Focus

Phototherapy: An update

Reena Rai

INTRODUCTION

Ultraviolet radiation used in the management of skin diseases is an essential part of dermatological therapy. Numerous studies have shown the beneficial effect of ultraviolet radiation for the treatment of chronic inflammatory or lymphoproliferative skin diseases. In the past, patients were treated with broad-band UVB (290–315 nm), long wave UVA (320–400 nm) or combination regimens. Advances in our understanding of the pathogenesis of these skin diseases has resulted in the development of new phototherapeutic modalities such as narrowband UVB (TL-01), long-wave UVA (UVA1), bath water delivery of 8-MOP followed by UVA (bath-PUVA) or the combination of salt water brine baths and UVA/B, extracorporeal photopheresis (ECP) and photodynamic therapy.

NARROW BAND UVB (NBUVB)

After the introduction of the Philips TL-01 lamp with an emission spectrum (311–312 nm) NBUVB is now the gold standard for the treatment of skin disorders. At this wavelength, there is a decrease in the erythemogenic wavelength with a 5-fold increase in longer wavelengths resulting in an increased therapeutic effect. Several studies comparing it with conventional photochemotherapy in patients with psoriasis reported greater therapeutic efficacy with narrowband UVB phototherapy.[1] Studies have shown that NBUVB is beneficial in the treatment of vitiligo, pruritus, and inflammatory dermatoses[2] and it has been reported to be safer and more effective than PUVA in repigmentation of vitiligo.[3]

Department of Dermatology, PSG Hospitals, Peelamedu, Coimbatore, India

Address for correspondence:
Dr. Reena Rai, Department of Dermatology, PSG Hospitals, Peelamedu, Coimbatore 641 004, Tamil Nadu, India.
E-mail: drreena_rai@yahoo.co.in

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The advantages NBUVB over PUVA are: 1) No gastrointestinaI upset associated with psoralen, 2) no need for eye protection during the post-treatment period, 3) safe to use for children and pregnant women, and 4) easier and less expensive to administer. For patients who require frequent courses, TL-01 confers a lower risk for non-melanoma cutaneous malignancy.

The combination of various drugs with NBUVB is used to achieve a faster and higher clearance rate and a longer disease-free interval with a decrease in the cumulative dose.[4] These include systemic agents such as methotrexate, cyclosporine, systemic retinoids, antioxidants,[5] and topicals such as tacrolimus,[6] pimecrolimus,[7] vitamin D analogues, retinoids, glucocorticoids, emollients, and saltwater baths.

BALNEOPHOTOTHERAPY

Balneophototherapy combines bath water delivery of 8-methoxypsoralen (bath PUVA) or different salt solutions with a subsequent UVB- or UVA-irradiation.[8] The combination of brine baths or 8-MOP-baths with UVB or UVA phototherapy using artificial light sources has been used in the treatment of psoriasis and atopic dermatitis.[9] Delivery of psoralens by bath prevents systemic adverse effects associated with oral PUVA. Bath PUVA has the advantage of selective and shorter photosensitization, leading to a significantly lower cumulative UVA exposure.[10,11]

The favorable effects of sun exposure and sea water (climatotherapy) for the treatment of psoriasis, especially near the Dead Sea area, have been known for decades.[12] Artificial regimens have been developed in an attempt to mimic the natural climatic conditions. For this purpose, patients are immersed in saltwater (SW) baths during (simultaneous application) or before (sequential application) UVB irradiation. Some studies have reported superiority of sequential SW phototherapy over UVB alone.[13] However, the effect of salt concentration and mineral composition on

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clinical outcome is unclear.[14] A large randomized controlled study has shown that bathing in salt water is superior to UVB monotherapy as well as to tap water baths before UVB exposure.[15] Both open prospective studies and recent randomized controlled trials have demonstrated that Balneophototherapy is a safe and well accepted treatment modality with no serious side effects.[16,17]

UVA1

UVA1 phototherapy utilizes long wave UVA radiation (340–400 nm) while filtering out the erythematogenic UVA and UVB wavelengths (290–340 nm). The therapeutic efficacy of high-dose UVA1 irradiation in the treatment of patients with acutely exacerbated atopic dermatitis was first reported in 1991 and was confirmed in several subsequent studies.[18,19,20] It has been shown to be very effective in the treatment of several inflammatory skin diseases such as atopic dermatitis, localized scleroderma, urticaria pigmentosa, disseminated granuloma annulare, and in some cases systemic sclerosis, lichen sclerosus et atrophicans, graft-versus-host disease, and cutaneous T cell lymphoma.[21] Different dosage regimens have been proposed for UVA1 phototherapy: low dose (10–20 J/cm^2 per single dose), medium dose (50–60 J/cm^2 per single dose), or high dose (130 J/cm^2 per single dose) UVA1 therapy. High dose UVA1 irradiation is useful in the treatment of patients with acutely exacerbated atopic dermatitis. It can be used as monotherapy for a limited period of time (10–15 exposures, maximum twice yearly) and is an alternative to long-term glucocorticosteroid use.[19] Medium UVA1-phototherapy is effective in the treatment of moderate severity atopic dermatitis and sclerotic disorders and 15–30 treatments are given.[21] Despite all the benefits of UVA1, little data exists on potential long-term safety risks such as photodamage and skin carcinogenesis in humans, particularly of the high-dose regimen.

PHOTODYNAMIC THERAPY

First described by Kennedy, *et al.* in 1990,[22] the increasing case reports and case series that followed supported the efficacy of the therapy, particularly in non-melanoma skin cancer.

Photodynamic therapy (PDT) aims to destroy the desired target selectively, thereby avoiding or minimizing damage to vital structures. The photodynamic reaction consists of the excitation of photosensitizers (mainly porphyrins) by visible light in the presence of oxygen, resulting in the generation of reactive oxygen species, particularly singlet oxygen. This results in a direct or indirect cytotoxic effect on the target cell.[23]

Topically active agents are preferable for PDT in dermatology and 5-aminolaevulinic acid is the main agent used. It is converted within cells into the photosensitizer protoporphyrin IX (PpIX) activated by intense pulse light or long pulse dye laser which then triggers the photodynamic reaction. Several light sources have been used in clinical PDT including lasers, xenon arc/discharge lamps, incandescent filament lamps, and solid-state light-emitting diodes (LEDs).[24] Accumulation of PpIX appears to result from increased penetration of aminolaevulinic acid through the abnormal epidermis overlying tumors, resulting in preferential intracellular accumulation of PpIX in proliferating, relatively iron-deficient, tumor cells.[25]

Advantages of topical 5-aminolaevulinic acid-photodynamic therapy are: 1) relatively selective treatment and minimal or no scarring, 2) noninvasive, 3) multiple lesions may be treated simultaneously, 4) safe, out-patient procedure, and 5) repeated treatments are possible.

The carcinogenic risk of ALA-PDT appears to be low. Current evidence indicates topical PDT to be effective in actinic keratoses of the face and scalp, Bowen's disease, superficial basal cell carcinomas, acne, and photodamge. PDT may prove advantageous where size, site, or number of lesions limits the efficacy and / or acceptability of conventional therapies.

EXTRACORPOREAL PHOTOPHERESIS

Extracorporeal photopheresis (ECP) was first introduced in 1987 by Edelson, *et al.* as a therapeutic regimen for Sezary's syndrome.[26] However, in recent years, it has been used successfully for other indications such as chronic graft-*versus*-host disease, cutaneous T cell lymphoma, systemic scleroderma, pemphigus vulgaris, rheumatoid arthritis, lupus erythematoses, allograft rejection, and even severe atopic dermatitis.[27] ECP is a discontinuous leukapheresis procedure that combines administration of 8-methoxypsoralen (8-MOP) with extracorporeal UVA irradiation to a fraction of the peripheral blood leukocytes. Therefore,

it targets the effects of photochemotherapy directly to circulating, pathogenic leukocytes. Photopheresis is performed on two successive days and is repeated at 2- to 4-week intervals. It is estimated that during one treatment session 5%–10% of the circulating T-cell pool is treated.

ECP has a low side effect profile. Some patients with Sezary syndrome are less responsive to ECP and combination therapy with IFN-α and interleukin-2 or bexarotene may be required.[28,29]

TARGETED PHOTOTHERAPY

Targeted phototherapy describes the use of ultraviolet light that is focused on specific body areas. It can be delivered by laser or by a non laser source. A laser source emits a coherent pulsed light of high power density. The non laser source is a monochromatic excimer light that is a noncoherent, continuous emission with a power density lower than the laser but higher than the TL-01 lamp.

The 308-nm excimer laser represents the latest advance in the concept of selective phototherapy in the treatment of psoriasis and vitiligo.[30,31] It emits a wavelength in the UVB spectrum and shares the same indications as conventional phototherapy. Like other laser devices, the 308-nm excimer laser can selectively treat a lesion while sparing surrounding healthy skin and can deliver high fluences with less irradiation time. It is recommended when the lesions involve less than 20% of the body. Initially, high fluences (minimal erythema dose) were used with excellent clinical results to treat psoriasis vulgaris. Erythema and blistering on the treated areas and the potential long-term carcinogenic risk associated with such fluencies have resulted in medium doses (about 3 minimal erythemal dose) being recommended. Newer treatment protocols adapt the dose to the lesion and not to the minimal erythemal dose, as is the case of conventional phototherapies.[32]

Many prospective studies have also shown the efficacy and the tolerance of the 308-nm excimer laser in the treatment of localized vitiligo. Induced rates of repigmentation seem to be higher than with NBUVB.[31] Morever, the selectivity of the treatment prevents irradiation of healthy skin and limits unsightly tanning of the surrounding skin. Combining the 308-nm excimer laser with 0.1% tacrolimus ointment has provided very interesting results that need to be confirmed in a larger study.[33] There is an absence of actual data concerning the long-term risk for skin cancer after treatment and so it should be considered with caution.

CONCLUSION

In the past, research in photodermatology has led to refinements of phototherapy modalities such as selective phototherapy, which includes UVA1, NBUVB, balneophototherapy, extracorporeal photopheresis photodynamic therapy, and targeted phototherapy. These new and promising approaches in the management of chronic inflammatory or lymphoproliferative skin diseases are effective, but a standardization of dosage regimen and quality control is necessary to avoid potential long-term safety risks such as photodamage and skin carcinogenesis. The development of improved phototherapeutic modalities and new indications has kept phototherapy from being obsolete even though it is as old as recorded history.

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