiation with visible light.
The development of cutaneous symptoms and signs immediately after sun exposure and the rapid disappearance suggest that type I (immediate) hypersensitivity reaction is the most likely pathogenetic mechanism. Harber et al had proposed a classification of solar urticaria into 6 types, based on the action spectrum. Leenutaphong et al, on the other hand, provided a more recent classification of solar urticaria into 2 types, both due to type I hypersensitivity reaction. This has been substantiated in a review article by Horio, concluding that solar urticaria may be an immediate type of photoallergic reaction mediated by an IgE antibody to endogenous serum factors, though such a photosensitizer has not been clearly identified.

Management of solar urticaria can be difficult. The combined modality of treatment employing sun avoidance and protection such as clothing, hats and gloves, the use of sunscreens and H1-receptor antihistamines has been the mainstay of treatment. Broad spectrum sunscreens are probably useful for UV-sensitive patients, but have little effect for patients who react to visible light. In such instances, physical sunscreens containing non-micronised zinc oxide and titanium dioxide may be more beneficial as they help to reflect and scatter visible light. The response to such combined treatment, however, may only be partial, and the patients still suffer from symptoms which can be rather distressing, especially for the young and active ones who participate in outdoor sports activities under the sun. For the recalcitrant cases who do not respond to antihistamines, phototherapy such as UVA, UVB and combined UVA/UVB, or photochemotherapy such as psoralen-UVA (PUVA), may be utilized to produce a ‘hardening’ effect on the skin, achieving a tolerance effect as well as providing an inhibiting effect on the provocation of solar urticaria, especially so if the inhibition spectrum has been determined. This, of course, has to take into account the eliciting wavelengths. In certain cases, plasmapheresis, with or without PUVA, has been used occasionally but it is more invasive and tedious. In our series, all patients had some improvement of symptoms in terms of the reduction of intensity of wheal formation. As they are not too distressed by the condition, none of the patients required the prophylactic use of phototherapy or photochemotherapy.

Solar urticaria is a chronic disease with variable course. Our data showed that our patients had the disease lasting 2 to 96 months (mean of 21.8 months) before consultation, and none of our patients achieved a complete remission within the follow-up period ranging from 1 to 72 months (mean of 15.6 months). In a series by Uetsu et al of 40 patients, none achieved a complete cure. On the other hand, 2 out of 30 patients had complete clearance in Frain-Bell’s series.

**Conclusion**

Solar urticaria is an uncommon photodermatosis and an unusual form of urticaria. In our series, it was most commonly elicited by visible light or UVA. All of our patients had partial improvement of their symptoms and signs with a combined use of sun avoidance, sun protection, sunscreens and H1-receptor antihistamines. None of the patients required phototherapy or photochemotherapy.

**References**

Demographic Characteristics of New Patients Seen At The National Skin Centre

Dr Lim Kar Seng*, A/Prof Roy Chan**

Abstract

Background: More than 77,000 diagnoses were made among the new patients seen at the National Skin Centre (NSC) in the year 2004. Aim: To review the demographic characteristics of these new patients by diagnosis categories. Methodology: A retrospective study was conducted on all diagnoses made for the new patients seen at NSC in year 2004. Diagnoses were categorised according to the International Classification of Diseases (ICD) code. A review of the patients in grouped ICD codes was done by gender, age group and ethnicity. Results: Chinese patients (79.3%) made up the majority of the new patients in terms of ethnicity. There was an under-representation of Malays (5.9%) amongst the new patients seen. The majority of the patients fell within the younger age groups, commonest being the 20-30 years age group (25.3%). There were significantly more females than males (8.3% to 3.8%) in the 31 - 40 years age group with a diagnosis of acne; and in almost all age groups for cutaneous lupus erythematosus (LE) (79.8%) and melanocytic naevi (66.3%). More males were seen with a diagnosis of psoriasis (63.6%), fungal (74.9%) and pyogenic infections (65.2%). Indian patients had significantly more lichen planus (50%), vitiligo (18%) and psoriasis (14%); whilst the proportion of Malays diagnosed with cutaneous LE (15%) and pemphigus (17%) was significantly higher compared to other diagnoses. Conclusion: The demographic characteristics of all new NSC patients by disease codes have not been previously studied before. This paper reveals patterns of diseases in ethnic groups, gender and age groups that were hitherto unknown in NSC. Further studies may be useful to determine the cause of apparent ethnic predilections for specific diseases.

Background and aims of study

The National Skin Centre represents the largest tertiary dermatology centre in Singapore. There were a total of 77,062 diagnoses made in new patients seen at NSC in 2004. This paper presents an analysis of these diagnoses by age group, gender and ethnicity.

Methodology

The diagnoses of new patients seen in the National Skin Centre were categorised according to the International Classification of Diseases (ICD) code. A retrospective review of the patients by grouped ICD codes was done by gender, age group and ethnicity. Analysis of ethnicity, gender and age group differences was performed using Chi-square test, SPSS Version 12.0. P values less than 0.05 were considered significant.

Results

The ethnic distribution of the new diagnoses revealed that 79.3% were made in Chinese, 5.9% in Malays and 8.1% in Indians. There was a slight predominance in male patients (52.1%), compared to females (47.9%). The median age group of the new cases fell within the 30 to 40 year old category. Comparisons of these demographics with the Singapore population, based on the latest Singapore Census1, are shown in Table 1. There was an under-representation of the Malays amongst the new patients in NSC.

Figure 1 shows the breakdown of the new diagnoses by age group and gender. The largest number of patients was in the 21 to 30 year age group, followed by patients between 11 to 20 years.

Table 1. Comparison of patients’ demographics with that of Singapore population

<table>
<thead>
<tr>
<th>Ethnic composition (by %)</th>
<th>New patients in NSC</th>
<th>Singapore population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>79.3</td>
<td>76.8</td>
</tr>
<tr>
<td>Malay</td>
<td>5.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Indian</td>
<td>8.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Others</td>
<td>6.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex Ratio (by %)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>52.1</td>
<td>49.9</td>
</tr>
<tr>
<td>Female</td>
<td>47.9</td>
<td>50.1</td>
</tr>
</tbody>
</table>

I. Frequency of diagnosis/diagnosis groups by age-group and gender

Fig. 1 Breakdown of new diagnoses by age group and gender

* Registrar
** Senior Consultant Dermatologist and Director, National Skin Centre
of age, and then the 31 to 40 year age groups. The proportion of males and females were almost equal in all the age groups.

The following figures (Fig. 2a-d) illustrate the age group and gender distribution of selected diagnoses categories. Table 2 shows the distribution of the rest of the disease categories by age group and gender.

For acne vulgaris (Fig. 2a), the higher proportion of female patients (8.3%) in the 31 to 40 year age group compared to males (3.8%) was statistically significant when compared to the sex ratio in the other age groups of the same disease \((p<0.001)\), as well as when compared to the sex ratio of the 31 to 40 year age group of all new patients in NSC \((p<0.001)\).

In the alopecia group (encompassing androgenetic alopecia, alopecia areata and telogen effluvium) (Fig. 2b), the higher proportion of males in the 21 to 40 year age groups with this problem reflects the higher incidence of androgenetic alopecia in males \([n=955 \text{ (males, 21-40years)}; n=436 \text{ (females, 21-40years)}]\).

The skin cancers (Fig. 2c) category included basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and cutaneous lymphoma. As expected, the age distribution of this disease is skewed to the right. A similar age distribution is seen in the bullous pemphigoid category (Fig. 2d) where the vast majority (75.2%) were over 70 years of age.

### Table 2. Frequency of diagnosis by age group and gender.

<table>
<thead>
<tr>
<th>Diagnosis groups</th>
<th>Frequency of diagnosis groups by age group/gender (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-10</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>10.8</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>9.4</td>
</tr>
<tr>
<td>Melanocytic naevi</td>
<td>7.1</td>
</tr>
<tr>
<td>Urticaria</td>
<td>5.6</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1.3</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>1.9</td>
</tr>
<tr>
<td>Tinea infection</td>
<td>0.9</td>
</tr>
<tr>
<td>Pyogenic skin infection</td>
<td>4.8</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>0.0</td>
</tr>
<tr>
<td>Cutaneous LE</td>
<td>0.0</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>3</td>
</tr>
<tr>
<td>Non-genital viral warts</td>
<td>7.2</td>
</tr>
</tbody>
</table>
A significantly higher proportion of females across the age groups were diagnosed with melanocytic naevi ($p<0.001$) and cutaneous lupus erythematosus (LE) ($p=0.001$). A higher proportion of males from ages 30 and above suffered from psoriasis ($p=0.009$). The predominance of males across all age groups was also seen for the diagnoses of fungal skin infections ($p<0.001$) and pyogenic skin infections ($p=0.009$).

No significant difference in the gender ratio was seen for the diagnoses of vitiligo, urticaria, adverse drug reaction, pemphigus, lichen planus and no genital viral warts ($p$ values $0.902$, $0.155$, $0.412$, $0.155$, $0.327$, $0.238$ respectively).

II. Frequency of diseases by ethnicity

Table 3. Frequency of diagnosis categories by ethnicity

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chinese (%)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>79.3</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>80</td>
</tr>
<tr>
<td>Acne</td>
<td>81</td>
</tr>
<tr>
<td>Alopecia</td>
<td>81</td>
</tr>
<tr>
<td>Skin cancers</td>
<td>81</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>65</td>
</tr>
<tr>
<td>Naevi</td>
<td>84</td>
</tr>
<tr>
<td>Urticaria</td>
<td>84</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>70</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>80</td>
</tr>
<tr>
<td>Fungal skin infections</td>
<td>71</td>
</tr>
<tr>
<td>Pyogenic skin infections</td>
<td>78</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>70</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>84</td>
</tr>
<tr>
<td>Cutaneous LE</td>
<td>75</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>33</td>
</tr>
<tr>
<td>Non-genital warts</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 3 illustrates the frequency of diagnosis categories by ethnicity. A higher proportion of Indians suffered from vitiligo ($p=0.001$) and lichen planus ($p=0.001$). When comparing psoriasis in patients of Indian ethnicity with non-Indians as a group, psoriasis was also more common among Indians ($p=0.031$). There were more Chinese and Other ethnicities (which included Eurasians and Caucasians) who had skin cancer ($p<0.001$) and melanocytic naevi ($p=0.002$). Significantly more Malays were diagnosed with cutaneous LE ($p=0.001$) and pemphigus ($p<0.001$) when compared to other diagnosis categories.

Discussion

This is the first study to examine the demographic characteristics of all diagnoses made in new patients attending NSC in a year. The under-representation of the Malay ethnicity when compared to the general Singapore population cannot be readily explained. The gender proportions and the age group distribution of the new patients approximate that of the Singapore population. Majority of the patients fell within the younger age groups, commonest being the 21 to 30 year age group, followed by the 11 to 20 and the 31 to 40 year age groups.

Dermatitis, acne, alopecia, psoriasis and non-genital viral warts represented the commonest disease categories in which the new diagnoses were made in our centre for the year 2004. These conditions were also the predominant entities reported in recent prevalence studies of skin diseases in ethnic populations, as well as in health-care settings. In the United Kingdom, the Lambeth study, a prevalence study of skin disease in the population, showed a similarly high proportion of people with skin disorders suffering from eczema, acne, tumours/vascular lesions/naevi and scalp and hair disorders.

The higher incidence of 31 to 40 year old female patients with acne vulgaris compared to the males has been previously reported in a limited number of studies. The possibility of greater treatment seeking behaviour of the female patients in this age group has to be considered as well. This behaviour may also be a major factor explaining the higher incidence of melanocytic naevi that we found in females. This finding concurs with an earlier study on melanocytic naevi reported from our centre by Kwok et al.

It may be postulated that the higher incidence of tinea infections seen in males may be due to the need for young adult males to serve their National Service military duties in Singapore. It is the authors’ observation that this skin condition is seen frequently in the above subgroup of patients. This epidemiological aspect of patients with tinea infection was not analysed in this study.

The higher incidence of psoriasis in males compared to females in the 31 years and above age groups, as well as in the Indian ethnicity are interesting findings. A recent study from this region corroborated both these findings as well. Conversely, the prevalence of psoriasis in African-Americans is lower compared to the rest of the US population. It appears that ethnicity, rather than skin of colour, is a risk factor in the development of psoriasis.

The incidences of lichen planus and vitiligo in Indians are markedly higher compared to the other diagnoses. Both these diseases are commonly seen in the Indian subcontinent. However, to our knowledge, no comparative studies between the incidence of the diseases in Indians and other ethnicities have been previously reported.
There were significantly more Malays with cutaneous LE (p=0.001) and pemphigus (p=0.001). The reasons for this are unknown and it remains to be discovered if Malays have a higher predilection for autoimmune cutaneous diseases.

**Conclusion**

This study reveals some interesting demographic characteristics of the different disease categories seen amongst the new patients in a year at the NSC. Some of these observations are consistent with previous reports. However, many of them have not been previously reported or elucidated as to the reasons for these findings. Further studies should be performed in order to corroborate the above findings and to exclude the possibility of sampling error.

**References**


Hydroa Vacciniforme In a Child

Dr Melvin Ee*, Dr Wong Su-Ni **

Abstract

An 11-year-old boy presented with photodistributed vesicles over the dorsum of both hands 2 days after outdoor activities with sun exposure. The lesions evolved to form crusted lesions, which healed with scarring. The clinical symptoms recurred upon subsequent sun-exposure. Phototests were normal and a skin biopsy showed an intraepidermal blister with confluent necrosis of the epidermis resulting in eosinophilic reticular degeneration. There was dermal papillary oedema and a dense perivascular infiltrate of lymphocytes. The histology was characteristic of hydroa vacciniforme.

Introduction

Hydroa vacciniforme (HV) is a rare, idiopathic photodermatosis with onset in childhood and characterized by acute vesiculation, crusting and scarring following sun exposure. Atypical clinical presentations have been reported in the literature. In this paper, we report a case of HV with proven classical histology. The literature for unusual manifestations in HV is also reviewed.

Case Report

An 11-year-old boy was referred with a few days' history of vesicles over the dorsum of both hands. They had appeared 2 days after outdoors activities. These lesions formed crusts and scabbed. He did not describe any family history of photosensitivity nor chemical contactants to the affected areas. A biopsy of a bullae on the volar aspect of the right wrist revealed an intracorneal bulla and a superficial perivascular lymphocytic infiltrate, while the immunofluorescence of the lesional skin did not reveal any immunoprecipitation.

A few weeks later, he developed a similar presentation over the same area, 3 days after sun exposure. On examination, there were vesicles on the hand. (Fig. 1)

Full blood count, anti-nuclear antibody, and urine and blood porphyrin screen were all unremarkable. Phototesting was carried out, using ultraviolet (UV) A delivered by Mutzhas (Crown Agent, Munich, Germany) light source, and UVB delivered by Dermaray (Eisai Torex, Tokyo, Japan). The minimal erythema dose for UVA and UVB were both normal for his skin type (>100 J/cm2 and >100mJ/cm2 respectively). He declined photoprovocation tests.

A repeat biopsy of a vesicle was obtained. This showed an intraepidermal blister with confluent necrosis of the epidermis resulting in eosinophilic reticular degeneration. (Fig. 2) There was dermal papillary oedema and a dense perivascular infiltrate of lymphocytes. The histology was consistent with hydroa vacciniforme.

He was advised on photoprotection and prescribed a broad-spectrum sunscreen.

Fig. 1 Multiple vesicles and necrotic lesions on the dorsum of both hands and wrists. Note the scarring.

Fig. 2 Confluent necrosis of keratinocytes with reticular degeneration. (H&E stain, x100)
Discussion

HV is a very rare chronic photodermatosis usually with onset in childhood and spontaneous resolution by adolescence or early adulthood. It is characterized by recurrent vesiculation that follows itching or burning macules or papules, crusting and, finally, varioliform scarring in sun exposed areas. It exhibits a bimodal distribution with disease onset in early childhood (1±7 years of age), or about puberty (12±16 years of age).1 There is an increased erythemal sensitivity to UVA in 53% of cases while isolated cases showed sensitivity to UVB.

The differential diagnosis of the photodistributed vesicular eruption in this case could include vesicular polymorphic light eruption (PMLE), bullous lupus erythematosus (LE) and erythropoietic porphyria (EPP). However, the histology, as well as the scarring that persisted after resolution of the vesicles, was not consistent with the diagnosis of PMLE. Bullous LE was excluded by paucity of clinical findings, a negative antinuclear antibody and histology, while the normal plasma and urinary porphyrin screen makes the diagnosis of EPP unlikely.

There are a handful of reports that describe clinical manifestations deviating from Bazin's original description of HV. Though a predominantly childhood photodermatosis which resolves spontaneously in early adulthood, Wong et al2 described 2 cases which presented at age 20, and its natural course can even be protracted till 60 years of age3. Rarer findings include painful subungual hemorrhages unrelated to trauma4. Blistering during a flare is a typical feature seen in HV. Leenutaphong et al5 described a case of non-vesicular HV with extensive crusting associated with hypertrophic scarring in sun-exposed skin. However, the patient previously presented with vesicular lesions in the same areas. As such, this might not represent a true “non-vesicular” variant. Scarring in HV can also result in debilitating finger contractures5 and severe ear mutilation6.

Treatment is aimed at prevention and this includes sun avoidance, sunscreens and protective clothing. Systemic therapies such as narrow band UVB, PUVA, antimalarials and beta carotene have been tried with variable success.7

References

Ageing

Dr Lim Yen Loo*

This joint teaching seminar was held on 30th August 2005. The following topics were discussed: I. Management of menopause by Prof Tay Boon Lin, Visiting Consultant, KK Women and Children’s Hospital; II. Geriatric Dermatology – The Ageing Skin by Dr Chong Wei Sheng, Associate Consultant, National Skin Centre; III. Male Ageing and Anti-ageing strategies by Dr Peter Lim, Consultant Urologist, Gleneagles Hospital.

Management of Menopause

Menopause is defined as a permanent cessation of menses. It is a result of ovarian failure, which can be natural or induced by surgery, chemotherapy or radiation. Menopause-related changes include vasomotor symptoms, sleep disturbances, vaginal dryness, skin dryness and wrinkling, and bone loss. Interventions in menopause aims to treat these symptoms, improve the quality of life, provide contraception (if needed), lower the risk of disease and increase longevity, is possible. Therapeutic options in the management of menopause include lifestyle modification, non-prescription remedies, complementary and alternative medicinal approaches, use of prescription drugs and surgical procedures.

Menopausal hormone therapy (HT) alleviates some of the menopause-related symptoms, but observational studies also showed other suspected risks and benefits associated with its use. Women’s Health Initiative (WHI) clinical trial of HT was conducted to evaluate the balance of chronic disease risks and the benefits of postmenopausal HT. The trial showed that the use of hormonal therapy containing conjugated equine oestrogen (CEE) plus medroxyprogesterone acetate (MPA) in older postmenopausal women (age range 50-79) has a 26% increase in risk of breast cancer, a 29% increase risk in coronary artery disease and a 41% increase in risk of stroke. The risks for dementia and venous thromboembolism were also above threshold level. That for hip fracture, total fracture, diabetes and colon cancer were below the threshold level. Thus there is an overall greater risk than benefit in patients treated with CEE+MPA. In older postmenopausal woman with prior hysterectomy, the use of unopposed oestrogen (CEE) is associated with an increased risk of stroke, decreased risk of hip fracture and total fracture, but no difference in the incidence of coronary heart disease. There are, however, some differences between observational and clinical trial participants, which are noteworthy (Table 1).

FDA-approved indications of HT include: (i) treatment of moderate to severe vasomotor symptoms, (ii) treatment of moderate to severe atrophic vaginitis, (iii) prevention (not treatment) of postmenopausal osteoporosis. Non-hormonal treatment of postmenopausal osteoporosis is advised and use of lowest effective dose for the shortest possible time is recommended for HT.

In summary, risks of HT exceed the benefits for the prevention of chronic diseases in postmenopausal women. HT remains an effective therapy for treating women with vasomotor symptoms and vaginal atrophy as well as retardation of osteoporosis in selected patients. Individualized benefits and risks should be discussed before initiation of HT and reassessed periodically. Recent data do not address the effect of HT during or soon after the menopausal transition and its subsequent impact on disease processes. Future research is critical to clarify optimal timing and duration of HT. Current data do not address benefits and risks in women with premature menopause.

Table 1. Summary of differences between observational and clinical trial participants

<table>
<thead>
<tr>
<th>Menopausal symptoms (flushing)</th>
<th>Observational</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age started HT</td>
<td>30-55 years</td>
<td>63(WHI)**</td>
</tr>
<tr>
<td></td>
<td>67 (HERS)*</td>
<td></td>
</tr>
<tr>
<td>Years since menopause</td>
<td>&lt;5 years</td>
<td>~ 15 (WHI)</td>
</tr>
<tr>
<td></td>
<td>~18 (HERS)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI</td>
<td>28.5</td>
<td>25.1</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>&gt;10-40 years</td>
<td>&lt;7 years</td>
</tr>
<tr>
<td>HT regimen</td>
<td>Unopposed, continuous</td>
<td>Unopposed, sequential</td>
</tr>
</tbody>
</table>

* Heart and Estrogen/Progestin Replacement Study
** Women’s Health Initiative

Geriatric Dermatology – The Ageing Skin

Ageing of the skin can be intrinsic or extrinsic. The former is genetically and hormonally determined, while the latter is secondary to environmental factors such as ultraviolet radiation. In practice, however, there is an overlap of the clinical features for both types of skin ageing. Apart from changes in the gross and histological appearance of the skin, various functions of the skin also decline with age.

Skin dryness, fragility, thinning, wrinkling, decreased elasticity, lentigines, seborrheic keratoses, ecchymosis, depigmented hair, diffuse hair loss, and thin or brittle nails characterize intrinsic skin ageing. In photoaged skin, freckling, stellate pseudoscars, telangiectasia and venous lakes are additional features. Elasticity is the histological hallmark of photoageing. Other histological findings include increased deposits of glycosaminoglycans and proteoglycans, reduction in the amount of collagen,
epidermal acanthosis or atrophy, keratinocytes atypia and reduced number of Langerhans cells.

Examples of skin disorders associated with photoageing are: sebaceous hyperplasia, cutis rhomboidalis nuchae, idiopathic guttate hypomelanosis, Favre-Racouchot syndrome, Poikiloderma of Civatte, colloid milia, actinic keratosis, Bowen’s disease, basal cell carcinoma, squamous cell carcinoma and melanoma.

As the skin ages, there is decline in its barrier function, sensory perception, wound healing ability, thermoregulation, sweat and sebum production, DNA repair and immune responsiveness.

Skin problems in the elderly can be largely grouped as primary dermatoses, dermatoses secondary to underlying systemic disease or its treatment, or dermatoses related to poor mobility or neglect.

Xerosis and pruritus are two major players in most of the skin disorders in the elderly. Itch can be secondary to a dermatological condition (e.g. atopic eczema, seborrhoeic dermatitis, stasis eczema), or an underlying systemic disease (e.g. metabolic or haematological). It can also be a manifestation of an underlying psychological problem such as depression in the elderly. It is thus important to look for an underlying cause in the evaluation of itch in the elderly.

Other common skin conditions in the elderly include skin infections such as herpes zoster and scabies; nutritional disorders e.g. scurvy and pellagra, often due to inappropriate diet, neglect or underlying illnesses; vascular disorders such as chronic venous and arterial insufficiency; photosensitivity disorders such as chronic actinic dermatitis and photo drug eruptions; immunobullous dermatoses such as bullous pemphigoid; connective tissue disease such as rheumatoid arthritis; malignancy-associated dermatomyositis, purpura, pressure ulcers, premalignant skin conditions such as actinic keratoses and Bowen’s disease; malignant tumours such as basal cell carcinoma, squamous cell carcinoma, extramammary Paget’s disease, angiosarcoma and Kaposi’s sarcoma.

Male Ageing and Anti-Ageing Strategies

Andropause, the male equivalent of menopause, is caused by hormonal and physiological changes in the male’s body, and this is part of ageing. Andropause usually affects men of age between forty and fifty-five, but hormonal changes can occur as early as thirty-five years of age. Apart from a reduction in testosterone production, other hormones such as growth hormones, insulin-like growth factor-1 (IGF-1), melatonin, dihydroepiandrosterone (DHEA), thyroxine and prolactin have also been shown to decrease as a person ages. Fatigue, erectile dysfunction, depression, irritability, bone aches and joint stiffness are common symptoms of andropause.

A person has both a chronological and a biological age. In the evaluation of biological age, biomarkers such as highest audible pitch, vibrotactile sensitivity, visual reaction time with and without decision, muscle movement with and without decision, lung FVC, lung FEV, memory length, body fat/muscle ratio and basal metabolic rate are useful. Other biomarkers which are examined include salivary levels of testosterone, oestrogen and progesterone; serum levels of IGF-1, IGF binding protein-3, free thyroxine levels (fT3 and fT4); and urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and urinary pentosidine.

Strategies in anti-ageing therapy include (1) a holistic approach with emphasis on diet, exercise, stress management and use of alternative medicines; and (2) a medical approach in which a physician, reproductive endocrinologist, urologist, cosmetic surgeon or genetic engineer may be involved. Whichever the approach, the aim of anti-ageing therapy is to keep a patient’s biological age stabilized at 10 years younger than his chronological age. In general, important factors to consider before initiating anti-ageing therapy include the patient’s profile, health assessment, biological markers, patient’s goal and expectation and his subjective symptoms score.

Testosterone replacement is part of the anti-ageing therapy. However, it has only been proven to be beneficial in men who have low levels of the hormone. Low level of testosterone is associated with cardiovascular mortality, osteoporosis and depression. Replacement of other hormones such as DHEA, growth hormone, thyroxine, or the use of IGF-1, growth hormone analogues and melatonin are other possible treatment strategies for anti-ageing. The use of these hormonal therapies requires knowledge of their contraindications and potential side effects.
The joint teaching seminar on sexually transmitted infections (STI) and HIV was held on 12 Dec 2005 and the following topics were discussed. I. Behaviour and biology in STI/HIV transmission by A/Prof Roy Chan, Senior Consultant and Medical Director, National Skin Centre; II. Behavioural intervention in STI/HIV control by A/Prof Wong Mee Lian, Department of Community, Occupational and Family medicine, National University of Singapore; III. Applying best practices to HIV/AIDS prevention in the gay community by Prof George Bishop, Department of Psychology, National University of Singapore.

I. Behaviour and Biology in STI/HIV transmission

Researchers have been trying to measure sexual behaviour for a long time. This intensified after the emergence of the HIV pandemic. Measurement of sexual behaviour served a number of distinct purposes including assessment and temporal monitoring of risk behaviours in populations, and the measurement of the role of sexual behaviour in the acquisition and transmission of diseases. In the process of measurement, it is important to define sexual behaviours to be measured, populations to be studied, time periods to be covered and the contextual parameters to be considered. Certainly, a “one size fits all” approach is inadequate for the diverse purposes at hand.

Reporting of sexual behaviour is highly sensitive to the study design. This in turn depends on the sample studied (high-risk group vs. general population sampling) and the method of interview used (structured face to face interview vs. unstructured repeated interviews). Other pitfalls in the methodology include accuracy of self reporting as a result of recall or social acceptability bias, wording of the questions, lack of biological outcome measures and lack of comparable data over time and place.

In modern times, due to the globalisation of the sex world, commercial sex is becoming more difficult to define and characterize.

Methodological developments in research include population probability samples with repeat measures over time; the use of computer-assisted methods to increase the reporting of socially censured behaviours; and, novel methods like “voting interviews” in resource poor settings. Informal confidential voting interviews can reduce social desirability bias in data on HIV associated risk behaviours (Gregon S et al). This is a 2-step process which allows the building of rapport between the respondent and the enumerator, as well as the address of sensitive issues at hand.

Behavioural self-reports are validated by comparing biological and behavioural outcomes. For example, inconsistencies were noted in studies in Tanzania; only 58% of males and 29% of females with biological markers (sexually transmitted infections and pregnancy) consistently reported sexual behaviour.

Currently, few countries have comparable data over time, and even fewer have both behavioural and biological or surveillance data. In studies of African countries, the proportion of people reporting multiple partnerships and not using a condom at last sexual encounter has declined since 1996. Unprotected sex with non-cohabiting partners is reported less frequently in the later surveys.

Between 1996 and 2003, reported sexual behaviour has changed in Zambia among both men and women. There is some evidence for an increase in men’s age at first sex. The socio-economic and demographic compositions of the survey samples have changed across the years, but the declines in behaviour remain statistically significant after adjustment for these changes. There is also evidence of a changing reporting bias over the period of interest, with respondents less likely to report a young age at first sex in later surveys.

On the subject of condom use, condoms were effective in reducing transmission of many sexually transmitted infections. Consistent condom use significantly reduced HIV incidence; and inconsistent condom use failed to do so. In Britain condom use increased from 61% in 1990 to 82% in 2000 in 16 to 24-year-old men, but only 35% of those with 2 or more partners in the last month were consistent users.

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In the research of population sexual behaviour, additional factors that were studied include partnerships, age mixing (in Singapore the peak age of HIV diagnosis amongst females was between 20-29 years of age, and 30-39 years for males), geographical mixing (with regards to homosexuals in Singapore, the internet was the second most common point of contact), ethnic mixing, demographic change, estimating the (changing) magnitude of susceptible populations, and study of networks (sexual or social).
In China, we are about to witness the impact of demographic change on the incidence of sexually transmitted infections. Soon, approximately 8.5 million ‘surplus men’, unmarried and disproportionately poor and migrant, will come of age in China’s cities and rural areas. Meanwhile, many millions of Chinese sex workers appear to represent a broad range of prices, places, and related HIV risk behaviours. Alongside a rapid increase in sexually transmitted disease incidence across developed parts of urban China, surplus men could become a significant new HIV risk group.

Therefore, the understanding of interaction between sexual behaviour and biology has changed from a static to a dynamic paradigm. Demography, culture, inequalities and changing social attitudes can impact on behaviours in unpredictable ways. In the pursuit of improved understanding of the relationship between ‘behaviour and biology’, one needs to take into consideration the following:

a) Standardized behavioural methods to improve comparability in time and place
b) Clarity about behavioural measures ‘fit for purpose’
c) Behavioural surveillance in general and sentinel high-risk populations
d) Accompanying biological measures of STI exposure
e) Measurement of relevant ‘upstream factors’ such as demography, migration
f) Measurement of social and sexual networks

II. Behavioural Interventions in STI/HIV Control

A. Behavioural change theories

There are several models of behavioural change theories: health belief model and Green’s framework model.

The health belief model is summarized by the following principles: (applied in a local intervention program to encourage regular condom use among commercial sex workers in Singapore)

1. Vulnerability/ Susceptibility: increase the level of awareness among commercial sex workers of their risk of acquiring an infection.
2. Seriousness of the disease: emphasise the incurability of diseases like HIV.
3. Benefits vs. costs: the protection from condom use far outweighs the inconvenience or costs incurred.
4. Barriers: address possible barriers such as inconvenience, fear of annoying clients.
5. Self-efficacy: develop social skills such as in persuading the clients to use condoms.
6. Cues: provide regular reminders through health care personnel.

However, despite the fact that the majority of sex workers surveyed (95%) knew that condoms would protect them against sexually transmitted infections, less than half (42%) actually insisted on condom use with their clients.

A further model, the Green’s framework model was used to look into the factors that enabled or hampered the behaviour:

1. Predisposing factors: knowledge, beliefs, attitudes, values
2. Enabling factors/Barriers: time, resources, skills, facilities
3. Reinforcing factors: attitudes, support from health staff

A study on the clients of sex workers (2001-2003) revealed the following reasons for not using condoms: reduced sensation (31%), sex workers did not ask (21%), condoms were not available (22%) , forget in the heat of the moment (19%), were drunk (19%), trusted that the sex worker was free of infections (6%), could not perform with a condom (2%). Therefore, Green’s framework could be applied in the following ways:

- Predisposing factors: relating condom use to what they valued most e.g. Personal health, family ties
- Enable factors: skills for negotiating condom use
- Reinforcing factors: support from brothel owners, health staff and peers

B. Conducting research on risk groups

The design and delivery of the questionnaire are crucial cornerstones of a study. Questionnaires can be administered through: face-to-face or telephone interviews, self-administered questionnaires, computer assisted personal interviews or sexual diaries.

Possible ways in which errors in measurements of behaviour may be reduced are:

1. Reduce non-participation, social desirability bias, false reporting
   - Increase anonymity, assure confidentiality
   - Explain purpose of survey, stress importance of honest answers
   - Use audio computer assisted self-interviews rather than face-to-face interviews
   - Use bogus pipeline i.e. respondents are led to believe that their responses are being monitored physiologically

2. Enhance recall
   - Use short reporting period e.g. 1-2 weeks/months or most recent event
   - Use behavioural logs or diaries e.g. reports of sexual behaviour over brief periods of time

3. Design questions carefully
   - Use familiar words
   - Ask the questions in such a way to assume that behaviour is practised
   - Avoid leading questions
   - Use appropriate and clear language

Continued on Page 44
Type-specific Serology Testing For Genital HSV Infection

Dr Priya Sen*

Introduction

Genital herpes simplex virus infection is a significant public health disease worldwide causing substantial morbidity and transmission potential. In Singapore, genital herpes is the most common cause of genital ulceration. Over the last 5 years there has been a dramatic increase in its incidence. The number of cases double from 564 in 2000 to 1143 in 2005. The majority of patients were males with an incidence ratio of 4:1 male to female patients.

Genital herpes is primarily caused by infection with herpes simplex virus (HSV), commonly by HSV type 2 and now increasingly by type 1. Both HSV-1 and HSV-2 infections are acquired from contact with infectious secretions on oral, genital or anal mucosal surfaces resulting in a variety of clinical presentations depending on the duration of the lesion at the time of presentation to the clinic. HSV-1 produces the same acute clinical picture but is associated with fewer recurrences, less frequent viral shedding and a better prognosis than HSV-2 infection. In addition to the risk of sexual transmission of the infection, there is also a small but significant risk of vertical transmission causing potential serious neonatal infection. Some infected individuals experience frequent relapses and as a result have major emotional and psychosexual effects. It has also been shown that HSV infection increases the risk of transmission of HIV among infected populations.

A large number of genital HSV infections are asymptomatic and it is important that an accurate diagnosis be made by clinicians, as this has a major psychological, social, as well as sexual impact on patients and their sexual partners. The majority of individuals are infected by a partner who is unaware of having the infection. Virus is shed intermittently from the genital tract of infected asymptomatic people and also between attacks in people with typical mucocutaneous symptoms. Thus, patients with undetected infections are potentially an important source of sexual transmission.

Serological tests are the only diagnostic tools available to identify individuals with asymptomatic HSV infection. A number of new type-specific serology tests (TSST) were introduced in 2001 that can effectively distinguish HSV-1 and HSV-2 with high sensitivities and specificities. They can differentiate antibody responses to both HSV-1 and HSV-2 and are based on either Western Blot or glycoprotein G assays. Older serological tests which detected antibodies to HSV were found to be unreliable due to cross reactivity between HSV-1 and HSV-2.

Western Blot

Western blot (WB) tests for a range of type specific antigens. They are expensive, take 2-5 days to complete the screening and confirmatory steps and require expertise to interpret the results. Interpretation of WB results is subjective and profiles may not always be definitive. They are unlikely to become commercially developed for use in routine clinical practice.

Glycoprotein G assays

Glycoprotein G assays detect antibodies to the type-specific proteins gG1 and gG2. There is minimal sequence homology between gG1 and gG2 allowing differentiation between HSV-1 and HSV-2 infection.

Available test kits:
1. HerpeSelect-1 ELISA and HerpeSelect-2 ELISA (Focus Technologies, formerly MRL Diagnostics, Cypress, CA) are enzyme-linked immunosorbent assays for detection of HSV-1 or HSV-2 antibodies, respectively.
2. HerpeSelect 1/2 Immunoblot (Focus Technologies) is a nitrocellulose strip immunoblot that simultaneously detects and distinguishes antibodies to HSV-1 and HSV-2. The kits use baculovirus recombinant gG1 and gG2 antigens.
3. POCkit HSV-2 by Diagnology (Belfast, Northern Ireland) offers the only point of care or “near patient” test for HSV-2 antibodies that is designed for clinic use.
4. Sorin Diagnostics Biomedica (ETI-HSVK-G2), Centocor (Captia Select HSV-2 EIA; marketed by Trinity Biotech and by Wampole Labs), and Roche (Cobas Core HSV-2 IgG EIA) produce gG2 based tests in formats that are cost effective and easy to perform. These tests are not FDA-approved and HSV-1 type-specific antibody detection is not offered by these companies.

The tests are comparable to each other and to gold standard tests such as western blot for specificity. These TSST assays require a median of 2-6 weeks with 80-100% of newly infected patients becoming positive by 3 months.

The following table shows the performances of gG-based type-specific antibody tests.

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* Associate Consultant Dermatologist, National Skin Centre

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Parameter by HSV antibody type

<table>
<thead>
<tr>
<th>Test</th>
<th>Parameter</th>
<th>HSV-1</th>
<th>HSV-2</th>
</tr>
</thead>
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<tr>
<td></td>
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<td>Specificity (%)</td>
<td>Sensitivity (%)</td>
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</tr>
<tr>
<td>Captia Select-HSV-2</td>
<td>NA</td>
<td>NA</td>
<td>90-92</td>
</tr>
</tbody>
</table>

* The POCkit-HSV-2, Cobas-HSV-2, and Captia Select-HSV-2 tests only detect HSV-2 antibodies

At the Department of STI Control (DSC) Clinic in Singapore, type-specific serology testing for HSV infection is performed using the HerpeSelect 1 and 2 Elisa (TSST) assay (Focus Diagnostics, Cypress, Ca90630 USA).

Local experience

At the DSC Clinic, we performed 2 studies using the TSST assays:

In the first study, we looked at the seroprevalence of HSV-1 and HSV-2 in attendees of the DSC Clinic. Two hundred male and 200 female participants had blood samples taken and analyzed using the HerpeSelect 1 and 2 Elisa IgG assays. HSV-1 was positive in 223 (55.8%) individuals, negative in 175 (43.8%) and indeterminate in 2 (0.5%). HSV-2 was positive in 114 (28.5%) individuals, negative in 284 (71.0%) and indeterminate in 2 (0.5%). The seroprevalence of HSV-2 was 26.0% and 31.0% in males and females respectively.

In the second study we looked at the seroprevalence of HSV-1 and HSV-2 in sex workers attending the DSC Clinic. The blood from 300 sex workers was taken and analyzed, using the HerpeSelect 1 and 2 Elisa IgG assay. HSV-1 serology was positive in 230 (76.7%), negative in 67 (22.3%) sex workers and indeterminate in 3 (1.0%) sex workers. HSV-2 serology was positive in 237 (79.0%) and negative in 63 (21.0%) sex workers. HSV-2 prevalence increased significantly with duration of years of practice of sex work.

When TSST may be helpful

- patients presenting with recurrent genital ulcers which are negative by other diagnostic methods such as culture or PCR.
- patients with recurrent symptoms suggestive of atypical or undiagnosed HSV infection.
- Discordant couples in a monogamous relationship where one partner has HSV infection.
- general STI screen for high-risk individuals (e.g. other STIs or HIV+).
- to identify pregnant women at risk of acquiring HSV-1 or HSV-2 infections close to term where there is a high risk of neonatal herpes

When TSST may be unhelpful or misleading

- TSST does not differentiate between HSV-1 antibodies as a result of oral infection and antibodies consequent to genital infection. Not all available assays test for HSV-1 and if they do, they tend to be 5-10% less sensitive than their HSV-2 counterparts and may require longer to reflect seroconversion.
- The tests may take between 2-12 weeks to become positive and a negative test during this “window period” does not rule out HSV infection. In contrast, a positive test does not distinguish between primary and non-primary attacks.
- The antibody response “seroreverts” to undetectable levels over time and this would result in the TSST assays producing a negative result in a patient with HSV infection. It is still unknown what the duration of this seroreversion is and it also differs between the currently available assays.
- Viral culture is still the “gold standard” test for use in medicolegal cases involving HSV infection and TSST assays are not validated to replace this.
- TSST assays have shown lower sensitivities and specificities when used in children and should be used with caution.

Ethical dilemmas

Should screening for HSV infection be conducted as part of a general STI screen? There is a potentially enormous psychological, social, as well as sexual impact on patients and their sexual partners especially if they are asymptomatic on discovering that they have a disease that is sexually transmissible, with no cure and lasts for life. There is also the issue of a high number of false positives when testing low prevalence populations. It would be reasonable to screen only those individuals with risk factors where there is a lower incidence of false positive results. A positive result not only affects the individual concerned, but also their sexual partners and potential offspring. Clinicians need to weigh the potential biotechnical, epidemiological and medical benefits with the social and psychosexual disadvantages of type-specific serological testing for HSV infection at both the individual and public health level.
References:


6. Theng TSC, Sen PR, Chio TWM et al. Seroprevalence of HSV Type I and Type II in attendees of a Sexually Transmitted Infections (STI) clinic in Singapore. (Unpublished data).


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Cutaneous photobiology is the study of the effects of sunlight or ultraviolet (UV) radiation on the skin. In our country, we are exposed daily to 8-10 hours of sunlight 12 months a year, which may potentially aggravate a variety of photodermatoses (e.g. solar urticaria and polymorphous light eruption) all year round, rather than in the summer months as is the pattern in temperate countries. This makes it more difficult to diagnose photodermatoses in the tropics. In addition to good history-taking and clinical examination, phototests are most useful in confirming the diagnoses of photodermatoses.

Types and aims of Phototests

1) Minimal erythema dose (MED) determination — To determine the threshold doses for erythema to UVA or UVB, and whether these are abnormally lowered

2) Photoprovocation test — To determine the response of the skin when subjected or exposed to a given spectrum of light. It aims to reproduce the lesions of a disease suspected to be related to UV radiation, and thereby determining the inducing wavelength and minimal inducing dose.

3) Photopatch test - To assess for photoallergic contact dermatitis to common photosensitisers, in conjunction with a patch test.

I. MED determination

MED is defined as the dose of UVA or UVB required to produce just perceptible erythema 24 hours after irradiation. Skin from a covered area, usually the buttock, is irradiated with different doses of UVA and UVB light, and the test reading is performed after 24 hours.

MED determination is used in 3 situations. The first is during the evaluation of photodermatoses, when a lowered MED to either UVA or UVB or both is a significant pointer to the diagnosis of a photodermatosis, whether idiopathic (reduced MED to UVA or UVB in various combinations) or drug-induced (reduced MED to UVA).

The second situation is before the administration of phototherapy for the first time for the treatment of various skin conditions. With narrow-band UVB (NBUVB) phototherapy, MED to NBUVB is first determined, and the starting dose for treatment is calculated based on this. This is to minimize the risk of burning and to maximize the efficacy of treatment, with faster attainment of clinically effective doses.

For first-time patients about to undergo bath/ full body soak PUVA treatment, MPD or Minimal Phototoxic Dose to PUVA is first determined. Using the same principle, patients are exposed to UVA doses after having soaked themselves (from neck down) in diluted meladinine solution. After 72 hours, assessment is done to determine MPD, after which the starting dose of bath PUVA is established.

Finally, MED determination may also be used for evaluating the efficacy of sunscreens and photosensitive potential of chemicals.

II. Photoprovocation test

Lesions of idiopathic photodermatoses and lupus erythematosus can be provoked by multiple exposures to polymorphic light sources of UVA, B or visible light.

The sun is perhaps the best source of irradiation if it is reliable and readily available. However, weather conditions are always unpredictable and difficult to standardize, therefore artificial light sources have to be used. This is not ideal as clinical photosensitivity is often caused by a wavelength mix of natural sunlight.

There are many regimes for provocative phototesting but the one used in NSC will be explained below:

Patients are informed prior to their test not to apply any topical steroids or sunscreens, especially on their forearms, and to avoid oral antihistamines or corticosteroids for at least 2 weeks before the test.

Skin from a covered site, usually the inner aspect of the upper arm or the buttock, is irradiated with the relevant light source, e.g. visible light from a slide projector for solar urticaria, or UVA for polymorphous light eruption or hydroa vacciniforme. This is repeated daily for 3 days or until skin lesions are provoked, whichever occurs earlier.

III. Photopatch test

This is performed when photoallergic contact dermatitis is suspected, usually to sunscreen chemicals or fragrances, less commonly with antiseptic agents in some soaps.

Two identical sets of allergens are patched onto opposite sides of the back. A first reading is performed on the 3rd day, to determine if allergic contact dermatitis has occurred to any of the allergens. One set is then irradiated with UVA, with the other set serves as a control. The 2nd reading is then performed on the 5th day.
The photopatch test is positive if there is well-defined erythema to an allergen after UVA irradiation at the time of the 2nd reading, but not in the unirradiated set. If there is well-defined erythema to the allergen in the unirradiated set as well, then the diagnosis of allergic contact dermatitis rather than photoallergic contact dermatitis is made.

**Practical Aspects of Phototesting**

1) **Sites of test**

   The back, including the buttocks, is usually chosen because it is usually not exposed to light, has a large area of skin and shows a uniform response to UV light. Skin within 3 cm of either side of the midline is avoided because of decreased sensitivity. The upper thighs may be used if the back/buttock is unsuitable, for instance, when there is insufficient uninvolved skin on the back/buttock.

   For visible light photoprovocation test, the inner aspect of the right upper arm is used.

2) **Radiation light sources**

   The irradiance of the light source must be measured with an appropriate radiometer, as it is necessary to calculate the required time to deliver the dose determined by the doctor.

   For visible light test, a slide projector with a quartz halogen lamp is used to shine onto an area of 5 X 5 cm² on the inner aspect of the right arm at a distance of 10 cm for a period of 20 minutes.

   For tests involving UVA light (MED determination, photopatch test, photoprovocation test), the Supuvasun 3000 (Mutzhas, Germany), which has a high irradiance of 30 mW/cm² is used.

   For determination of MED to UVB, a Dermaray machine M-DMR-100 (Eisai, Japan) is used.

3) **Dose range and increments**

   The dose range and increments must be such as to demonstrate the desired response. The threshold response or minimal erythema dose (MED) is usually taken as a measure of erythemal reactivity.

   Appropriate templates with small test fields exposed are placed on the skin, with gradual exposure of different parts to different doses of light in a specified pattern, which is recorded in the notes. Markings are made on the skin using a skin marker.

4) **Positioning**

   Patients are required to lie in the prone position for UVA and UVB light testing on their buttocks. The distance from the light source to patient is about 30 cm.

   The nurse performing the test should wear gloves and UV-protective eye shields to prevent eye damage.

5) **Assessment**

   This is done visually, immediately and 20 minutes after irradiation, looking for lesions of solar urticaria at both visible light and UVA/B irradiated-sites, and subsequently at 24 hours post-test, for MED determination. Patients are advised to avoid scratching and exposure of the test sites to sunlight.

   Reactions to look out for are: itch, urticarial rash, erythema, or any abnormal lesions such as papules or vesicles. Occasionally, lesions of PMLE may be provoked by MED testing and are visible 24 hours post-test.

**Conclusion**

Phototests are a useful adjunct to a good history and examination in the diagnostic workup of a patient suspected to have a photodermatosis. MED determination can help to confirm the diagnosis of drug-induced photosensitivity or idiopathic photodermatosis, while a photopatch test is able to both confirm the diagnosis of photoallergic contact dermatitis and elicit the inciting allergen. Photoprovocation test is rapidly diagnostic in solar urticaria.

A point to note: suppressing disease activity is important before the test as a positive reaction may induce a generalized flare, thus complicating the interpretation of results. Nonetheless, it remains a useful tool in the investigation of photosensitivity problems.
Management of Chronic Plaque Psoriasis

Prepared by Dr Wong Su-Ni*

Introduction

Psoriasis is usually diagnosed clinically, based on typical appearance on typical sites. Chronic plaques of psoriasis is the most common subtype, seen as well-defined pink plaques with silvery white scales, most commonly on the scalp, extensor aspects of the limbs and joints and the lower back.

Management should be tailored according to patient age, sex, occupation, intelligence, personality and access to resources, as well as disease severity, duration and response to previous treatments.

Potential precipitating factors should be elicited and addressed accordingly. These include:
- drugs e.g. beta-blockers, anti-malarials, withdrawal of oral or potent topical corticosteroids
- stress
- environmental factors e.g. heat
- trauma (Köbner phenomenon) - physical, chemical, electrical, surgical, infective and inflammatory
- infection e.g. streptococcal throat infection
- HIV infection
- Metabolic e.g. hypocalcaemia (in pustular psoriasis)

General Treatment Principles

Induction therapy aims to achieve clearance or substantial improvement. This is usually followed by maintenance therapy to maintain the level of improvement. In times of flare, treatment may be stepped up again.

Rotational therapy (where a switch is made to another therapy after a specified period of time) or sequential therapy (where a stronger agent is used initially to achieve faster clearance, followed by a weaker but less toxic agent in the maintenance phase) may be employed to reduce long-term toxicity of any one therapy, and reduce resistance to any given therapy.

Combination therapy often results in greater efficacy and enables lower doses of more toxic agent to be used (e.g. retinoids-NBUVB, re-PUVA, MTX-NBUVB, PUVA + UVB, MTX + cyclosporin)

1. First line: Topical therapy

Coal tar (LPC 5%, 10%, 15%) (Grade A) is a safe and time-honoured treatment for mild to moderate plaque psoriasis. However, it stains clothes and bed sheets and has a strong odour. It may be used as monotherapy, or in conjunction with moderate potency topical steroids for faster initial response.

For localized thick scaly plaques, salicylic acid (Grade C) may be added to coal tar or to potent topical corticosteroids (Grade A). Dithranol 1-2% ointment as 1/2 hour short-contact therapy is useful for localized thick plaques, but care should be taken to avoid application to surrounding normal skin as it can be irritating, and can stain both skin and clothes.

Calcipotriol cream or ointment (Daivonex®) (Grade A) has been shown to be as effective as potent topical steroids in several trials. Its main advantage is the lack of steroid associated adverse effects (e.g. skin atrophy, striae formation, iatrogenic Cushing’s, rebound). Combination therapy with calcipotriol and a potent or superpotent topical steroid (Grade A) works better than calcipotriol alone, and is useful in the induction phase, either used at separate times of the day, or used in combination as Daivobet(r) once daily, with calcipotriol monotherapy used in the maintenance phase.

Mild to mid-potency topical corticosteroids (e.g. 1/4 str Betamethasone valerate cr) are preferred for the face, hairline and flexures. Calcitriol ointment (Silkis®) (Grade A) is a useful alternative without risk of steroid side effects, especially around the eyes.

Patients are also advised on use of adjunctive therapies such as moisturizers (e.g. 10% urea cream, white soft paraffin: liquid paraffin, aqueous cream) and soap substitutes (e.g. coal tar bath or soap, emulsifying ung).

2. Second line: Phototherapy

Phototherapy should be considered in patients with extensive plaque psoriasis affecting more than 10-15% BSA (body surface area) or those not responding to topical therapy or have intolerable side effects to topical therapy. Adverse effects are limited to the skin, and it is considered safer than systemic agents.

Narrow-band UVB phototherapy (NBUVB) (Grade A) is the first line phototherapy for extensive chronic plaque psoriasis because of its safety and convenience relative to oral PUVA. Combination therapy with coal tar (Goeckerman regimen), dithranol (Ingram’s regimen) or calcipotriol may be employed, but there is some evidence that combination with topical steroids may lead to shorter remission.

If the response is suboptimal, addition of acitretin or methotrexate results in a synergistic effect with lower doses of the systemic agent as well as lower cumulative doses of NBUVB required for clearance. Oral or bath PUVA (Grade A), or even re-PUVA, may be effective when NBUVB fails

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For localized stubborn plaques persisting after a course of phototherapy, excimer laser (Grade C) may be useful in inducing clearance.

3. Third line: systemic therapy

This includes:
- methotrexate (Grade B)
- acitretin (Grade A)
- cyclosporin (Grade B)
- fumaric acid esters (Grade B)
- azathioprine (Grade C)
- mycophenolate mofetil (Grade C)
- hydroxyurea (Grade B)
- combinations (Grade A)

Methotrexate (Grade B)

Considered a DMARD (Disease Modifying Anti-Rheumatic Drug), methotrexate (MTX) is particularly beneficial for patients with psoriatic arthritis in addition to their skin involvement. It is given as single dose weekly, with starting dose of 5-7.5mg/week, and average dose in local involvement. It is given as single dose weekly, with starting dose of 5-7.5mg/week, and average dose in local dermal use of 5-15mg/week.

It is contraindicated in pregnancy or possibility thereof (teratogenic, active infections, liver disease and alcoholism). Caution is recommended in obesity, diabetes (fatty liver, increased risk cirrhosis) and renal impairment (renally excreted).

Common side effects are nausea, tiredness, dizziness and macrocytosis (improves with folic acid 5mg daily). Less common but serious adverse effects include: bone marrow suppression, transaminitis, liver cirrhosis, pulmonary fibrosis (idiopathic) and increased risk of malignant lymphomas.

FBC, LFT, Cr and Hep B sAg and sAb are taken at baseline, with FBC repeated every visit, and LFTs monitored every 3 months. A liver biopsy is indicated after every 1.5g of methotrexate to assess for the development of liver fibrosis, which, if present, is a contraindication for further treatment with MTX.

Potential drug interactions to note are with salicylates, NSAIDs, sulphonamides, sulphonylureas, phenytoin, tetracyclines, chloramphenicol, pyrimethamine (may increase toxicity by displacement from protein binding). Penicillins also reduce the excretion of MTX.

Acitretin (Neotigason®) (Grade A)

This is regarded as one of the safest systemic psoriasis therapies currently available. As monotherapy, it is not as effective as methotrexate in chronic plaque psoriasis, but when used in combination with phototherapy, can dramatically improve the response to phototherapy or photochemotherapy. It may temporarily suppress development of non-melanoma skin cancers and has been employed in chemoprophylaxis of non-melanoma skin cancers in patients with PUVA-damaged skin.

Starting dose is usually 25mg/day, increasing to 50mg/day as necessary. The maximum dose is often limited by mucocutaneous side effects. Average dose locally is 20-35mg/day. Lower doses are required if combined with phototherapy (e.g. 10-25mg/day).

Acitretin is teratogenic and contraindicated in pregnancy or possibility thereof. Common side effects are mucocutaneous effects (e.g. cheilitis, conjunctivitis, dry skin, hair loss), hyperlipidaemia and liver transaminits. Rare side effects are pseudotumour cerebri, osteoporosis, skeletal hyperostoses and calcification of ligaments.

Baseline tests should include LFT, fasting lipids, pregnancy test and documentation of last menstrual period. Repeat LFT and fasting lipids are recommended every 3 months, with pregnancy test as indicated.

Cyclosporin (Grade A)

This is a very effective suppressive treatment for all forms of psoriasis, and may be used with caution in pregnancy (category C).

There are 2 approaches to dosing: a high-dose approach and a low-dose approach. With the high-dose approach, treatment is initiated at 5mg/kg/day in 2 divided doses, then tapered after maximal therapeutic response. With the lower dose approach, starting dose is 2.5mg/kg/day with dose increments of 1mg/kg/day every 2-4 weeks. Cyclosporin is rapidly effective, and if there is no response by 8 weeks, therapy is deemed to have failed.

After maximal therapeutic response is achieved, the dose is tapered by 1mg/kg/day every 2 weeks to maintenance dose of 0.5-1mg/kg/day. Cyclosporin is not recommended for use beyond 1 year because of nephrotoxicity, and rotational therapy to other modalities, or sequential therapy with use of acitretin in the maintenance phase is recommended.

Cyclosporin is contraindicated in acute infections, all malignancies, uncontrolled hypertension, and renal disease (except nephrotic syndrome where renal function improves).

Common side effects are hypertension (easily controlled with calcium channel blockers), nephrotoxicity, gastrointestinal upset (e.g. nausea and abdominal pain), gingival hyperplasia and hirsutism. Derangements of liver function, hyperlipidaemia, hyperkalaemia, hyperuricaemia, hypomagnesaemia may occur and should also be monitored for. Malignancies such as skin cancers and lymphoproliferative disorders have been reported in transplant doses taken for long duration.

Importantly, there are many possible drug interactions, and patients are advised to carry a list with them, such as that in Table 1. Grapefruit juice is also prohibited as it decreases cyclosporin metabolism.

Baseline monitoring includes FBC, U/E/Cr, LFT, UFEME, Mg, uric acid, serum lipids and blood pressure measurement. Serum Cr and BP measurement is
monitored fortnightly for 2 months, then monthly thereafter. LFT, serum lipids, UFEME, Mg and uric acid are checked at 4 weeks, with urinalysis repeated at 3 months and 6 months.

Table 1. Common drugs that interact with cyclosporin

<table>
<thead>
<tr>
<th>Drugs increasing cyclosporin levels</th>
<th>Calcium antagonists</th>
<th>Diltiazem, nicardipine, verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimycotics</td>
<td>Ketoconazole, itraconazole, fluconazole</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>High-dose methylprednisolone</td>
<td></td>
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<tr>
<td>Antiemetics</td>
<td>Metoclopramide</td>
<td></td>
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<tr>
<td>Anti-arthrythmics</td>
<td>Amiodarone</td>
<td></td>
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<tr>
<td>Anti-gout agents</td>
<td>Allopurinol</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs lowering cyclosporin A levels</th>
<th>Anti-epileptics</th>
<th>Carbamazepine, phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin analogues</td>
<td>Octreotide</td>
<td></td>
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<tr>
<td>Tuberculostatics</td>
<td>Rifampicin</td>
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<tr>
<th>Drugs that increase risk of nephrotoxicity</th>
<th>Aminoglycosides</th>
<th>Gentamicin, tobramycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Diclofenac, naproxen, sulindac</td>
<td></td>
</tr>
<tr>
<td>Antimycotics</td>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Ciprofloxacin</td>
<td></td>
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<tr>
<td>Alkylating agents</td>
<td>Melphalan</td>
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<table>
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<tr>
<th>Drugs with increased blood levels when used concomitantly with cyclosporin</th>
<th>Anti-gout agents</th>
<th>Colchicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Diclofenac</td>
<td></td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>Digoxin</td>
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<tr>
<td>Corticosteroids</td>
<td>Prednisolone</td>
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</tbody>
</table>

Grading
A: Double-blind study – at least one prospective, randomized, double-blind, controlled study without major design flaws
B. Clinical trial > 20 subjects – prospective trial with 20 or more subjects; trials lacking adequate controls or another key facet of design
C. Clinical trials < 20 subjects - small trials with < 20 subjects with significant design limitations; very large numbers of case reports (at least 20 cases in the literature); retrospective analysis of data
D. Series with 5 or less subjects – series of patients reported to respond; at least 5 cases in the literature
E. Anecdotal case reports – individual case reports amounting to published experience of less than 5 cases

A rise in serum creatinine of 30% or more above baseline necessitates repeat testing, with dose reduction of 25% if there is no improvement. Further reduction of 25% is indicated if there is no improvement, with cessation of treatment if this fails to resolve.

4. Fourth line: biological therapy

This is indicated for moderate to severe psoriasis not responding to above therapies, or patient has had adverse reactions or medical conditions precluding use of above therapies.

These include alefacept (Grade A), efalizumab (Grade A), etanercept (Grade A) and infliximab (Grade E). In general, a baseline chest X-ray should be done to assess for latent pulmonary tuberculosis. FBC, LFT, Cr should be taken at baseline and monitored regularly (e.g. 3 monthly), with FBC monthly for 3 months during initiation of efalizumab, and CD4 count fortnightly with use of alefacept.

References
Phototherapeutic Treatment Of The Sclerosing Dermatoses

Dr Chong Wei Sheng*

Introduction

The treatment of the sclerosing dermatoses, such as systemic sclerosis, morphea, lichen sclerosus, lichen myxoedematous/scleromyxoedema, scleroedema of Buschke and nephrogenic fibrosing dermopathy is often challenging. The introduction of the various phototherapeutic options has considerably widened our therapeutic armamentarium, providing the dermatologist with alternative modalities to treat the sclerosing dermatoses, especially when topical therapy has failed.

In the treatment of the sclerosing dermatoses, 2 main phototherapeutic modalities have been found to be useful. They are the psoralen-UVA (PUVA) photochemotherapy and the long-wavelength UVA (UVA1) phototherapy. Worthy of note is that at best, small-scale open clinical trials, cases series and case reports are available in the current medical literature. No large-scale, randomized controlled trials have been conducted so far.

The objectives when treating such skin diseases are to clear the early inflammatory lesions and to soften established sclerotic lesions, so as to improve the cosmetic outcome and more importantly, to prevent future disability that may limit joint mobility as in systemic sclerosis.

The general principle is to administer localized phototherapy such as UVA1 and topical PUVA if the lesions are solitary or limited in size and number, so as to avoid unnecessary systemic or widespread phototoxicity, hyperpigmentation and side effects of oral 8-methoxypsoralen (8-MOP, oxsoralen) ingestion. UVA1 is generally preferred to topical or bath PUVA because of a lower risk of phototoxicity and ease of administration. However, for more extensive lesions, bath PUVA or oral PUVA may be needed (whole-body UVA1 phototherapy is not available at NSC).

How does UVA work in treating the sclerosis?

UVA plays an important role in the treatment of the sclerosing dermatoses via various mechanisms although they are only partially understood. UVA decreases the number of infiltrating T cells by triggering different apoptotic pathways, resulting in an immunosuppressive and anti-inflammatory effect. Such pathways also induce cell death of B cells and fibroblasts, resulting in reduced dermal production of collagen. UVA also increases the expression of the matrix metalloproteinases, which show a proteolytic specificity for interstitial collagen, whose enhanced degradation may soften the sclerotic tissue. UVA decreases the activity of prolyl-hydroxylase, an enzyme that stabilizes the triple helix structure of collagen. Moreover, UV radiation may impair cross-linking of collagen fibres.

1. Morphoea

A. Localised involvement:

• First line: UVA1 3-5 times per week

Localised UVA1 can be administered 3-5 times per week, starting at 20 J/cm². The dose of 20 J/cm² can be kept throughout the treatment period (low-dose UVA1 phototherapy), increased gradually at 10-20 J/cm² intervals till a maximum dose of 50 J/cm² (medium-dose UVA1 phototherapy), or till a maximum dose of 130 J/cm² (high-dose UVA1 phototherapy), or as tolerated by the patient in terms of phototoxic reactions such as erythema, blistering and hyperpigmentation.

High-dose UVA1 phototherapy has been found in one study by Stege et al to be superior to low-dose UVA1 phototherapy in terms of lesion clearance and softening. However, medium-dose UVA1 phototherapy and low-dose UVA1 phototherapy have also been found in several other studies to induce significant clinical improvement as well.

• Second line: Topical PUVA 2-3 times per week

Topical PUVA can be administered 2-3 times per week with the use of meladinine (8-MOP) paint starting from 0.01% for the face/neck lesions and 0.05-0.1% for the trunk/limb lesions. The paint is left on the lesions for 30 minutes, followed by irradiation with UVA, starting from a dose of 0.25 J/cm².

B. Generalised involvement :

• First line: Bath PUVA 2-3 times per week

Bath PUVA is administered 2-3 times per week, based on the Minimal Phototoxic Dose (MPD) regimen. The MPD for the meladinine (8-MOP) is first determined 72 hours after the test dose. The meladinine solution is diluted to a concentration of 3.75-7.5 mg/L, the patient soaks in the bath tub filled with the psoralen solution for 20 minutes, and, immediately after drying, is irradiated with UVA, starting at a dose of 70% MPD.

• Second line: Oral PUVA 2-3 times per week

Oral PUVA can be administered 2-3 times per week, with oral ingestion of 8-MOP (oxsoralen) tablets at a dose of 0.6 mg/kg and UVA irradiation 1½ hours later, starting at a dose based on the Fitzpatrick’s skin phototype regimen.

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2. Systemic sclerosis

- **First line:** Bath PUVA 2-3 times per week
- **Second line:** Oral PUVA 2-3 times per week

3. Lichen sclerosus (extragenital lesions only):

- **First line:** UVA1 3-5 times per week, starting at 20 J/cm²

  Several studies have shown that low-dose UVA1 phototherapy (20 J/cm²) is effective in the treatment of extragenital lichen sclerosus.

- **Second line:** Topical PUVA or bath PUVA 2-3 times per week

  There is currently not enough evidence to support the use of phototherapy or photochemotherapy in the treatment of genital lichen sclerosus, and there is a potential added risk of UV-induced skin malignancy in the genital area.

4. Other sclerosing dermatoses

  There are reports on the use of bath PUVA and topical PUVA in the treatment of sclerodema of Buschke. Oral PUVA has been reported with success in the treatment of one patient with lichen myxoedematous. Although at present, the use of UVA1 phototherapy in sclerodema of Buschke and lichen myxoedematous/scleromyxoedema has not been reported, UVA1 may also pose a promising therapeutic option.

  There is one report on a patient with nephrogenic fibrosing dermopathy treated successfully with high-dose UVA1 phototherapy (130 J/cm²).

References


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III. Applying Best Practices To HIV/AIDS Prevention in the Gay Community

There is currently little hard evidence with regards to same-sex transmission of HIV/AIDS in Singapore. However, homosexuality was recently highlighted by the health ministry as a significant portal of HIV transmission. In an Action for AIDS (AFA) survey of men who have sex with men (MSM) in Singapore, about 35% of respondents engaged in unprotected anal sex. The reasons cited for not using condoms were: the partner was a friend they trusted, the partner seemed healthy, the partner had previously tested negative for HIV, no condoms were available, and finally, the reduction of personal enjoyment when a condom was used.

Some issues have been identified as important in understanding unsafe sex among MSM:
1. Negative social attitudes (homophobia)
2. Internalised homophobia
3. Gay self-acceptance
4. Self-esteem
5. Optimism
6. Anger
7. Emotional control
8. Social support
9. Role models
10. Social skills – ability to negotiate condom use in sexual situations

Optimism and anger were associated with high-risk behaviour while gay self-acceptance and emotional control were associated with the reverse.

Therefore, if intervention with young gay men is to be achieved, the following issues need to be addressed:
1. Clearing up misconceptions about safer sex
2. Thinking creatively about safer sex
3. Reinforcing condom use
4. Verbal and nonverbal safer sex strategies
5. Informal outreach with friends

In Singapore, possible effective interventions could come in the form of:
1. Identification of critical issues in the gay community
2. Use of peer-led interventions
3. Addressing psychosocial issues such as self-acceptance, self-esteem, social support
4. Addressing social attitudes
5. Addressing legal barriers (Since homosexuality is illegal in Singapore, this prevents the open discussions of many related issues, driving it underground)