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Clinical Photodynamics

In Dermatology

An International Newsletter for PDT and FD in Clinical Practice

Editorial

It is Euro-PDT time again, with the 2008 meeting hosted by Professor Alejandro Camps-Fresneda in Barcelona. The Euro-PDT Board has been busy pulling together a programme that is fresh and innovative. The meeting will be the most comprehensive event in the calendar on the current use of PDT in dermatological applications. Professor Allan Oseroff, from the Roswell Park Cancer Institute in Buffalo, NY, will offer one of the keynote lectures, 'Learning the hard way – different protocols with PDT in NMSC', discussing what we can conclude as optimal therapeutic parameters, given the variety of protocols employed in delivering PDT worldwide. The current status of the use of PDT in emerging indications, including acne, will be discussed, and techniques to minimise treatment-associated pain will be reviewed in an Experts Forum. For readers unable to make the meeting, ***Clinical Photodynamics*** will bring a report on the meeting in our next issue.

In this issue of ***Clinical Photodynamics***, we include reports from around the world on the place of PDT in dermatological practice. Given the considerable interest in PDT at the recent World Congress in October, we have invited experts to comment on the current level of use of PDT in their region, where PDT is most used, what barriers exist to wider usage – and solutions, as well as inviting their vision of where they hope to see PDT in the next few years. We welcome correspondence – comments and personal views on this theme would be appreciated.

The USA, as the largest single pharmaceutical market, remains a country where the provision of PDT is limited. Currently, only the Levulan® formulation of ALA is marketed for AKs, although Metvix® (MAL) is FDA-approved in this indication. Recent improvements in remuneration may help to see PDT find its place as a useful therapy for actinically-challenged Americans. It is hoped that a wider licence for PDT use in the US might follow, once practitioners gain greater experience of this therapy and discover how it can find a useful place in our treatment armamentarium for NMSC.

We also carry a report on the posters from the American Academy of Dermatology AGM. If programme content is anything to go by, PDT has a bright future – with workshops, forums and talks on its potential. There is certainly considerable off-label use of PDT in acne and photo-rejuvenation in the USA, with many impressive before-and-after pictures! ***Clinical Photodynamics*** is pleased to receive reports on readers' experience of PDT.

Colin Morton
Stirling, Scotland

PDT in Dermatology: Where Are We Now?

We asked a number of dermatological PDT specialists around the world to give us a summary of the current use of PDT in their countries/regions and a prediction of how this might change in the future. To make the replies more directly comparable, we asked them to answer four main questions:

a. What is the current level of use of PDT in dermatological practice in your region?

b. Where is PDT having its greatest impact in clinical practice and how might other regions learn from your example?

c. What are the barriers to wider use? How might these be resolved?

d. Where do you hope to see PDT in routine use in the next few years?

If you would like to submit a similar report on the status of PDT in your own country/region, please contact the editorial office at: **eurocommunica@compuserve.com**

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Also in this Issue

PDT in the United Kingdom

by: Dr Colin Morton
Consultant Dermatologist
Stirling, Scotland

What is the current level of use of PDT in dermatological practice in your region?

Topical PDT is now practised across the UK, usually at regional level and predominantly provided from teaching hospitals. A number of centres are very active, with waiting lists for treatment, but my impression remains that PDT is still not available to all patients who could benefit, with a number of UK cities being devoid of a PDT service. The majority of centres use the only licensed product for topical PDT in the UK, Metvix® (Methyl Aminolevulinate [MAL]: Galderma), although some centres continue to use non-formulary aminolevulinic acid (ALA) products employed before Metvix® gained its approval.

The majority of topical PDT for skin applications is provided within the National Health Service (NHS), where patients are not charged for therapy. PDT is also delivered by a number of dermatologists in private practice, with specific codes now available for PDT by most insurers. The office-based style of private practice does require the planning of PDT, often as a 'day-case' procedure in private rooms/hospital, with a need to group patients in a single session for the most efficient delivery of treatment. The cost of PDT remains an issue for private self-pay patients.

Where is PDT having its greatest impact in clinical practice and how might other regions learn from your example?

Topical PDT has been used in a number of centres in the UK for up to 12 years, giving practitioners considerable experience in identifying which patients and lesions can derive the greatest benefit. Bowen's disease is a particularly good indication for PDT, given its typical presentation on the lower legs of elderly patients, a site recognised for poor healing by conventional therapies. The ability often to avoid surgery for large superficial basal cell carcinoma (BCC) has also seen the common use of PDT for this indication.

The routine use of PDT for actinic keratosis (AK) is less common, unless patients have large numbers of thin and moderate thickness lesions on the face and scalp. Thin nodular BCC are treated with caution, following careful lesion preparation and close follow-up. The use of PDT for non-licensed indications remains limited. Gaining experience of PDT is key to the recognition of where it is best used for its current licensed indications.

What are the barriers to wider use? How might these be resolved?

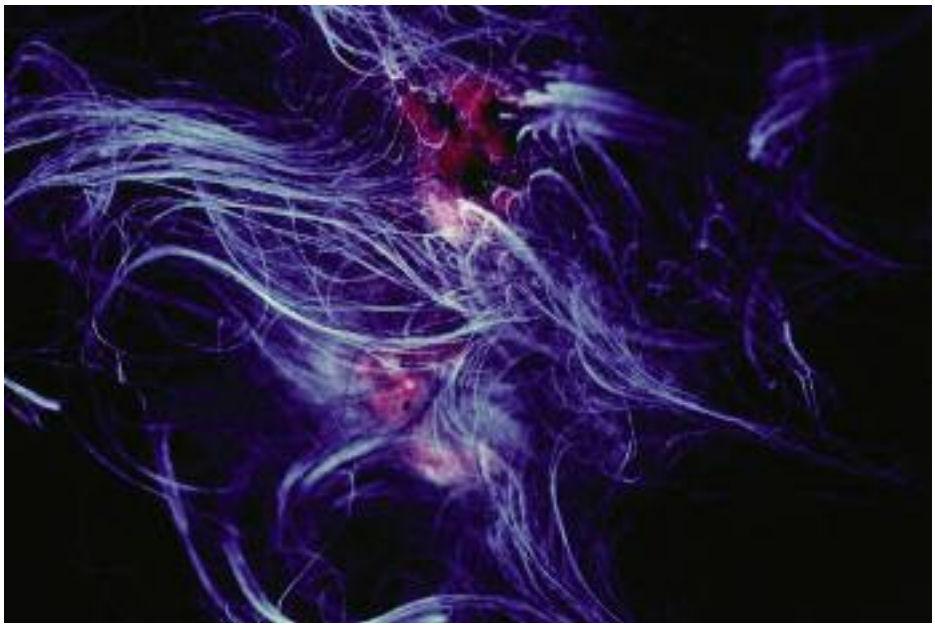
Achieving funding for the delivery of new therapies in the NHS remains challenging, even when a strong evidence base exists. There remains a perception that the treatment is complex to deliver and time-consuming.

When topical PDT was first developed, the first generation of light sources used were inefficient and/or required the close support of a medical physics technician. In addition, the topical photosensitisers, at that time unlicensed, required pharmacy preparation, adding to the time required to deliver treatment.

The situation is now much improved, and Metvix® is approved in the UK for AK, Bowen's disease, superficial and thin nodular BCC. No photosensitiser preparation is required and the current efficient red LED light sources deliver treatment in under 10 minutes. PDT enthusiasts should be encouraged to advise their colleagues how straightforward the therapy now is to deliver, with multiple patients able to receive treatment in one therapy session.

Pain is perceived as a significant drawback to PDT, but current protocols, especially where smaller lesions are treated, often require little pain management. Nevertheless, several effective techniques, such as cold-air analgesia, are emerging as methods for reducing discomfort, and I hope that we shall see a uniform delivery of PDT using protocols that can ensure the minimum possible discomfort to patients.

There remains a hesitancy by some colleagues to include PDT in their treatment armamentarium, probably for several reasons. Some clinicians question the



Fluorescence of two poorly defined BCCs before PDT.

Patient receiving PDT for widespread actinic keratoses.

advantage of PDT over conventional therapy, being concerned about the potential for recurrence, and are not yet persuaded by the good cosmesis conferred by PDT. The large body of study data on PDT may have actually worked against the therapy, suggesting its use, for example, in recurrent BCC. Instead, clinicians should first become comfortable with its use in other presentations perhaps more appropriate for PDT – i.e. licensed indications where the pathology is superficial.

I hope that the recent updating of the 2002 PDT guidelines, endorsed by the British Association of Dermatologists (BAD), and currently at a draft consultation stage, will help clarify its current place in practice. Certainly, disease-specific guidelines produced by the BAD on AK and Bowen's disease make clear its useful role, and updated guidelines for BCC are also expected to confirm its benefits.

Where do you hope to see PDT in routine use in the next few years?

I wish to see easy access for UK patients to PDT, to ensure that those who can benefit most are able to receive it. Updated guidelines should help pinpoint its optimal indications, and pain protocols should diminish concerns regarding side-effects. Finally, I hope that funding for research into particular presentations of acne and certain other new indications will see PDT take the next step in development, becoming a general therapy option in dermatology practice. ■

PDT in Australia

by: Dr Peter Foley
Consultant Dermatologist
Melbourne, Australia

What is the current level of use of PDT in dermatological practice in your region?

Topical PDT in Australia is only approved for the use of Metvix® (MAL) as the photosensitiser. Since the launch of MAL-PDT for the indications of AK and nodular and superficial BCC, we have also gained approval for Bowen's disease – or intraepidermal carcinoma (IEC), as it is referred to in the northern part of Australia. A number of centres spanning the country began using MAL in 1999 with involvement in one of PhotoCure's phase III studies utilising the Curelight®. Following the 310 and 308 BCC studies, there was a lull in proceedings as MAL was unavailable, having not at that time received Therapeutic Goods Administration (TGA) approval. A number of centres experimented for a period with extemporaneous ALA and various light sources, including the Curelight® and the Omnilux® lamp. Since approval has been granted for the proprietary product Metvix®, there has been a gradual uptake of this treatment modality across the nation. To date, no success has been achieved in gaining reimbursement status for PDT: the regulatory body governing procedures (Medicare Benefits Schedule, MBS) has deemed the major cost to be the topical agent and have suggested reimbursement from the Pharmaceutical Benefits Scheme (PBS), who in turn have denied reimbursement on the grounds that PDT is a procedure.

Most centres offering PDT only use Metvix®, as ALA is not TGA-approved, although it is quite legal for pharmacists to import the ALA powder and formulate it as a solution or ointment as required. This significantly reduces cost, but the ALA is considerably less stable and must be used quickly. MAL tends to be applied for three hours, followed by 7-9 minutes illumination with 630nm red light, repeated 1-4 weeks later. The Aktilite® lamp is the most frequently used illumination source, although other light sources, including Omnilux® lamps, Waldmann lamps, Pulsed Dye Laser (PDL), and Intense Pulsed Light (IPL) are used in some centres.

Most PDT is performed in private (office-based) practice on a user-pays basis. The majority of practitioners offering PDT are dermatologists, although some general practitioners with an interest in skin cancer or cosmetic procedures do offer PDT.

The cost of PDT has to a certain extent limited the uptake of the technique as, whilst Australians are happy to pay for cosmetic procedures, they appear to have become accustomed to low-cost healthcare. Although PDT is not reimbursed by government bodies, some private insurers will cover the cost of the cream. Patients covered by the Department of Veteran's Affairs (DVA) can have the cost of MAL-PDT covered completely on a named-patient basis with written application, where the medical practitioner can justify why other therapies are not appropriate. A number of public hospitals offer PDT through their dermatology departments. These patients are treated without direct cost. However, despite these units being very active, the numbers are limited and waiting lists are extensive. The majority of patients receiving PDT have AK, BCC or Bowen's disease, with a relatively small proportion undergoing photodynamic photorejuvenation or having PDT for acne, rosacea or other non-oncologic indications.

Where is PDT having its greatest impact in clinical practice and how might other regions learn from your example?

Over the last 3-4 years, PDT has slowly gained acceptance as a mainstream treatment modality, and registrars are expected to fully understand and have gained experience with the technique at the time of their Fellowship examination. Exposure of registrars to PDT during their training has enabled a new generation to gain insights into the technique in its proper perspective as a part of the dermatologist's armamentarium.

To date, the greatest impact seems to have been in elderly patients with Bowen's disease on the legs, large superficial BCC and BCC in cosmetically sensitive areas, particularly young patients with facial lesions. With over 250,000 people (in a population of 21 million) having at least one BCC treated by all techniques annually, there is no shortage of clinical material.

The poor healing often seen on legs of patients with Bowen's disease treated with other modalities (e.g. cryotherapy, serial curettage and diathermy, and 5-fluorouracil) has been dramatically curtailed by using PDT. Likewise, BCC on the lower leg, where a graft or flap would be required, has seen many patients prepared to pay the cost involved to avoid the bed rest, immobilisation and limitation of activities such surgery would entail. Large superficial BCCs are a popular indication. Although some lesions do not clear completely, or develop smaller occurrences, the ensuing surgery is considerably easier (and without the problems associated with superficial radiotherapy fields).

Widespread use for fields of AKs has not been seen due to the increased cost (cream use) and difficulty in achieving adequate analgesia. The recent introduction of Penthrox® (methoxyflurane) seems to be helping to overcome this.

Another area in which PDT seems to be having an impact is the transplant population, where extensive fields of actinically induced lesions are a therapeutic nightmare in this sunburnt land.

What are the barriers to wider use? How might these be resolved?

The most significant barrier to widespread use of PDT in Australia appears to be the cost. Apart from DVA patients covered under a different reimbursement scheme, most patients are out of pocket, relatively significantly, and baulk at the cost. Should Metvix cream or the PDT technique gain reimbursement status from the PBS or MBS, respectively, one would expect to see more widespread employment of the technique.

The perceived cost of topical photosensitiser also limits availability in the public system. The Aktilite® lamp is relatively inexpensive for a hospital with a capital expenditure budget, but the recurrent cost of the cream limits numbers, even though having PDT available reduces skin cancer surgery waiting list times and means fewer patients needing inpatient care post-flap/graft.

One of the advantages of PDT over 5-FU for Bowen's disease or imiquimod for superficial BCC, apart from the morbidity associated with the inflammatory response seen with these agents, is the removal of the issue of compliance. Unfortunately, some clinicians have failed to recognise this benefit.

Pain can be a significant issue when large fields (bald scalps) or very sensitive sites (e.g. nose) are treated. Improved methods of analgesia with cold air units (e.g. Cryo5) and inhalational agents (methoxyflurane) seem to be helping with this issue. Unfortunately, some patient's or practitioner's first PDT experience has been with large areas and inadequate analgesia, resulting in reluctance to treat smaller lesions on less sensitive areas.

The character of the nurse or technician responsible for the illumination process is extremely important. An astute, outgoing, garrulous nurse/technician distracting the patient with conversation, sprayed cold water, cold air, fans and music, often makes the 7-9 minutes of illumination appear to fly past rapidly and tolerably.

Dermatologists in Australia are a relatively conservative bunch. Many have been reassured by the five-year follow-up data, but there remains a hard core of cynics, happy to use techniques such as cryotherapy and serial curettage and diathermy, with an absolute paucity of corroborative evidence, who discount PDT, as it is still in its infancy 'Downunder'.

Where do you hope to see PDT in routine use in the next few years?

Over the next few years, one would hope PDT will become more widely available in the public hospital system in Australia. This would result in equity of access. As the administrators see the benefits in treating patients on an outpatient/day-case basis, with reduced need for inpatient care for large excisions, and reduced morbidity, introduction into more centres should be seen.

Hopefully, in the not-too-distant future, reimbursement status will be granted for both the photosensitising pharmaceutical product and the technique itself. Reduced cost should enhance uptake.

Continued refinement in analgesic delivery should remove one of the barriers to large field treatment, allowing more zones of AKs to be treated, hopefully resulting in fewer skin cancers developing.

Photosensitisers with even greater lesion specificity, enhanced tumour uptake and penetration, and reduced pain would add to the attractiveness of the technique. Further research into non-oncological indications to maximise benefits and minimise discomfort will see greater interest, particularly for indications such as acne, where growing angst with isotretinoin may result in reduced availability and new methods of treatment will be required. Modification and maximisation of protocols (e.g. fractionation of dose) should see greater response rates and more widespread acceptance. ■

PDT in Brazil

by: Luis Torezan, MD
Dermatologist, PDT group Hospital da Clinicas São Paulo- Brazil
I-PDT member

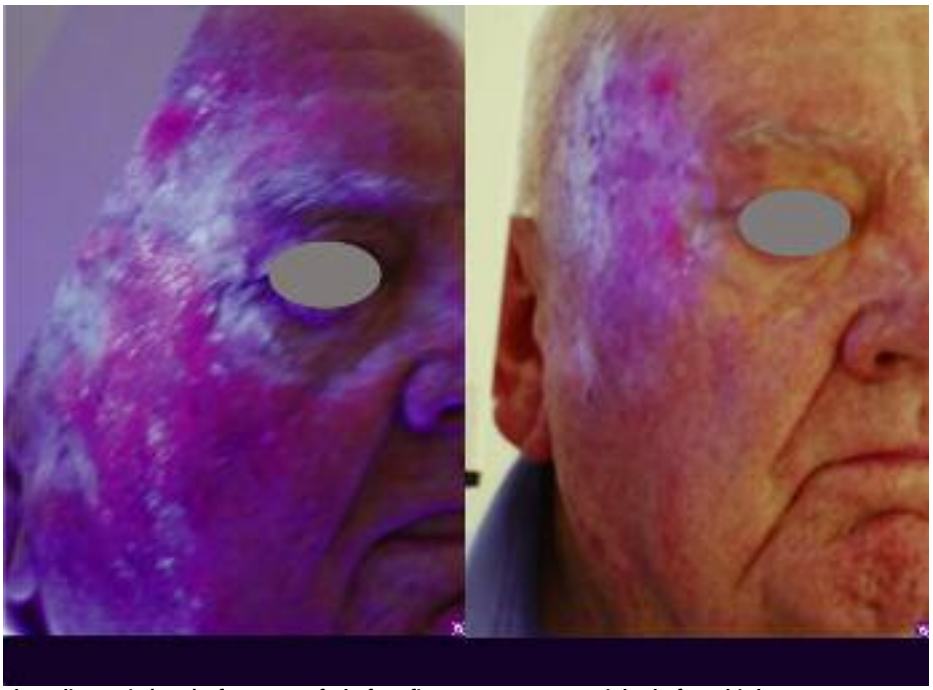
What is the current level of use of PDT in dermatological practice in your region?

Topical PDT has recently been introduced in Brazil and Latin America, although I have been using it in my clinical practice since 1997. Metvix® (Galderma) was introduced in 2006 and Levulan Kerastick® (DUSA Pharmaceuticals) has just been released in our country. Although most dermatologists use these two approved drugs, some centres continue to use non-formulary ALA products. The great majority of PDT use is provided by a few private hospitals and clinical private practice (mainly dermatologists). Very few public institutions, mostly focused on oncologic diseases, also provide PDT, and patients are not charged for therapy. Because insurance does not cover this therapeutic modality, I think that PDT is still below its potential in our country.

Where is PDT having its greatest impact in clinical practice and how might other regions learn from your example?

The greatest impact of topical PDT is on the treatment of large and multiple non-melanoma skin cancer (NMSC). These lesions are commonly seen in skin types I-III, and the culture of sun tan and sun exposure in our country is very well established. The possibility of using a topical procedure with very little side-effects, excellent cosmesis and high cure rates has attracted many dermatologists who were not familiar with this therapy before. The greatest indications are for multiple superficial BCC, Bowen's disease (which I consider the best indication) and very thin nodular BCC, especially for those patients who are not suitable for surgery. Its use in AK is currently limited to those patients with multiple lesions and prone to field cancerisation, rather than for single or a few AKs, because no insurance covers the therapy expenses.

PDT has also had an impact on photorejuvenation. Many dermatologists use PDT as a tool for the improvement of photodamaged skin, combining short-contact ALA and IPL, which is an off-label use of PDT. I am greatly concerned about this, because I have seen inexperienced physicians using PDT as the 'ultimate' modality for cosmetic purposes. Using different ALA compounds and concentrations combined with different IPLs, they are offering something that is totally unrealistic, in my opinion. I think that PDT has to be provided for patients with the best indications, following the steps of the Guidelines for PDT in Dermatology. Its off-label use has to be established and, in my experience, many physicians are unconcerned that PDT is an oncological treatment modality in its original definition.



Photodiagnosis (PDD) of cancer. Left: before first PDT treatment. Right: before third PDT treatment.

What are the barriers to wider use? How might these be resolved?

One of the main barriers remains the refusal of the insurance companies to cover the expenses. Proving that patients prone to multiple NMSC, and also those with large lesions, will benefit more with topical PDT is the main issue that I see.

Another problem is that many dermatological surgeons prefer conventional surgery to PDT, even for superficial and large lesions. Maybe the reason for this is based on the incorrect widespread use of topical PDT for photorejuvenation purposes. Why should one rely on a drug that may be used for NMSC and also for the improvement of photodamaged skin? Fortunately, this concept is changing, although very slowly. If we keep in mind that PDT is an oncological therapy with great potential for other skin diseases, I think we will be able to convince the whole dermatology community of its unique and unquestionable benefits.

The current use of licensed products (Metvix® and Levulan®), respecting the main indications as well as the guidelines for PDT, will provide the best results and, thus, lead to a wider use of the modality in our country.

Pain is also perceived as a significant drawback to PDT, but current protocols may diminish the discomfort, in combination with skin-cooling techniques, such as fans.

Where do you hope to see PDT in routine use in the next few years?

I wish to see easy access for Brazilians to PDT, ensuring that those who can benefit most will be able to receive it. I hope that PDT will definitely gain a place in every dermatology community as a unique tool for NMSC treatment and prevention of new lesions. I think that PDT has an important role in the treatment of field cancerisation.

This includes the treatment of visible and non-visible AKs, covering large surface areas. As a consequence of large-surface PDT, a photochemoprevention effect will probably be expected. I do not expect to see PDT for photo-rejuvenation on a routine basis. Instead, I wish to see it largely used for severely photodamaged skin and multiple AKs, which remains, in my opinion, the best treatment choice for these patients. Also, I hope that other skin diseases, such as acne, will benefit from new protocols and indications. Updated guidelines should help the optimal indications, and pain-relieving protocols should reduce concerns about side-effects. ■

AK field treated with MAL-PDT. Left: pre-treatment. Right: post-treatment.

PDT in Canada

by: Dr Robert Bissonnette
Innovaderm Research
Montreal, Canada

What is the current level of use of PDT in dermatological practice in your region?

There are important provincial variations in PDT use and access in Canada. The service is not available in certain provinces, but dermatologists performing PDT can be found in most major Canadian cities. These dermatologists mostly practice PDT as an office-based procedure. They use ALA (Levulan®: DUSA Pharmaceuticals) as this is currently the only approved photosensitiser for use in dermatology in Canada.

ALA is approved in combination with blue light (Blu-U®: DUSA Pharmaceuticals) for the treatment of actinic keratoses (AK). However, many dermatologists use ALA in combination with other light sources, such as IPLs and red LEDs, for the treatment of AK, as well as for other indications such as photoageing and acne.

The current Canadian product monograph for ALA states that the solution should be applied on lesions only, followed by light exposure 14-17 hours after application. Very few Canadian dermatologists are using PDT with such a long incubation time. Most physicians use a 45-minute to 2-hour incubation period before light exposure. With skin preparation (acetone wash or microdermabrasion), this is usually long enough to get a good response when treating AK.

Where is PDT having its greatest impact in clinical practice and how might other regions learn from your example?

PDT with ALA has its greatest impact on patients with ill-defined, numerous AKs and who don't accept the long downtime period associated with the use of 5-fluorouracil (5-FU) or imiquimod. These patients have too many lesions to be treated with liquid nitrogen or surgical modalities. They need a treatment option that can eradicate numerous lesions, including sub-clinical ones. There are a number of published studies showing that ALA or MAL-PDT can decrease the appearance of new AKs, squamous cell carcinoma (SCC) or BCC in mouse models. Evidence from clinical studies is emerging for a possible role for PDT in the prevention of AKs. Additional studies, looking at multiple large surface PDT sessions as a preventive modality for BCC, AK and SCC in both immunocompetent and immunosuppressed patients, are needed to confirm these findings and to define the best treatment regimen for prevention.

ALA-PDT can also have a large impact on certain patients with Bowen's disease or BCCs. Even if ALA is not approved for Bowen's disease or BCC, some dermatologists will use it off label in patients who have failed with, or who have contraindications to, standard therapies.

What are the barriers to wider use? How might these be resolved?

Reimbursement for ALA and for the procedure is the main limiting factor. Public (provincial) insurance does not cover ALA. Some private insurance companies will pay for ALA when it is used for the treatment of AK, but others will refuse to reimburse for any indication, including AK. The fairly extensive use of ALA-PDT for cosmetic purposes may in part explain the limited coverage of private payers. The absence of a PDT code is also a limiting factor. Coding and billing in Canada is established by each province. In Quebec, there is still no PDT code to use. Changes in billing and coding could expand the use of PDT by Canadian dermatologists.

Another limiting factor is the availability of the light source. Some physicians who do not already have access to a light source to activate ALA have been hesitant to buy a device specifically for the procedure.

Where do you hope to see PDT in routine use in the next few years?

If MAL is eventually approved in Canada, we will see more and more dermatologists using PDT for the treatment of Bowen's disease and BCC. A number of small studies have shown very good efficacy of ALA- and MAL-PDT in the treatment of acne, and both are currently in phase II trials for the treatment of acne vulgaris. These studies, as well as phase III studies, will determine the best parameters for the treatment of acne. There are other photosensitisers currently under study for the treatment of various dermatological conditions. The eventual availability of more photosensitisers will expand the use of PDT in dermatology in the future. ■

PDT in China

by: Xiuli Wang[1] and Zheng Huang[2]
[1] Shanghai Skin Diseases and STD Hospital, Shanghai, PR China
[2] University of Colorado, Denver, USA
Email: xiuliwang2001@yahoo.com.cn

What is the current level of use of PDT in dermatological practice in your region?

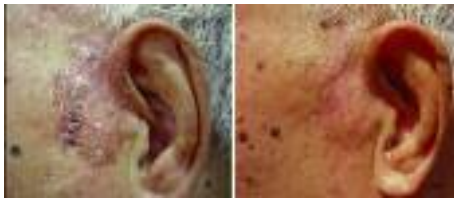
The use of PDT in dermatological practice started in mainland China in the early 1990s. First, the combination of domestically made haematoporphyrin derivatives (HpD) and laser was used for the treatment of port wine stain (PWS) birthmarks. In the mid-1990s, the Wuhan University Hospital began to use topical ALA-PDT to treat non-melanoma skin cancers (e.g. BCC, SCC and Bowen's disease). Soon after this, we continued to study the usefulness of ALA-PDT for the treatment of genital condylomata acuminate.

Recently, a drug-grade ALA (Aila®: Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co. Ltd) has become available. The company's registration of ALA-PDT for the treatment of condylomata acuminate became the first dermatological PDT protocol approved by the State FDA in 2007. The same company is currently seeking the approval of ALA for the treatment of acne vulgaris and haematoporphyrin monomethyl ether (HMME) for the treatment of PWS.

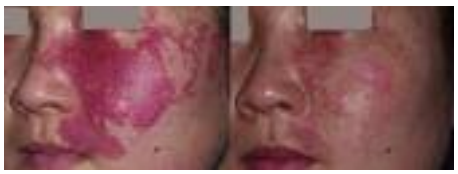
Some local physicians have begun to use PDT as first-line therapy for treating PWS, AK and urethral condylomata acuminate. Some also use ALA-PDT to treat off-label indications such as skin cancer and acne vulgaris. Although Asian populations are considered to have a lower incidence of AK, we and other local dermatologists have begun to see more and more Chinese AK patients, so we expect to see an increased use of ALA-PDT in China.

PDT experts visiting the Shanghai Skin and STD Hospital (27 March, 2007). Xiuli Wang (middle) and Zheng Huang (second from right).

As of 2007, there are at least 100 dermatology or laser clinics nationwide using PDT in their practices. Typically, those clinics belong to city or university teaching hospitals. Big cities like Shanghai, Beijing, Wuhan and Guangzhou are relatively more active. Although our protocols are similar to those reported by western colleagues, there are no national guidelines available for dermatological PDT practice in China.



A male Bowen's disease patient – before and after six sessions of imiquimod + ALA-PDT.



A female PWS patient – before and after one session of HMME-PDT (provided by Dr. Kaihua Yuan, Laser Plastic and Aesthetic Center, PLA General Hospital of Guangzhou District).

Where is PDT having its greatest impact in clinical practice and how might other regions learn from your example?

Chinese clinicians have successfully treated several thousands of PWS patients, using various PDT protocols before any of those protocols have been officially registered by the State FDA. A recent study indicates that PDT is as effective as conventional pulsed dye laser (PDL) and even better for certain types of PWS. We hope Chinese data and experience can convince western colleagues to resume their interest in PWS PDT.

According to our own experience, we believe that AK, Bowen's disease and superficial BCC are particularly good indications for Chinese patients. Compared to these indications, nodular BCC and SCC respond less to PDT. Mild and severe acne also show good response to PDT. Urethral condylomata acuminata respond well to PDT and show little side-effects and low recurrence. Our preliminary clinical study also suggests that the combination of PDT with a topical application of immunomodulators (e.g. imiquimod cream) might have a synergistic effect in treating some dermatological conditions.

What are the barriers to wider use? How might these be resolved?

The use of PDT in dermatological practice is still in its early stages in China. Like PDT in other fields, it experiences its 'highs and lows'. The barriers include, but are not limited to, the few approved indications, the limited knowledge and acceptance by dermatologists and patients, limited availability of photosensitising drugs and light sources, and the relatively high cost of PDT treatment. The longer waiting time in clinic and pain associated with ALA-PDT might discourage some patients and clinicians. More resources are needed to strengthen basic and clinical research in order to optimise current protocols and make them more accessible to patients and clinicians.

Several local dermatology and laser clinics, together with industrial companies, have been engaged in organising PDT training courses and seminars for local clinicians who are interested in PDT. Although one of the motivations of such courses is to try to establish standardised protocols, it is true that each individual might adapt his or her own (best) PDT protocol. Nonetheless, because of the large patient population, there is still room for dermatological PDT to grow in China.

Where do you hope to see PDT in routine use in the next few years?

The coverage of PDT by regional Medical Bureaux (a State medical insurance programme) might be a key step towards establishing dermatological PDT as a routine therapy option in China. The approval of ALA for the treatment of acne vulgaris and HMME for the treatment of PWS will certainly give PDT a boost. Guidelines are needed to ensure the quality of PDT applications in dermatological practice. Along with many off-label uses, dermatological PDT applications might soon be expanded to photorejuvenation and anti-infection. ■

PDT in Sweden

by: Prof Ann-Marie Wennberg
Consultant Dermatologist
Göteborg, Sweden

What is the current level of use of PDT in dermatological practice in your region?

PDT in Sweden started in the early 1990s as a method used for research purposes only. In the Dermatology Department of Sahlgrenska University Hospital, PDT was introduced into regular clinical practice in 1995. Apart from its clinical use, PDT and the related field of fluorescence diagnostics are major areas of research for the department.

At the beginning of the 21st century, PDT became ever more popular all over the country. Today, it is in daily use in clinical practice in all University Dermatological Clinics. It is also well established in the larger regional hospitals, wherever there is a Dermatological Department, i.e. most major cities in the country. Some private practitioners also perform PDT.

In most centres, PDT is given as an outpatient therapy. The patients arrive in the morning for their cream application, which may follow a differentiated curettage procedure, depending on what type of lesion is being treated. Most centres use Metvix® cream and the Aktilite® lamp as the illumination source. However, some centres use ALA and either make their own ALA cream or let the local pharmacist make the ALA. The licensed indications are for AKs, superficial and nodular BCCs and SCCs in situ (Bowen's disease).

Where is PDT having its greatest impact in clinical practice and how might other regions learn from your example?

Patients with numerous AKs and areas of field cancerisation are the main target of interest. Large BCCs and BCCs on cosmetically sensitive areas are other types of indications, as well as Bowen's disease on sensitive areas and where other methods are not as easily used.

Since PDT is in the hands of doctors/nurses, the doctor in charge can be sure of a total patient compliance. PDT is also a one- or two-shot treatment, so the patients do not have to endure a long downtime period. One other advantage for the patient is that inaccessible areas on the back can easily be treated.

One important group of patients that are steadily increasing are organ transplant recipients with large areas of AKs and in situ SCCs. These patients are a particular challenge to the dermatologist, who needs to consider a number of different treatment modalities, and PDT can play an important role in the future.

In our Department of Dermatology (Sahlgrenska University Hospital, Göteborg), we have solved the problem of pain during PDT. A method using nerve blockage has been developed at the clinic, where we pre-treat all patients with this before they undergo PDT on the facial region. The issue will be addressed during Euro-PDT in Barcelona (6-8 March, 2008) by Dr. John Paoli.

What are the barriers to wider use? How might these be resolved?

The barriers we see in the future are the cost issues of PDT treatment. Most dermatological departments in Sweden must pay for the whole treatment and that includes the cost of the cream. There is seldom a reimbursement for expensive drugs. In our country, the price of Metvix® went up by 70% at the end of 2007. The departments must therefore cut down on other items or convince the hospital administration to reimburse in order to be able to continue with MAL-PDT. This will be a major challenge.

Where do you hope to see PDT in routine use in the next few years?

We see two areas where focus is required:
1. To be able to continue the good work with the indications we have today.
2. The development of a good protocol for the use of PDT in acne patients, as well as for organ transplant recipients with pre-malignant NMSC.

PDT in Germany

by: Dr Sigrid Karrer
Consultant Dermatologist
University of Regensburg, Germany

What is the current level of use of PDT in dermatological practice in your region?

PDT using Metvix® (Galderma) in combination with red light is approved in Germany for the treatment of AKs, BCCs and Bowen's disease. Since the approval of Metvix®, PDT for these tumours has become a routine practice, not only in many hospitals all over Germany, but also in a growing number of private dermatological practices. Thus, PDT is available for most patients all over the country. In addition to Metvix®, the most widely used and approved drug, some

doctors also use non-approved extratemporaneous formulations with ALA. The most widely used light sources in Germany are the Aktilite® lamp (LED) or the Waldmann PDT 1200L lamp, both emitting red light. The use of blue light is not recommended, due to the inferior depth of penetration into the skin. Recently, IPL has also been used in order to reduce the pain during irradiation.

In private practices, patients without PDT-specific private insurance are often charged directly for this treatment, whereas other routine treatments, such as curettage or cryo-surgery, are reimbursed by their insurance companies. Thus, patients have to decide if they want to pay the extra money for this special therapy that offers them a better cosmetic result.

In clinical practice, PDT is usually performed on an outpatient basis. The patients receive their drug application in the morning and return some hours later for illumination. When larger areas have to be treated, several sessions might be necessary to limit possible side-effects. In some patients with many lesions, the whole area can be treated in one session, using i.v. analgesia; the patients then stay in the hospital for one night.

Where is PDT having its greatest impact in clinical practice and how might other regions learn from your example?

PDT has a long history in Germany. At the beginning of the 20th century, a German medical student, Oscar Raab, discovered that acridine orange was lethal for paramecia in the presence of sunlight. At that time, the term 'photodynamic reaction' was coined by Hermann von Tappeiner, director of the Institute of Pharmacology at the University of Munich. In 1903, Albert Jesionek in Munich treated conditions like skin cancer, lupus vulgaris and psoriasis with topical photosensitisers, such as eosin red or erythrosine. However, these experiments were abandoned for many decades, until a renaissance of PDT occurred about 20 years ago. Firstly, the mechanisms of action of PDT were studied in vitro and in vivo in a select few University Hospitals, trying different topical and systemic photosensitisers and different light sources. Since the approval of Metvix®, the use of PDT for non- melanoma skin cancer has rapidly grown, especially for elderly people with widespread AKs and field cancerisation of the face and scalp, for whom topical PDT is now considered as a first-line therapy. Also, due to the excellent cosmetic results, patients with BCCs or Bowen's disease often present to the dermatologist with the precise wish to be treated with PDT. Whilst superficial BCCs on the trunk or Bowen's disease are considered excellent indications for PDT, other types of BCCs, such as nodular, infiltrating, morphoeic or pigmented BCCs, should still be treated by surgery or Moh's surgery. In selected cases, where the patient's condition excludes surgery or where cosmesis is mandatory, PDT is also used in non-superficial BCCs. For example, nodular BCCs or BCCs on the face are treated by PDT.

Besides the routine use for the licensed indications, some new and very promising off-label indications, such as human papilloma virus-induced lesions (condylomata acuminata, vulgar warts, plane warts), acne, facial rejuvenation, localised scleroderma, Leishmaniasis, etc., are also being investigated in some specialist hospitals, with the aim of broadening the use of PDT in dermatology.

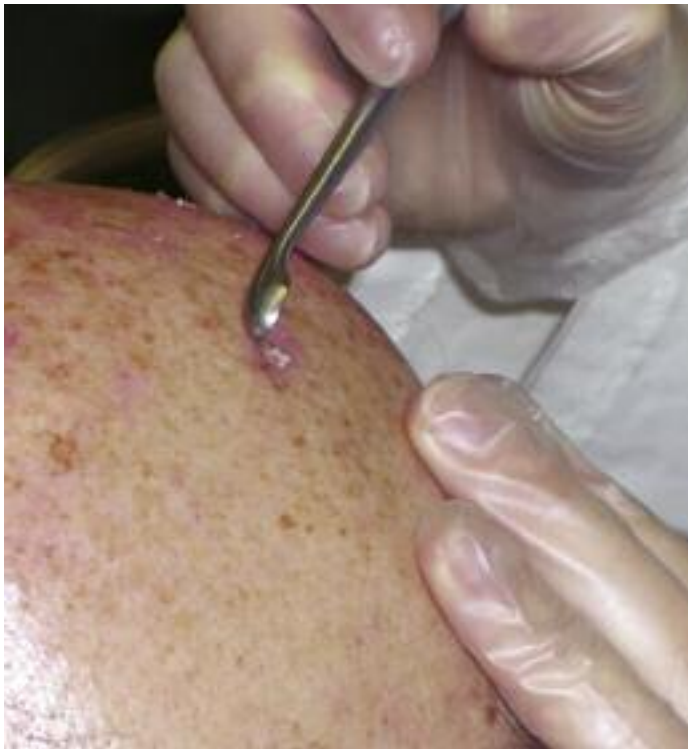


Figure 1: Patient with multiple AKs and field cancerisation on the scalp. 'Lesion preparation' of hyperkeratotic AKs prior to incubation with the photosensitiser.

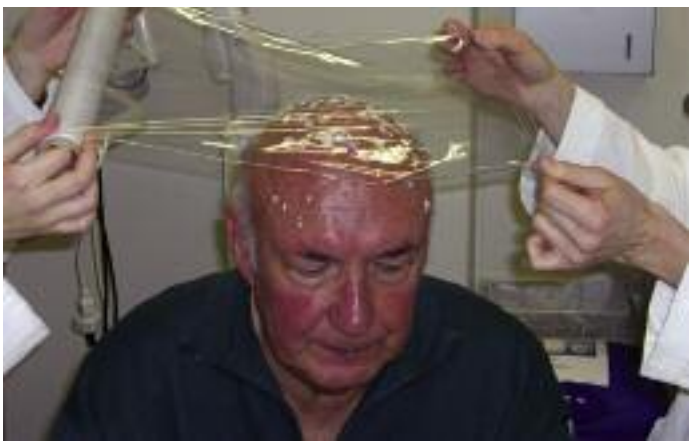


Figure 2: After application of the photosensitiser, lesions are first covered with an occlusive dressing.

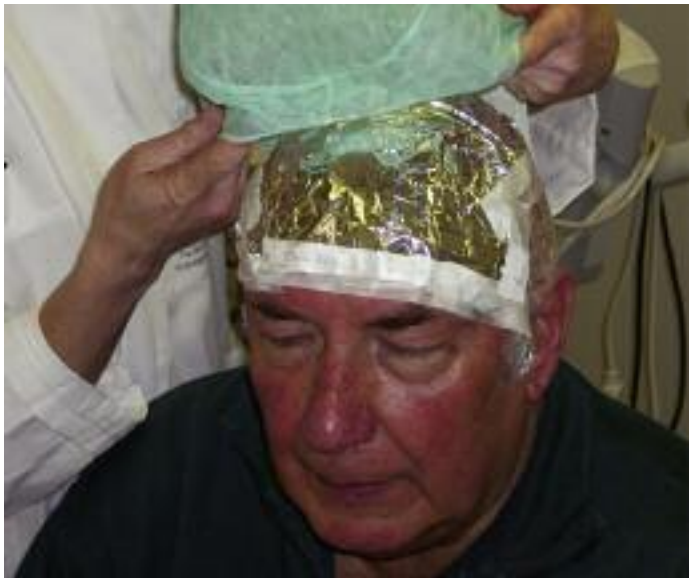


Figure 3: After occlusion, the area is also protected from light.

Figure 4: After 3 hours of incubation, the lesions are irradiated with red light. For pain reduction, cooling is provided, using liquid nitrogen.

What are the barriers to wider use? How might these be resolved?

PDT is a therapeutic modality that requires the dermatologist to have experience with the procedure, for best results. Thus, a good way to resolve this potential barrier is to inform and train doctors about the procedures, indications and side-effects of PDT. Special PDT training courses are being offered, in which theoretical questions are considered and also demonstrations of actual patients receiving PDT are given.

Some colleagues might have experienced recurrences after PDT of, for example, non-superficial BCCs, and thus have lost their confidence in this therapy. Such frustration can be avoided when the doctors are trained from the beginning to choose the right indication and to correctly perform the treatment (e.g. prior curettage, repeated treatment, etc.).

Some doctors worry about the pain that can accompany the treatment. Indeed, when treating larger areas, pain is often an issue. However, this problem can be handled by an adequate pain management protocol using cooling devices or different kinds of oral, local or intravenous analgesia. Thus, 'pain-management' should also be part of the training courses offered for PDT.

Additionally, the costs of the treatment, including the purchase of a lamp and of the relatively expensive drug Metvix®, is an issue for the dermatologist willing to apply this therapy. Hopefully, a wider use of Metvix®-PDT will reduce the relative costs for the photosensitiser in the near future.

Where do you hope to see PDT in routine use in the next few years?

With growing clinical experience, well-founded study data and International Guidelines, PDT should become a universally available treatment modality for patients with multiple AKs and field cancerisation, superficial BCCs and Bowen's disease. In particular, the increasing number of immunosuppressed post-transplant patients with multiple non-melanoma skin cancers will benefit from PDT.

As the development of PDT is continuously advancing, it can be hoped that PDT for other non-oncologic indications might become a routine treatment in the near future, again offering several advantages over standard therapies. ■

Prime Time PDT

An international roundup of PDT-related papers and publications

Enhancement of MAL-PDT by Iron Chelation with CP94 in Nodular BCC

A Pye *et al* 2008 *J Cancer Res Clin Oncol* **February 1** (E-Pub ahead of print)

Treatment of nodular basal cell carcinoma (BCC) with topical PDT has been problematic, regularly resulting in recurrence. The combination of iron chelators with methyl aminolevulinate (MAL) reduces the bioconversion of protoporphyrin IX (PpIX) to heme and so allows an increased accumulation of PpIX in the target tissue. The authors examined the iron chelator CP94 in conjunction with MAL, firstly in vitro in a number of human cell lines (including three dermatological cell types), with fluorometrical measurement of PpIX accumulation, and then in an open, dose-escalating pilot study in patients with nodular BCC, to determine the safety of this pharmacological modification.

Large enhancements of PpIX accumulation were seen in the cell cultures. In the clinical pilot study, CP94 plus MAL-PDT was found to be feasible and safe. Moreover, greater reductions in tumour depth were seen in the MAL/CP94 co-incubated tumours. The addition of CP94 to MAL-PDT showed enhanced nodular BCC tumour clearance both clinically and histologically, even though the study was small and intended only to assess the safety of CP94 addition to the MAL photosensitising cream. The authors conclude that CP94 and MAL-PDT should be examined in a larger, controlled clinical trial.

Evidence-Based Review of Lasers, Light Sources and PDT in Acne

M Hædersdal *et al* 2008 *J Eur Acad Dermatol Venereol* **January 23** (E-Pub ahead of print)

The authors identified 16 randomised controlled trials and 3 controlled trials for treatment of acne vulgaris, involving a total of 587 patients. Treatments included PDT, infrared lasers, broad-spectrum light sources, pulsed-dye lasers, intense pulsed light and one instance of a potassium titanyl phosphate laser. The most consistent outcomes were achieved with PDT (with up to 68% improvement using either ALA or MAL and red light). Only two trials compared optical treatments with conventional therapies; the authors called for more comparative studies and recommended that patients should be informed pre-operatively of the existing evidence for optical treatments.

Violet Light PDT in Melanotic Melanoma

L Ma *et al* 2007 *J Environ Pathol Toxicol Oncol* **26** 165-172

Melanin absorbs light over the whole wavelength region used for PDT (400-750nm). Therefore, photobleaching of melanin offers a route to overcome this problem in using PDT to treat melanotic melanomas. Using reflectance spectroscopy to measure depigmentation in nude mice and human skin, the authors concluded that violet light MAL-PDT has the ability to bleach melanin in these tumours and thus increase their sensitivity to red light MAL-PDT given thereafter. ■

American Academy of Dermatology Annual General Meeting: Posters

1-5 February, 2008 San Antonio, USA

by: Dr Colin Morton
Stirling, Scotland

The Alamo.

The latest annual general meeting of the American Academy of Dermatology (AAD) saw 10 posters presented which were specific to PDT. The posters are now presented in an electronic format, reducing the health value of the AAD, when several miles were traditionally trod in pursuit of finding posters of interest amongst the thousands on display. An advantage, however, is that members of the AAD can remotely access any of the posters via the AAD website during this year at:

www.aad.org

The posters are briefly summarised here.

POSTERS

The results from two randomised, multicentre, vehicle-controlled studies evaluating the efficacy and safety of MAL-PDT for patients with 4-10 suitable actinic keratoses (thin or moderate thickness AK, face and scalp) were reported together. **David Pariser** (Chicago, USA) and **Rolf-Markus Szeimies** (Regensburg, Germany) reported complete lesion responses with MAL-PDT to be superior in both studies (86% and 83%) compared to response rates with the vehicle cream placebo (52% and 29%) after two treatments, seven days apart. The high placebo response noted is probably explained by the preparatory curettage performed before cream application.

Tim Maisch and colleagues (Regensburg, Germany) displayed a poster on '*Protoporphyrin IX fluorescence induction after application of different 5-aminolevulinic acid formulations*'. Using a new full thickness porcine skin model (freshly excised porcine skin embedded in Hepes-agar), the skin sections were incubated with five different 20% 5-ALA formulations: 5-ALA + DMSO (5-ALA gel + 40% DMSO [penetration enhancer]); 5-ALA w/o DMSO (5-ALA gel without 40% DMSO); 5-ALA lipophilic (5-ALA cream oil/water); 5-ALA hydrophilic (5-ALA ointment water/oil, LKS); and 5-ALA HCl/alcohol solution (Levulan Kerastick®). Fluorescence intensities of PpIX increased in order of: ALA hydrophilic < ALA lipophilic < ALA gel w/o DMSO < ALA gel + DMSO < LKS. The LKS formulation showed a significantly earlier fluorescence induction of PpIX, evident at two hours, as compared to the other formulations, and the intensity of PpIX was 10-fold higher after LKS application, in contrast to 5-ALA hydrophilic ointment. Although only a model, this study offers useful information, contrasting different formulations of ALA and observing that 40% DMSO did not enhance penetration of a 5-ALA gel.

There is considerable interest in PDT in Brazil, with three posters detailing its effects on acne and photo-rejuvenation. **Otavio Macedo** and colleagues (São Paulo, Brazil) reported MAL-PDT for ten patients with mild-to-moderate inflammatory acne. Metvix® was applied on the whole face under occlusive dressing for one hour. The face was illuminated with blue light (Clear Light®) for 20 minutes, with three treatments, one month apart. Four weeks after the third treatment, a reduction in inflammatory and non-inflammatory lesions and also the fluorescence related to *P. acnes* was observed.

In a separate poster, **Beatriz Niwa** (São Paulo, Brazil) reported the response of 10 patients with moderate to severe acne to three MAL-PDT treatments at 4-week intervals, using 90-minute application and red light. Total inflammatory lesion count presented a median reduction of 37% and 49% after the first and second treatment sessions. Three patients received three sessions and showed a 71% reduction in inflammatory lesions. No reduction in the number of non-inflammatory lesions was observed. The maximal pain score was 7 (range 5-10), despite using a cool air device. At 6-month follow-up, three patients had limited recurrence. Although blue light may be useful for mild to moderate severity acne, red-light PDT might be required to impact significantly on moderate to severe disease, with inevitable issues around increased pain. More studies in this area are clearly required.

Otavio Macedo also reported the use of MAL-PDT in 10 patients with AK and mild to severe facial photodamage. After 3-hour MAL application, red LED light (Aktilite CL 128) illuminated the treatment fields. After the first PDT session, all visible AKs had cleared. Clinical improvement of photo-ageing, mottled hyperpigmentation, fine lines, roughness and sallowness were seen in all patients. There was also smoothing and softening of perioral and periorbital rhytides.

Jens Thiele and colleagues (Boston, USA) reported two organ transplant recipients, one with chronic radiation dermatatis and one with erythroplasia of Queryat (EQ), where the EQ cleared and other treated skin sites showed a reduction in the formation of new NMSC, using ALA-PDT and blue light.

Daniel Wasserman and colleagues (Boston, USA) reported the use of ALA-PDT in five patients with basal cell naevus syndrome with numerous basal cell carcinomas (BCC). There was clearance of most treated lesions, despite using blue light, although several lesions were injected with ALA 1:1 with 1% lidocaine containing epinephrine. The authors also observed a striking decrease in the number of new BCC developing during follow-up of up to five years.

Eric S. Schweiger *et al* (Kansas City, USA) presented one of two posters on the use of ALA-PDT for hidradenitis suppuritiva. His open-label study investigated PDT using two blue light sources and an intense pulsed light (IPL) for photo-activation. Twelve subjects with active HS received PDT once weekly for four weeks, with follow-up visits four and 12 weeks later. For the nine patients who completed the study, mean lesion counts reduced by 50.8%, with a 27% improvement in mean Dermatology Life Quality Index scores. Blue light was better tolerated than the IPL.

Erin C. DeVita and **Amy Taub** (Lincolnshire, USA) also reported the effective use of blue-light or IPL-delivered ALA-PDT (30-60 minute application) in patients with hidradenitis suppuritiva. Two patients achieved 75% improvement, sustained for at least nine months after three treatments at 2-week intervals. Improvement was less impressive for the two other cases. The authors point out that 10/14 patients, treated with PDT and reported in the literature, to date, achieved moderate to outstanding results. The four who did not had treatment with ALA in an oily vehicle under occlusion for four hours, which may have exacerbated the condition.

Sima Torabian and colleagues (University of California-Davis, USA) used ALA-PDT in a patient with refractory Flegel's Disease, a disorder of keratinisation. Improvement in appearance, with 80-90% reduction in visible lesions, was achieved following six treatments with ALA-PDT (ALA for 60-90 minutes) using a blue light.

San Antonio Riverwalk.

Calendar of Events 2008-2009

March 6-8, Barcelona, Spain
EURO-PDT 8th Annual Congress
Contact: Claudia Zange, Department of Dermatology
University of Regensburg, Franz-Josef-Strauss-Allee 11
93053 Regensburg, Germany
Fax: +49 941 944 9662
e-mail: claudia.zange@euro-pdt.org URL: www.euro-pdt.org

March 27, London, UK
Medical Dermatology
Contact: Conference and Event Services
The British Association of Dermatologists, 4 Fitzroy Square
London W1T 5HQ
Tel: +44 (0)20 7391 6358 Fax: +44 (0)20 7388 0487
e-mail: conference@bad.org.uk
URL: www.bad.org.uk

May 15-17, Athens, Greece
9th Congress of the European Society for Pediatric Dermatology (ESPD)
Contact: Penelope Mitroyianni
Tel: +30 2 107 257 693 Fax: +30 2 107 257 532
e-mail: info@espd2008.com URL: www.espd2008.com

June 5-7, Athens, Greece
12th COSMODERM – Joint Meeting of ESCAD/Hellenic Society of Dermatology and Venereology
Contact: Penelope Mitroyianni
Tel: +30 2 107 257 693 Fax: +30 2 107 257 532
e-mail: info@erasmus.gr

September 17-21, Paris, France
EADV 2008 – 17th Annual Congress of the European Academy of Dermatology and Venereology
Contact: EADV 2008/MCI
Tel: +33 153 858 270 Fax: +33 153 858 283
e-mail: info@eadvparis2008.com
URL: www.eadvparis2008.com

October 7-11, Brixen/Bressanone, Italy
7th International Symposium on PDT and Photodiagnosis in Clinical Practice
Contact: Prof G Jori
Tel: +39 049 827 6333 Fax: +39 039 827 6344
e-mail: giulio.jori@unipd.it
or
Prof H Kostron
Tel: +43 512 504 27278 Fax: +43 512 504 27460
e-mail: herwig.kostron@uibk.ac.at
URL: www.bio.unipd.it/PDT2008

2009

March 6-10, San Francisco, USA
67th Annual Meeting of the American Academy of Dermatology (AAD)
Contact: AAD Secretariat
Tel: +1 202 842 3555 Fax: +1 202 842 4355

May 3-6, Tel Aviv, Israel
12th World Congress on Cancer of the Skin (WCCS)
Contact: WCCS Meeting Organiser
Tel: +41 229 080 488 Fax: +41 227 322 850
e-mail: wccs2009@kenes.com

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