Guidelines of care for the management of psoriasis and psoriatic arthritis

Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy

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Psoriasis is a common, chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations affecting approximately 2% of the population. In this fifth of 6 sections of the guidelines of care for psoriasis, we discuss the use of ultraviolet (UV) light therapy for the treatment of patients with psoriasis. Treatment should be tailored to meet individual patients' needs. We will discuss in detail the efficacy and safety as well as offer recommendations for the use of phototherapy, including narrowband and broadband UVB and photochemotherapy using psoralen plus UVA, alone and in combination with topical and systemic agents. We will also discuss the available data for the use of the excimer laser in the targeted treatment of psoriasis. Finally, where available, we will summarize the available data that compare the safety and efficacy of the different forms of UV light therapy. (J Am Acad Dermatol 2010;62:114-35.)

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.

Abbreviations used:

AAD:	American Academy of Dermatology
BB:	broadband
FDA:	Food and Drug Administration
MED:	minimal erythema dose
NB:	narrowband
PUVA:	psoralen plus ultraviolet A
SCC:	squamous cell carcinoma
UV:	ultraviolet

SCOPE

This fifth section will cover the management and treatment of psoriasis with phototherapy.

METHOD

A work group of recognized psoriasis experts was convened to determine the audience and scope of the guideline, and identify clinical questions to structure the primary issues in diagnosis and management discussed in American Academy of

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Dermatology (AAD) psoriasis guidelines sections 1 and 2.[1,2] Work group members completed a disclosure of commercial support.

An evidence-based model was used and evidence was obtained using a search of the MEDLINE database spanning the years 1960 through 2009. Only English-language publications were reviewed.

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*). This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the evidence of scientific studies.[3] Evidence was graded using a 3-point scale based on the quality of methodology as follows:

I. Good-quality patient-oriented evidence.
II. Limited-quality patient-oriented evidence.
III. Other evidence including consensus guidelines, opinion, or case studies.

Clinical recommendations were developed on the best available evidence tabled in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence.
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C. Recommendation based on consensus, opinion, or case studies.

In those situations where documented evidence-based data are not available, we have used expert opinion to generate our clinical recommendations. Prior guidelines on psoriasis were also evaluated. This guideline has been developed in accordance with the AAD "Administrative Regulations for Evidence-based Clinical Practice Guidelines," which include the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.

GENERAL PRINCIPLES

In the past, conventional psoriasis therapies—phototherapy, photochemotherapy, methotrexate, cyclosporine, and acitretin—were used when psoriasis was too extensive for topical therapy. Although a minimum body surface area (eg, 10%) has been traditionally used as a prerequisite to starting ultraviolet (UV) light or systemic therapy for psoriasis, a subset of patients with limited disease have debilitating symptoms. For example, whereas severe psoriasis of the palms and soles or severe scalp psoriasis affects less than 5% of the body surface area, the significant negative effect on the quality of life of the patient makes treatment with systemic therapies an appropriate approach to the management. Although treatment options for psoriasis have expanded in recent years, UV light therapy remains an essential therapeutic option for patients with psoriasis. Phototherapy is efficacious, is cost-effective, and generally lacks the systemic immunosuppressive properties of both traditional and biologic systemic therapies.

Various spectra of UVB and UVA wavelengths have been used to treat psoriasis. Although it has been known for many centuries that some skin diseases improve with sun exposure, scientific investigation of phototherapeutic modalities did not begin until the late 19th century with the work of Niels Ryberg Finsen who received the Nobel Prize in 1903 for his work developing phototherapy for the treatment of cutaneous tuberculosis. Goeckerman[4] first described the use of broadband (BB)-UVB in combination with day and night applications of crude coal tar for the successful treatment of psoriasis. This therapy was carried out while patients were admitted to the hospital for several weeks. During the years after the development of the Goeckerman[4] regimen, several modifications and simplifications were made. In the 1950s, the Ingram[5] regimen was developed, which replaced crude coal tar with anthralin. Subsequent studies have demonstrated that a lubricating base may be used instead of crude coal tar. However, a 1983 study demonstrated that suberythemogenic doses of UVB and coal tar were more efficacious than UVB and a lubricating base.[6,7] Clear emollients such as mineral oil also enhance the efficacy of UVB by improving the optical properties of the skin; their use facilitated the shift of UVB as an outpatient, rather than an inpatient or day hospital, treatment modality.[8-10] In the 1980s, a new type of UVB bulb with a narrow emission between 311 and 313 nm was developed and found to have superior efficacy to BB-UVB light[11]; this new UVB treatment is now commonly referred to as narrowband (NB)-UVB therapy.

Because keratinocyte hyperproliferation is a hallmark feature of psoriasis, it was originally believed that the mechanism of action of UV light treatment in psoriasis was through a direct effect of UV light on DNA by inhibition of cellular turnover. With newer evidence firmly demonstrating that psoriasis is an immunologic disease, the role of the immunosuppressive effects of UV light in the treatment of psoriasis has been better appreciated. UV light (both

UVB and UVA) is locally immunosuppressive by its direct effects on Langerhans cells and indirect effects on numerous cytokines and adhesion molecules, which can lead to a switch from a T-helper (Th) 1 to a Th 2 phenotype.[12,13] Other effects of UV light include inhibition of both epidermal hyperproliferation and angiogenesis. Furthermore, UV light causes a selective reduction in T lymphocytes within psoriatic skin via apoptosis. BB-UVB, NB-UVB, and psoralen plus UVA (PUVA) can all induce apoptosis of T lymphocytes,[14-16] which may play an important role in the mechanism involved in remissions of psoriasis.

Ancient Egyptians knew that natural photosensitizing compounds found in plants, combined with exposure to natural sunlight, were effective for the treatment of vitiligo. Trimethylpsoralen, a synthetic psoralen, was first used for the treatment of vitiligo and has since been used to successfully treat many other inflammatory photosensitive diseases such as cutaneous T-cell lymphoma, atopic dermatitis, and lichen planus.[17] In the 1970s, oral ingestion of 8-methoxypsoralen combined with high-intensity UVA (known as PUVA photochemotherapy) was shown to be effective for the treatment of psoriasis[18]; in 1982 PUVA was Food and Drug Administration (FDA) approved for psoriasis.

All patients who are considered for treatment with phototherapy or photochemotherapy must have a complete history and physical examination. Patients with a known history of lupus erythematosus or xeroderma pigmentosum should not be treated with phototherapy or photochemotherapy. Patients with a history of a photosensitivity disorder, taking photosensitizing medications, with a history of melanoma, with atypical nevi, with multiple risk factors for melanoma, with multiple nonmelanoma skin cancers, or who are immunosuppressed as a result of organ transplantation should be screened carefully before initiating phototherapy or photochemotherapy. They should also be advised that adherence to their follow-up visits is imperative to obtaining maximal results. Office phototherapy and photochemotherapy should be performed under the direction of a dermatologist with the appropriate training and expertise in this area. Experts recommend that patients be examined approximately once a month or more often if necessary, although specific data on the frequency of evaluations during phototherapy or photochemotherapy are lacking. Each patient's treatment should be closely monitored by a nurse or phototherapy technician with proper training, and any abnormal findings should be transmitted to the treating dermatologist. All phototherapy equipment should be maintained and regularly calibrated by appropriately trained personnel. Accurate records of the dosage and number of treatments along with any side effects should be maintained for every patient.

UVB PHOTOTHERAPY

Traditional BB-UVB radiation has been used for the treatment of psoriasis for more than 75 years. In recent years phototherapy has maintained its important role in the treatment of psoriasis, either as monotherapy or in combination with topical or systemic agents. In a study published in 1975, it was shown that 313 nm was the most effective wavelength in clearing psoriasis.[19] Further study using monochromatic UV radiation ranging from 254 to 313 nm revealed that suberythemogenic exposure to 313-nm light led to significant improvement of psoriasis.[20] UVB interferes with the synthesis of proteins and nucleic acids, which leads to a decreased proliferation of epidermal keratinocytes. Early changes after exposure to UV radiation include formation of pyrimidine dimers, membrane lipid peroxidation, and induction of transcriptional factors. Delayed changes include alteration of antigen-presenting cells and cellular signaling mechanisms.[13] UVB decreases the number of Langerhans cells[21] thus inhibiting the ability of dendritic cells to present antigens, secondary to membrane damage and reduction in the expression of cell surface molecules while altering the secretion of cytokines in the macrophages.[22] The newly discovered subset of T cells, Th17 cells, are now considered to play a central role in the immunopathogenesis of psoriasis and are likewise down-regulated by UVB.[23]

Efficacy

Early studies demonstrated the efficacy of BB-UVB monotherapy in psoriasis. One study reported resolution of psoriasis in 20 of 28 patients treated with erythemogenic doses of home-based UVB therapy[24] whereas another study demonstrated efficacy in 18 of 20 patients treated with 3 times weekly outpatient UVB phototherapy with concomitant white petrolatum.[25] Similar observations were made by Levine and Parrish[10] when white petrolatum was combined with UV. Remission times were prolonged using maintenance therapy.[26-28]

The advent of NB-UVB lamps improved the use of UVB therapy in psoriasis and is widely considered to be preferable to BB-UVB therapy. NB-UVB use was initially popularized in the United Kingdom and Europe in the mid-1980s, and became available in the United States approximately one decade later. Many of the studies evaluating NB-UVB were right-left half body comparisons of NB-UVB with BB-UVB.[11,29-31] One such study demonstrated that although 60% of patients had the same efficacy

regardless of which type of UVB was used, 40% of patients treated with NB-UVB had superior results.[29] Other similar studies have demonstrated more rapid clearing in patients treated with NB-UVB compared with those treated with BB-UVB[11,30] and treatment with NB-UVB was more likely than BB-UVB to lead to histopathological resolution of psoriasis lesions (88% compared with 59%).[31] The potential value of maintenance therapy with NB-UVB has also been evaluated. After 12 weeks of NB-UVB therapy, 55% of patients who received NB-UVB twice weekly for 4 weeks followed by once weekly for 4 weeks were in remission at 1 year compared with 33% of patients who did not receive maintenance therapy.[24]

Dosage and scheduling

A standard protocol is recommended for the use of phototherapy in the management of psoriasis. Basic phototherapy education should be given to all patients. This must include education about the use of goggles in all patients and the use of genital shields in male patients. The dosage of UVB may be administered according to the Fitzpatrick skin type[32] or the minimal erythema dose (MED), with subsequent dosages adjusted accordingly. (Please see Tables I and II for examples of well-accepted, published guidelines for dosing of both BB-UVB and NB-UVB.)

Toxicity

BB-UVB. Acute side effects with BB-UVB therapy include erythema, itching, burning, and stinging. The use of eye protection with goggles is required to decrease the risk of UVB-related cataract formation. Reactivation of herpes simplex virus infection may occur after UVB treatment. Photoaging is a long-term side effect, and features of dermatoheliosis including wrinkling, lentigines, and telangiectasias may occur. Photocarcinogenesis is a potential adverse effect of UVB phototherapy; however, numerous studies have failed to show such an effect in patients with psoriasis after UVB therapy.[33,34] Long-term exposure to BB-UVB (>300 treatments) may be associated with an increased risk of genital tumors in men treated without genital shielding; the routine use of shields has been recommended to avoid such an effect.[35] In addition to genital shielding, standard practice involves covering the face as long as there are no lesions of psoriasis on the face or, if there are, minimizing the dose to the face as lesions on the face tend to respond to lower doses of UVB compared with lesions on trunk or extremities.

NB-UVB. Burning with NB-UVB is generally comparable with that observed with BB-UVB exposure. Although NB-UVB is reported to be less phototoxic than BB-UVB in some studies,[36,37] other studies failed to show this discrepancy.[31,38] Although an unusual occurrence, lesional blistering has also been reported after exposure to NB-UVB.[39] Murine models of photocarcinogenesis suggest that NB-UVB may be 2 to 3 times more carcinogenic per MED as compared with BB-UVB.[40,41] However, because of the higher efficacy of NB-UVB, the total MED equivalent of UVB dose that occurs with NB-UVB treatment is far less than that occurs with BB-UVB, suggesting that the long-term risk of carcinogenesis may not be enhanced.[42] In fact, in a recent review of 3867 patients treated with NB-UVB in which the median number of treatments was 29 with 352 patients receiving more than 100 treatments, there was no significant association found with basal cell carcinoma, squamous cell carcinoma (SCC), or melanoma, with a median follow-up period of 5.5 years.[43] Pregnant patients should be counseled about a possible increased incidence of melasma. See the "General Principles" section for relative contraindications or cautions.

Table I. Dosing guidelines for broadband ultraviolet B

According to skin type:		
Skin type	Initial UVB dose, mJ/cm^2	UVB increase after each treatment, mJ/cm^2
I	20	5
II	25	10
III	30	15
IV	40	20
V	50	25
VI	60	30

According to MED:	
Initial UVB	50% of MED
Treatments 1-10	Increase by 25% of initial MED
Treatments 11-20	Increase by 10% of initial MED
Treatments ≥21	As ordered by physician

If subsequent treatments are missed for:	
4-7 d	Keep dose same
1-2 wk	Decrease dose by 50%
2-3 wk	Decrease dose by 75%
3-4 wk	Start over

MED, Minimal erythema dose; *UV*, ultraviolet.
Administered 3-5×/wk.
Adapted with permission from Zanolli et al.[169]

Pregnancy

Pregnancy is not a contraindication to the use of UVB therapy.[44] NB-UVB therapy has been used successfully in the treatment of psoriasis in pregnancy[45-47] and should be considered first-line therapy in pregnant patients with plaque and guttate psoriasis who need a systemic approach to

Table II. Dosing guidelines for narrowband ultraviolet B

According to skin type:

Skin type	Initial UVB dose, mJ/cm^2	UVB increase after each treatment, mJ/cm^2	Maximum dose, mJ/cm^2
I	130	15	2000
II	220	25	2000
III	260	40	3000
IV	330	45	3000
V	350	60	5000
VI	400	65	5000

According to MED:

Initial UVB	50% of MED
Treatments 1-20	Increase by 10% of initial MED
Treatments $\geq$ 21	Increase as ordered by physician

If subsequent treatments are missed for:

4-7 d	Keep dose same
1-2 wk	Decrease dose by 25%
2-3 wk	Decrease dose by 50% or start over
3-4 wk	Start over

Maintenance therapy for NB-UVB after >95% clearance:

1×/wk	NB-UVB for 4 wk	Keep dose same
1×/2 wk	NB-UVB for 4 wk	Decrease dose by 25%
1×/4 wk	NB-UVB	50% of Highest dose

MED, Minimal erythema dose; *NB*, narrowband; *UV*, ultraviolet.
Administered 3-5×/wk.
Because there is broad range of MED for NB-UVB by skin type, MED testing is generally recommended.
It is critically important to meter UVB machine once weekly. UVB lamps steadily lose power. If UV output is not periodically measured and actual output calibrated into machine, clinician may have false impression that patient can be treated with higher doses when machine is actually delivering much lower dose than number entered.
Minimum frequency of phototherapy sessions required per week for successful maintenance as well as length of maintenance period varies tremendously between individuals. Above table represents most ideal situation where patient can taper off phototherapy. In reality, many patients require 1×/wk NB-UVB phototherapy indefinitely for successful long-term maintenance.
Adapted with permission from Do and Koo.[170]

treatment. Neither BB-UVB nor NB-UVB therapy are known to have any teratogenic effects.

Pediatric use

Literature regarding the use of phototherapy in the pediatric population is limited. In a review of 20 patients treated with BB-UVB, 10 of whom had psoriasis, all patients responded well and none had any serious side effects.[48]

In a retrospective review of 77 children treated with NB-UVB, of whom 35 had psoriasis, phototherapy was effective and well tolerated. Clearance was observed in 63% of patients with psoriasis. Erythema was the most common side effect. Anxiety was of significant concern in 5 patients, reactivation of herpes simplex occurred in two patients, and varicella occurred in one patient.[49] Measures to make the phototherapy unit more child–friendly have been suggested.[50] Although there are no studies documenting the long-term safety of UVB phototherapy in childhood psoriasis, judicious use of this therapy as a second-line therapy in children whose disease fails topical therapy is reasonable for appropriately selected patients.

Home UVB

Home UVB has been available for many years,[24] however, until recently there was no well-controlled study that assessed its efficacy. In 1999, the British Photodermatology Group recommended against the routine use of home UVB treatment because of the potentially greater risks of this therapy except for patients who have overwhelming difficulties in obtaining clinic or hospital-based phototherapy units.[51] However, a recent multicenter, single-blind, randomized clinical trial of 196 patients from the Netherlands demonstrated that home NB-UVB is just as effective as outpatient-administered NB-UVB. In this study, 70% of patients treated at home compared with 73% treated in the outpatient setting reached Psoriasis Area and Severity Index 50.[52] Although quality of life improved equally in both groups, patients treated at home more often rated their experience as "excellent" (42%, 38 of 90) compared with patients treated in the outpatient department (23%, 20 of 88; P = .001). Based on these findings, patients with psoriasis who are compliant, motivated, and adherent with instructions and follow-up examinations could, under dermatologist supervision, be considered appropriate candidates for home UVB therapy.

UVB COMBINATION THERAPY

Combination UVB with topical therapies

Topical agents form the mainstay of treatment in psoriasis and all other treatment modalities are often used with concomitant topical therapy. Emollients increase the transmission of UV radiation by altering the optical properties of psoriatic skin lesions and improving therapeutic efficacy.[53,54] Application of a thin layer of emollient such as petrolatum before UV exposure is traditionally used. However, there are no randomized controlled studies to prove the benefit of concomitant use of emollients with UVB. It is important to pay attention to the application of sunscreens or salicylic acid–containing preparations that may interfere with the penetration of UV radiation. UV-

blocking properties may be used to cover uninvolved skin with preparations such as zinc oxide to prevent unnecessary exposure and adverse effects.

Despite the documented efficacy of topical corticosteroids as monotherapy in psoriasis, the addition of topical corticosteroids does not produce added benefit when studied in combination with UVB when compared with UVB monotherapy. Early trials demonstrated a more rapid clearing of psoriasis when UVB was used in conjunction with topical fluocinolone or clobetasol propionate (used in combination with UVB and topical anthralin).[55] However, other studies failed to demonstrate a benefit in either the clearance or the remission rate, and some studies suggest that the use of topical corticosteroids in conjunction with UV therapy may be associated with a higher relapse rate.[56-58] Thus, it is unclear whether the use of topical steroids in combination with UVB is beneficial.[59]

There are conflicting reports regarding the efficacy of combining of vitamin D analogues such as calcipotriol with UVB. A beneficial effect of the combination of calcipotriol and UVB was demonstrated in a study comparing calcipotriol as monotherapy with the combination of calcipotriol and UVB radiation.[59] A reduction in relapse rate was observed in a left-to-right comparison study comparing the combination of UVB and calcipotriol with either therapy alone.[60] A multicenter randomized controlled trial showed that twice weekly UVB in combination with calcipotriol was equal in efficacy to thrice weekly UVB alone requiring fewer UVB exposures.[61] However, a meta-analysis revealed no significant beneficial effect of the combination when compared with UVB alone.[62] Similarly, conflicting results have been obtained in studies assessing the efficacy of NB-UVB with calcipotriol.[63] Randomized controlled studies suggest that combining NB-UVB with calcipotriol has a UVB-sparing effect.[64] Because some vitamin D analogues may be degraded after exposure to UV radiation,[65,66] it is recommended that the vitamin D analogue be applied after UV exposure, whereas emollients such as mineral oil may be applied before UV exposure.

Topical tazarotene used in combination with UVB may improve the therapeutic efficacy while reducing the number of treatment sessions and lower cumulative UVB dosage. Because the use of tazarotene may lead to enhanced susceptibility to burning after UV exposure, consideration should be given to reducing the UVB dose to prevent adverse effects. A randomized study of 40 patients treated with UVB and 0.1% tazarotene revealed a 75% improvement in the plaques at a median of 28 days earlier than that with UVB monotherapy.[67] Goeckerman[4] therapy and Ingram[5] regimen combine UV therapy with topical tar and anthralin, respectively. The observation that suberythemogenic doses of UVB therapy are effective when used in combination with crude coal tar[6] paved the way for the use of less aggressive UVB therapy. Although highly effective in clearing psoriasis, the time-consuming nature of the Goeckerman[4] and Ingram[5] regimens, the messiness of many tar and anthralin products, and changes in the reimbursements for inpatient dermatologic care for psoriasis have made these combinations far less popular in recent years. Short-contact anthralin has little additional beneficial effect when added to UVB treatment. Thus, in a right-left comparison study of 15 patients treated with UVB and 0.3% to 3% anthralin, only 4 patients showed a moderately better clearance.[68] Similar results were observed in a study assessing the addition of short-contact anthralin therapy to UVB.[69] The combination of tar and UVB does not increase the incidence of nonmelanoma skin cancers over UVB alone.[70,71]

Combination UVB with traditional systemic therapies

The combination of methotrexate with UVB therapy is of potential value because of the synergistic effects of these two therapies, with the promise of a reduction in dose-related toxicity. In a study of 26 patients treated with 15 mg weekly of methotrexate followed by combining with UVB, clearing was observed in a median of 7 weeks with less than half the cumulative dose of UVB required, however, there was a severe psoriasis flare after methotrexate was discontinued.[72] In a randomized controlled study of methotrexate combined with UVB in 24 patients, clearance was observed in a median of 4 weeks in patients treated with the combination of methotrexate and UVB whereas more than half of the patients treated with placebo and UVB failed to achieve clearance.[73] A limitation of this study was the lack of a monotherapy methotrexate arm.

The combination of cyclosporine and UVB has not been studied extensively because of the increased risk of nonmelanoma skin cancer that occurs in patients treated with cyclosporine monotherapy. Although cyclosporine in combination with UVB has been used in the short term without any significant side effects, there are no studies documenting the longer-term safety of the combination and it should generally be avoided. One study used a sequential approach to the use of cyclosporine and UVB. Thirty patients were initially treated with low-dose cyclosporine (2.5 mg/kg) for 4 weeks followed by a rapid cyclosporine taper while NB-UVB therapy was instituted.[74] Comparing this with the group of patients

who received NB-UVB alone, the total number of UVB exposures and cumulative UVB dosages were significantly lower (12.11 ± 5.87 vs 19.59 ± 4.66, $P < .01$ and 8.94 ± 6.41 J/cm^2 vs 18.34 ± 8.49 J/cm^2, $P < .01$, respectively).[74]

Retinoids combined with UVB have been extensively studied and accelerate the response to phototherapy, reducing the cumulative dosage of UVB and the dose of acitretin required to achieve psoriasis clearance. In a randomized controlled study by Lowe et al,[75] psoriasis cleared to a greater degree (74%) in patients treated with acitretin and BB-UVB with fewer treatments required as compared with BB-UVB alone (35%). In another multicenter randomized controlled trial of 82 patients, the psoriasis severity decrease was 79% in the group receiving acitretin and BB-UVB combination compared with 35% in the placebo and BB-UVB group; marked differences in the effective cumulative dose of UVB were noted.[76] Similar results have been obtained with NB-UVB when combined with acitretin.[77] In a randomized controlled trial comparing the combination of acitretin with NB-UVB versus acitretin and PUVA therapy, clearance was observed in 57% of patients in the former group compared with 63% in the latter.[78] When phototherapy is combined with acitretin, acitretin should be started approximately 2 weeks before the initiation of phototherapy, the standard dose being 25 mg/d for patients weighing 70 kg or more, or 10 mg/d for those weighing less. The dosage and scheduling of BB-UVB or NB-UVB is managed according to the patient's skin type with appropriate reductions (approximately 25%) in the initial dosages of UV radiation. Acitretin has also been used in combination with home NB-UVB phototherapy.[79,80] Acitretin in combination with UV therapy, despite the reduction of cumulative dosing, costs, and potential systemic toxicities, remains less used than expected given the potential benefits.[81]

Combination UVB with PUVA

Concomitant treatment with PUVA and UVB therapy may be associated with more rapid clearing than either therapy used alone. In a bilateral comparison study of 42 patients with recalcitrant psoriasis, the mean UVB dose at clearing and the mean cumulative PUVA dose at clearing were both less than half, and the total cumulative UVB dose was 18% of that normally required to achieve clearance based on historical controls.[82] However, in view of the known photocarcinogenicity of PUVA, further studies are required to clearly document the risk-benefit ratio of this combination, particularly over the long term.

Combination UVB with biologics

Although there are isolated case reports,[83] very few evidence-based studies evaluate the effect of combining UVB phototherapy and biologic agents. One open-label study of 60 patients compared alefacept alone with the combination of alefacept with NB-UVB or BB-UVB.[84] Combination therapy was well tolerated and patients treated with combination therapy achieved a more rapid onset of response and a higher response rate than those treated with alefacept monotherapy. However, because of the absence of a UVB monotherapy arm, it cannot be deduced that the combination of alefacept and UVB is better than UVB alone. In a randomized half body comparison study of 14 patients treated with either alefacept alone or in combination with UVB, the mean Psoriasis Area and Severity Index score was reduced by 81% and 62%, respectively, in the combination as compared with the alefacept monotherapy group.[85] A multicenter, open-label study evaluated the efficacy and safety of etanercept with NB-UVB in 86 patients. Etanercept given 50 mg twice weekly along with NB-UVB given thrice weekly was highly effective. The safety profile of combined etanercept and NB-UVB was no different from that of the individual therapies.[86] Large-scale studies and long-term data including remission times are needed to properly evaluate the efficacy and safety of the combination of UV light with biologic therapies. The design of these studies should include 3 arms: combination therapy, monotherapy with a biologic, and monotherapy with NB-UVB.

Contraindications

UVB treatment is contraindicated in patients with a known history of lupus erythematosus or xeroderma pigmentosum. Caution should be exercised in patients with skin types I and II who tend to burn easily, patients with a history of arsenic intake (eg, Fowler solution) or previous treatment with ionizing radiation therapy (grenz ray or x-ray), those with a history of melanoma or multiple nonmelanoma skin cancers, and in any medical condition significant enough that the patient cannot tolerate heat or prolonged standing in the light box. Recommendations for the use of both BB-UVB and NB-UVB are shown in Table III. The strength of recommendations for the treatment of psoriasis using BB-UVB and NB-UVB are shown in Table IV.

TARGETED PHOTOTHERAPY

Although phototherapy has been previously used to treat localized lesions, this approach became more practical and available with the introduction of a 308-nm monochromatic xenon-chloride laser for

Table III. Recommendation for ultraviolet B (broadband and narrowband)

Indication:
- Generalized psoriasis (including guttate) unresponsive to topicals

Dosing:
- BB:
  - Initial dosing according to skin type (20-60 mJ/cm^2) or MED (50% of MED)
  - Subsequent dosage increase by 5-30 mJ/cm^2 or $\leq$25% of initial MED
  - Treatment 3-5×/wk
- NB:
  - Initial dosing according to skin type (130-400 mJ/cm^2) or MED (50% of MED)
  - Subsequent dosage increase by 15-65 mJ/cm^2 or $\leq$10% of initial MED
  - Treatment 3-5×/wk

Duration of treatment:
- BB:
  - Initial improvement often occurs within 4 wk of therapy
  - Single course is 20-25 treatments
  - Maintenance therapy may prolong remission
- NB:
  - Response observed at 8-10 treatments
  - Single course is 15-20 treatments
  - Maintenance therapy may prolong remission

Short-term results (clearance):
- BB:
  - Average of 20-25 treatments to induce clearance
- NB:
  - More effective than BB-UVB, clearance within 2 wk may be seen
  - Average of 15-20 treatments to achieve clearance

Long-term results (remission):
- BB:
  - Remission rate of 5% after 1 y
- NB:
  - Remission rate of 38% after 1 y

Contraindications:
- Patients with known lupus erythematosus or xeroderma pigmentosum

Caution should be exercised in:
- Patients with skin types I and II who tend to burn easily, those with history of arsenic intake or previous treatment with ionizing radiation therapy, those with history of melanoma or multiple nonmelanoma skin cancers and any medical condition that is severe enough that patient cannot tolerate heat or prolonged standing in light box

Toxicity:
- Acute:
  - Erythema
  - Pruritus
  - Burning
- Long term:
  - Photoaging, lentigines, telangiectasias
  - Theoretical risk of photocarcinogenesis
  - Advise use of protective goggles and genital shields during treatment

Drug interactions:
- Cautious use with other photosensitizing medications
- When used in conjunction with systemic retinoids, dose of both retinoids and UVB may need to be lowered

Baseline monitoring:
- Full body skin check before initiation of therapy

Ongoing monitoring:
- Regular full skin examination to monitor signs of photoaging, pigmentation, and cutaneous malignancies

Pregnancy:
- Generally considered safe (expert opinion)

Continued

Table III. Cont'd

Nursing:
Generally considered safe (expert opinion)
Pediatric use:
No adequate study; may be used with caution in individuals aged<18 y
Psoriatic arthritis:
No studies

BB, Broadband; *MED*, minimal erythema dose; *NB*, narrowband; *UV*, ultraviolet.

psoriasis in 1997.[87] Delivering a monochromatic and coherent beam of photons, excimer lasers selectively target affected lesions of psoriasis while leaving unaffected skin untreated. The chromophore for the excimer laser is cellular DNA.[88] Breakage of strands of DNA in T lymphocytes and expression of mitochondrial proteins related to cell death has been noted after exposure to the 308-nm laser.[89] After psoriatic lesions are exposed to 308-nm excimer light, there is T-cell depletion accompanied by decreased epidermal proliferation.[90] Although working on the same premise as NB-UVB, the excimer laser focuses directly on individual lesions of psoriasis and penetrates deeper into the skin where it may lead to apoptosis of reticular dermal T lymphocytes. The excimer laser has the advantage of treating only involved skin, therefore minimizing potential risks of exposing normal-appearing skin to UV radiation. The excimer laser is, therefore, not limited by the MED, which renders this mode of UV therapy more efficacious when supra-erythemogenic doses are used.

Efficacy

An early study to assess the efficacy of the 308-nm excimer laser used high-dose therapy, 8 to 16 times the MED.[91] In all, 11 of 16 patients had a greater than 75% improvement within 1 month. Even a single treatment with the excimer laser can have a beneficial effect.[92] Because high doses of UVB administered by the excimer laser led to blistering and burning in almost half of the patients, lower doses in the range of 1 to 3 MED were subsequently used and the dosage was adjusted according to response; a greater than 95% clearance was observed with an average of 10.6 treatment sessions.[93] In a multicenter open-label study of 124 patients with psoriasis treated with an initial dose of 3 MED, subsequent doses were adjusted according to clinical response. In all, 84% of the patients achieved more than 75% clearance after two treatment sessions; 72% cleared at an average of 6.2 treatments.[94] In another open-label study of 120 patients with psoriasis treated with an initial dose of 3 MED followed by an increase of 1 MED per session, two thirds of patients cleared more than 90% after 10 treatments whereas 85% of patients showed a Psoriasis Area and Severity Index 90 or greater after 13 sessions with an average treatment duration of 7.2 weeks.[95] In a study of 40 patients with psoriasis, an improvement of approximately 90% was noted in patients with macular psoriasis and 77% in plaque psoriasis in an average of 13.7 treatments.[96]

Although treatment with the 308-nm excimer laser can clear psoriasis, there is limited information on the duration of remission. One study suggests that the mean remission time is 3 to 4 months after cessation of therapy.[91-93] After a follow-up of 1 year, 26 of 28 patients had long-term improvement.[97] Efficacy of the excimer laser has been demonstrated in scalp psoriasis when combined with a blower device that displaces the hair interfering with the laser beam.[98-100] Palmoplantar psoriasis has also been treated with the excimer laser. In an open-label study of 54 patients with palmoplantar psoriasis, complete clearance was observed in 57% of patients; the average number of treatments required was 10 for palmar psoriasis, and 13 for plantar psoriasis.[101]

Dosage and scheduling

Evidence-based studies on the dosage and scheduling of excimer laser therapy are limited. The dose of energy delivered is guided by the patients' skin type and thickness of the plaque; further dosages are adjusted based on the response to therapy or development of side effects (Table V). Initially, most of the protocols for treatment with the 308-nm excimer laser were based on the MED, but more recently dosing according to the thickness of the plaque has become used (Table V). The frequency of treatment with the excimer laser is 2 to 3 times a week, with a minimum of 48 hours between treatments.

Toxicity

As excimer laser therapy is delivered directly to the affected areas by a handheld device with a spot

Table IV. Strength of recommendations for use of phototherapy and photochemotherapy

Agent	Strength of recommendation	Level of evidence	References
BB-UVB	C	III	8, 24–27, 31
NB-UVB	B	II	28–30, 52, 63
Combination of UVB and topical agents	B	II	55, 57, 58, 60, 61, 63–65
Combination of UVB and systemic agents	B	II	74–76, 78
Combination of UVB and biologics agents	B	II	84, 86
Combination of UVB and PUVA	C	III	82, 156, 157
Excimer laser	B	II	94, 95, 100, 101
Topical PUVA	B	II	107, 108
Oral PUVA	A	I	103, 104
Combination PUVA and topical agents	A	I	139, 141
Combination of PUVA and systemic agents	B	II	145, 146

BB, Broadband; *NB*, narrowband; *PUVA*, psoralen plus ultraviolet A; *UV*, ultraviolet.

size of 14 to 30 mm, adverse effects are limited to the area irradiated. These include erythema, burning, and hyperpigmentation.[93-95] Blisters are noted more often with the use of higher fluences.[91,92] The long-term safety of excimer laser therapy has not yet been fully established.

Pregnancy

Although the use of the excimer laser has not been studied in pregnant patients with psoriasis, its targeted nature suggests that the excimer laser is unlikely to have any teratogenic effects.

Pediatric use

Data regarding the use of the 308-nm excimer laser in children for psoriasis are limited but expert opinion is that it is safe.

Contraindications

Excimer laser therapy should be used with caution in patients with photosensitivity disorders. Recommendations for the treatment of psoriasis using the excimer laser are shown in Table VI. The strength of recommendations for the treatment of psoriasis using the excimer laser is shown in Table IV.

GRENZ RAY THERAPY

Grenz ray therapy has been used in the treatment of psoriasis for more than half a century. Although there are a limited number of studies and this therapy is now uncommonly used, grenz ray treatment may be an alternative to UV light therapy for localized, recalcitrant areas (eg, scalp and palms) in situations where UV light is not feasible or psoriasis is unresponsive to conventional treatments. It is imperative that only fully trained personnel conversant with all aspects of this therapy administer grenz rays using correctly calibrated machines and meticulous protection techniques with a lifetime exposure for patients no more than 50 Gray.

PUVA PHOTOCHEMOTHERAPY

"PUVA" is a term applied to a group of therapeutic techniques that use psoralens, a group of photosensitizing compounds, to sensitize cells to the effects of UVA light (320-400 nm). Psoralens are tricyclic furocoumarins that occur naturally in some plants and are also synthetically produced. Currently, the only available orally prescribed psoralen in the United States is 8-methoxypsoralen, whereas in Europe 5-methoxypsoralen is more commonly used because of its lower potential for phototoxicity. Trimethylpsoralen is used for bath water–delivered PUVA, which is largely used in Scandinavia. UVA irradiation has effects on epidermal keratinocytes and Langerhans cells (similar to UVB irradiation) but because it readily penetrates into the dermis, there are also effects on dermal dendritic cells, fibroblasts, endothelial cells, and mast cells as well as skin-infiltrating inflammatory cells including granulocytes and T lymphocytes.[102] Psoralen intercalates between DNA base pairs and, on exposure to UVA, forms psoralen DNA cross-links that prevent DNA replication. In addition, PUVA induces reactive oxygen species formation that leads to cell membrane and mitochondrial membrane damage and eventual death of antigen-presenting cells.[13]

Efficacy

The introduction of PUVA for the treatment of generalized psoriasis was a major advance and afforded the availability of an outpatient therapy for patients with severe disease who had often previously required hospitalization. Although there are many studies evaluating the efficacy of oral PUVA therapy, these trials have significant variations in the population studied, the dosage, frequency of

Table V. Dosing guidelines for targeted therapy

Initial dose for psoriasis				
Plaque thickness	**Induration score**	**Fitzpatrick skin type I-III (dose in mJ/cm^2)**		**Fitzpatrick skin type IV-VI (dose in mJ/cm^2)**
None	0			
Mild	1	500		400
Moderate	2	500		600
Severe	3	700		900
Dose for subsequent treatments				
No effect	Minimal effect	Good effect	Considerable improvement	Moderate/severe erythema (with or without blistering)
No erythema at 12-24 h and no plaque improvement	Slight erythema at 12-24 h but no significant improvement	Mild to moderate erythema response 12-24 h	Significant improvement with plaque thinning or reduced scaliness or pigmentation occurred	
Typical dosing change from prior treatment dose				
Increase dose by 25%	Increase dose by 15%	Maintain dose	Maintain dose or reduce dose by 15%	Reduce dose by 25% (treat around blistered area, do no treat blistered area until it heals or crust disappears)

XTRAC Treatment Guidelines (Xtrac Inc, Indianapolis, IN), 12-95359-01 Rev. A March 2007.

treatment, and criteria for success. There are two large, multicenter studies demonstrating the efficacy of PUVA in the treatment of psoriasis, one from Europe and one from the United States.[103,104] Although these studies used slightly differing protocols, both proved the efficacy of PUVA treatment. Although the European study used the minimal phototoxic dose to initiate therapy, the US study used the Fitzpatrick skin type to ascertain the initial dose. Incremental increases in dosage were fixed in the US study and were individualized based on skin response in the European study. Although 89% of patients in both studies achieved skin clearing, the US approach required more PUVA sessions spread over a longer time period and a higher cumulative UVA dosage than the European approach.[103,104] Two systematic reviews of the large majority of PUVA studies verified these efficacy findings demonstrating that between 70% and 100% of patients treated with PUVA achieved clearing of lesions.[105,106] PUVA treatment often leads to clearing of psoriasis within about 24 treatments with remissions lasting between 3 and 6 months.[105,106] After clearing, some patients may be treated with a maintenance regimen of one to two times per month, depending on the aggressiveness of the psoriasis. There is not consensus on the need for maintenance PUVA regimens as the data do not clearly demonstrate longer remissions in patients given maintenance compared with those who are not.

Topical PUVA therapy (direct application of psoralen to the skin combined with subsequent exposure to UVA) is another form of PUVA. Bath PUVA with trimethylpsoralen is commonly used in Scandinavian countries for generalized psoriasis to reduce systemic psoralen exposure and thereby minimize toxicities. Because of the lack of FDA approval for bath PUVA with trimethylpsoralen in the United States along with the high cost of establishing an efficient bath PUVA unit, this form of PUVA is rarely used in the United States. Several studies demonstrate that bath PUVA therapy is as effective as oral PUVA with bath PUVA therapy having a 2- to 6-fold lower cumulative UVA dose than oral PUVA.[107-110] Paint and soak PUVA are both commonly used for psoriasis localized to the palms and soles. For paint PUVA, 8-methoxypsoralen in an ointment or lotion form is painted directly on lesions; in soak PUVA, affected areas are immersed in a basin of water containing 8-methoxypsoralen. When using any form of topical PUVA, the UVA should be administered within 30 minutes after the psoralen is applied to the skin.

Dosing and administration

Oral PUVA with 8-methoxypsoralen should be administered 1.5 hours before exposure to UVA

Table VI. Recommendations for use of topical targeted phototherapy

Indications:
Adult and pediatric patients with mild, moderate, or severe psoriasis with <10% BSA involvement
Dosage:
Initial dose depends on individual's skin type (including formal MED testing), plaque characteristics, and thickness (500-900 mJ/cm^2 for XTRAC*)
Subsequent doses adjusted according to clinical response and/or side effects
Duration of treatment:
Dosing 2-3×/wk until patient is clear, usually average of 10-12 treatments are needed
Short-term results:
Initial response within 8-10 treatments; depends on multiple factors such as device used, protocol used, lesion characteristics, and site
Long-term results:
Mean remission times of 3.5-6 mo
Caution should be exercised:
In patients with photosensitivity disorders
Toxicity:
Erythema
Hyperpigmentation
Blistering, particularly with higher doses
Drug interactions:
May need to lower dosing based on presence of photosensitizing medications (note: action spectrum of most photosensitizing medications is in UVA range)
Baseline monitoring:
None
Ongoing monitoring:
For efficacy and for burning
Pregnancy:
No studies in pregnancy have been performed but expert opinion is that it is safe
Nursing:
No studies in nursing mothers have been performed but expert opinion is that it is safe
Pediatric use:
No large-scale studies in children have been performed but expert opinion is that it is safe
Psoriatic arthritis:
No studies

BSA, Body surface area; *MED*, minimal erythema dose; *UV*, ultraviolet.
*Manufactured by Xtrac Inc, Indianapolis, IN.

radiation (please see Table VII for dosing guidelines). Although it is preferred that patients avoid food for 1 hour before and 1 hour after dosing as food slows and diminishes absorption of 8-methoxypsoralen, sometimes as a result of nausea it becomes necessary to have a patient ingest food along with the dose of 8-methoxypsoralen. To minimize the variation in absorption of 8-methoxypsoralen, the type and amount of food ingested before 8-methoxypsoralen and the time interval between food ingestion and 8-methoxypsoralen administration should be kept consistent for a given patient. Starting dosages, incremental increases, and final clearing dosages are generally determined by the Fitzpatrick skin type (please see Table VIII for an example of a well-accepted, published guideline for dosing of oral PUVA). During the clearance phase, treatments are usually given 2 to 3 times weekly with at least 48 hours between treatments allowing sufficient time to assess for the degree of erythema induced by the previous dose. If there is no erythema, the UVA dosage should be increased at the next session, if there is transient erythema that clears before the next session the UVA dosage should be maintained and if there is persistent erythema from the previous treatment the next session should be cancelled unless the erythema is very minimal and can be protected with clothing or an opaque ointment.[111]

Toxicity

Common relatively minor acute toxicities of PUVA therapy include erythema, which peaks at 48 to 96 hours, pruritus, xerosis, irregular pigmentation, and gastrointestinal symptoms such as nausea and vomiting. Although these toxicities are common, most can be managed by altering the dosage of the psoralen or

Table VII. Dosing of 8-methoxypsoralen for oral psoralen plus ultraviolet A

Patient weight		
lb	kg	Drug dose, mg
< 66	<30	10
66-143	30-65	20
144-200	66-91	30
> 200	>91	40

Adapted with permission from Zanolli et al.[169]

Table VIII. Dosing of ultraviolet A radiation for oral psoralen plus ultraviolet A

Skin type	Initial dose, J/cm^2	Increments, J/cm^2	Maximum dose, J/cm^2
I	0.5	0.5	8
II	1.0	0.5	8
III	1.5	1.0	12
IV	2.0	1.0	12
V	2.5	1.5	20
VI	3.0	1.5	20

Adapted with permission from Zanolli et al.[169]

the UV light, the liberal use of emollients and antipruritic agents, and holding therapy when clinically indicated. Other acute toxicities may include blisters, photo-onycholysis, and melanonychia. Patients with gastrointestinal symptoms while being treated with oral PUVA may experience improvement by dividing their 8-methoxypsoralen dosage over 15 minutes or taking it with food, particularly milk. Hepatic toxicity from psoralens is uncommon. With long-term PUVA therapy, most patients develop photoaging, characterized by elastosis and poikiloderma. Some may develop hypertrichosis and dark brown to black macules known as PUVA lentigines.[103] Because psoralens bind to proteins in the lens, the potential for an increased incidence of cataract formation in patients treated with PUVA has been a concern with this therapy. Patients must be counseled to use eye protection during and for the remainder of the day after PUVA treatments. A 25-year prospective study of patients treated with PUVA from the large US cohort study did not demonstrate an increased risk of either visual impairment or cataract formation with increasing exposure to PUVA,[112] perhaps because practitioners have been careful to recommend eye protection. High cumulative exposure to oral PUVA is associated with a dose-related increase in the risk of nonmelanoma skin cancer, particularly SCC.[113-115] An increased risk of skin cancer with oral PUVA has not been demonstrated in the non-Caucasian population,[116] or those who have been treated with PUVA bath therapy.[116-118]

A meta-analysis of several PUVA trials revealed a 14-fold increased incidence of SCC in patients who received high-dose PUVA (>200 treatments or >2000 J/cm^2) compared with those who received low-dose PUVA (<100 treatments or <1000 J/cm^2).[119] The risk of SCC of the male genitalia is particularly elevated,[120] which is the genesis of the recommendation for shielding of this area during PUVA treatments. A history of treatment with PUVA also puts patients at significantly greater risk for the development of SCC if they are subsequently treated with cyclosporine. For example, the risk of SCC in patients with a history of PUVA and any use of cyclosporine is similar to the risk of SCC in patients with psoriasis who have received greater than 200 PUVA treatments.[121]

Whether exposure to oral PUVA increases the risk of developing melanoma is an area of controversy. Numerous studies of patients with psoriasis from Europe treated with PUVA have not shown an increased risk for developing melanoma.[122,123] However, one long-term US study of PUVA-treated patients found that after a latency period of 15 years, exposure to more than 200 PUVA treatments increases the risk of melanoma by 5-fold.[124] These results are in contrast to several other US studies that do not show an increased risk of melanoma in patients treated with PUVA.[125,126] The risk of melanoma in the US PUVA cohort is increased in patients who have been exposed to the highest dosages but these findings also have been the subject of debate and controversy.[127]

Pregnancy

Three small studies of women who received methoxsalen photochemotherapy at the time of conception or during pregnancy revealed the absence of any congenital anomalies among a total of 59 infants.[128-130] Although the rate of congenital malformations among 504 infants who were conceived and born after their mothers had received methoxsalen photochemotherapy was not higher than that found in the general population, there was an increased number of low-birthweight infants who were born to these women.[128] Oral psoralen carries a pregnancy category C rating.

In a topical PUVA study, psoralen was not detectable in the blood of patients with palmoplantar psoriasis who washed their topically applied psoralen off after use.[131] However, systemic levels may be detectable if psoralen is applied over a large body surface area.[132] There are no epidemiologic studies evaluating the incidence of congenital anomalies among infants born to women who received topical PUVA during pregnancy.

Pediatric use

Oral PUVA is uncommonly used to treat children with psoriasis. Because of the photocarcinogenicity of PUVA, its use in the pediatric age group should be undertaken with great caution. In the original US PUVA cohort study, 26 of 1380 patients were aged 15 years or younger at the time of their first treatment and 5 of these patients received greater than 200 PUVA treatments.[133] There is a single report of one of these patients developing two basal cell carcinomas at the age of 17 and 20 years.[133] Although bath PUVA is not FDA approved, it may be preferred when considering PUVA therapy for children because of the lowered systemic absorption, as beneficial effects have been seen in small numbers of children with psoriasis.[134]

Drug interactions

Drug interactions with PUVA therapy may occur when patients are concurrently being treated with other photosensitizing agents such as nonsteroidal anti-inflammatory drugs, diuretics, antifungals, neuroleptics, and certain antibiotics such as the tetracyclines and the fluoroquinolones.[135]

Combination of PUVA with other therapies

Because of the increased risk for developing cutaneous malignancies with PUVA, PUVA may be administered in combination with other medications such as retinoids or in rotation with other therapies to minimize the total dosage of PUVA.[136] It is not clear whether topical steroids combined with oral PUVA is a useful combination as one study found that the combination led to faster clearing without any shortening in the duration of remission whereas another study found that adding topical steroids results in shorter remissions.[137,138] The combination of topical calcipotriol cream or ointment with PUVA leads to a decrease in the duration of PUVA therapy along with an improved clinical response.[139-141] The combination of PUVA and tazarotene has been anecdotally reported to be synergistic.[142,143]

The combination of oral retinoids with PUVA is more effective compared with monotherapy with either acitretin or PUVA alone.[144-146] In addition to being synergistic, each of these therapies may reduce the potential side effects of the other. When adding an oral retinoid to a regimen of PUVA therapy both the number of PUVA treatments and the total amount of UVA exposure are decreased.[146,147] Because oral retinoids may suppress the development of nonmelanoma skin cancers,[148-151] their use in combination with PUVA, which increases the risk of nonmelanoma skin cancer, appears prudent. In fact, acitretin, when combined with PUVA therapy, is associated with a decreased incidence of SCC.[152] The optimal approach to combination therapy is to initiate treatment with an oral retinoid for approximately 2 weeks before adding PUVA treatment. Because of their teratogenicity, oral retinoids are contraindicated in women of childbearing potential.

Because patients who have previously received PUVA treatment have an increased risk for developing SCC when subsequently treated with cyclosporine,[121] this combination should be avoided. Although some studies suggests that the combination of PUVA and methotrexate is more effective than either therapy alone,[153,154] the safety of this combination has been questioned.[155] Small studies suggest that the combination of PUVA and BB-UVB,[82] NB-UVB,[156,157] or excimer laser[158] may lead to improved results within shorter periods of time. There are no studies evaluating the safety and efficacy of the combination of any biologic agents with PUVA.

Contraindications

PUVA treatment is contraindicated in patients with known lupus erythematosus, porphyria, or xeroderma pigmentosum. Caution should be exercised in patients with skin types I and II who tend to burn easily and patients with a history of arsenic intake (eg, Fowler solution) or previous treatment with ionizing radiation therapy (grenz ray or x-ray). In addition, those with a history of melanoma or multiple nonmelanoma skin cancers, any medical condition that is severe enough that the patient cannot tolerate heat or prolonged standing in the light box, severe liver disease that could lead to toxic levels of psoralens and pregnancy or nursing, or possibly patients who have been previously treated with cyclosporine or methotrexate should be approached with caution. As topical PUVA can be associated with significant toxicity if not correctly administered by fully trained personnel, patients need to be appropriately educated about the potential risks. Recommendations for the use of systemic and topical PUVA are shown in Tables IX and X. The strength of recommendations for the treatment of psoriasis using topical and systemic PUVA is shown in Table IV.

COMPARISON STUDIES

BB-UVB compared with NB-UVB

Several small, half body comparison studies have evaluated the efficacy of BB-UVB compared with NB-UVB therapy in the treatment of psoriasis and these small studies suggest that NB-UVB has improved efficacy when compared with BB-UVB therapy.[11,29,36,37,159] A randomized controlled trial of 100 patients demonstrated that NB-UVB was more likely to clear psoriasis compared with selective BB-UVB

Table IX. Recommendations for use of systemic psoralen plus ultraviolet A

Indications:
- Adults with generalized psoriasis who are resistant to topical therapy

Dosing:
- 8-Methoxypsoralen (Oxsoralen Ultra), 0.4-0.6 mg/kg, taken 1-2 h before exposure to UVA
- Other available forms of psoralen include 5-methoxypsoralen and trimethylpsoralen
- UV protective eye wear should be worn when outdoors for 12 h postingestion
- Treatment 2-3×/wk

Duration of treatment:
- Initial improvement frequently seen within 1 mo of therapy
- Single course is 20-25 treatments
- May be repeated as indicated

Short-term results:
- 89% Clearing with average of 25 treatments in US and 20 treatments in Europe
- 11.6 wk to Clear in US studies compared with 5.3 wk to clear in European studies

Long-term results:
- Once clearance has been achieved, maintenance treatment may or may not be used
- Remission times: 3-12 mo

Contraindications:
- Patients with known lupus erythematosus, porphyria, or xeroderma pigmentosum

Caution should be exercised:
- In patients with skin types I and II who tend to burn easily, those with history of arsenic intake or previous treatment with ionizing radiation therapy, those with history of melanoma or multiple nonmelanoma skin cancers, any medical condition that is severe enough that patient cannot tolerate heat or prolonged standing in light box, those with severe liver disease that could lead to toxic levels of psoralens, possibly those who have been treated with cyclosporine or methotrexate and patients who are pregnant or nursing

Toxicity:
- Acute:
  - Nausea and vomiting are common
  - Dizziness and headache are rare
  - Erythema: peaks at 48-96 h
  - Pruritus
  - Tanning: starts 1 wk after PUVA
  - Blisters, photo-onycholysis, melanonychia
- Chronic:
  - Photocarcinogenesis (SCC, BCC, and possible melanoma)
  - Increased risk of photocarcinogenesis in Caucasians with skin types I-III after 200 treatments; this risk not present for non-Caucasians
  - Photoaging and lentigines are common, especially in patients of skin types I-III and are cumulative UVA dose dependent

Drug interactions:
- Caution when patient is taking other photosensitizing medication
- Should decrease UVA dose by one-third if oral retinoids are started while patient is receiving PUVA

Baseline monitoring:
- Skin cancer screening
- Eye examination; however, recent evidence demonstrates no increased risk of cataract in patients who receive PUVA
- If indicated by history:
  - ANA panels (anti-Ro/La antibodies)
  - Liver enzymes

Ongoing monitoring:
- Regular full skin examination because of potential increased risk of photocarcinogenesis in Caucasians
- In patients who are noncompliant with eye protection, yearly eye examination

Pregnancy:
- Category C

Nursing:
- Contraindicated for period of 24 h after ingesting psoralen

Pediatric use:
- No studies; may be used with caution in individuals aged <18 y

Psoriatic arthritis:
- No studies

ANA, Antinuclear antibody; *BCC*, basal cell carcinoma; *PUVA*, psoralen plus ultraviolet A; *SCC*, squamous cell carcinoma; *UV*, ultraviolet.

Table X. Recommendations for use of topical psoralen plus ultraviolet A

Indications:
- Topical PUVA for adults with psoriasis of palms and soles
- Bath PUVA for adults and children with generalized psoriasis

Dosing:
- Topical
  - Use 0.1% 8-methoxypsoralen in emollient and treat 2-3×/wk
    - Apply 30 min before UVA
    - Start at 0.25-0.5 J/cm^2, increase by 0.25-0.5 J/cm^2
- Bath
  - 50 mg of 8-Methoxypsoralen (Oxsoralen Ultra) in 100 L of water
  - 20-30 min pre-exposure
  - Schedule similar to oral PUVA

Duration of treatment:
- May take 30 treatments to have noticeable response
- Single course usually is 30-40 treatments
- May be repeated as indicated

Short-term results:
- Clinically is beneficial

Long-term results:
- Once clearance has been achieved, maintenance treatment may be used
- Remission: 3-12 mo

Contraindications:
- Patients with known lupus erythematosus, porphyria, or xeroderma pigmentosum

Caution should be exercised:
- In patients with skin types I and II who tend to burn easily, those with history of arsenic intake or previous treatment with ionizing radiation therapy, those with history of melanoma or multiple nonmelanoma skin cancers and patients who are pregnant or nursing

Toxicity:
- Acute:
  - Erythema, blistering, hyperpigmentation
- Chronic:
  - No increased risk of skin cancer demonstrated

Drug interactions:
- None

Baseline monitoring:
- None

Ongoing monitoring:
- For efficacy and monitor for burning

Pregnancy:
- Category C

Nursing:
- No data available

Pediatric use:
- Safe provided patient can follow instructions; however, no systemic absorption studies have been performed

Psoriatic arthritis:
- No studies

PUVA, Psoralen plus ultraviolet A; *UV*, ultraviolet.

(56% vs 40%). Although this difference did not achieve statistical significance (P=.10), this study did not have enough statistical power to detect clinically meaningful differences in efficacy between NB-UVB and selective BB-UVB.[160] One potential limitation of studies comparing BB-UVB and NB-UVB is the possibility that one or both treatments are not being used in an optimized dosing schedule.

One study of 52 patients treated with NB-UVB found that 1 year after clearance, the remission rates of patients treated with NB-UVB were better than the remission rates of patients in another study treated with BB-UVB.[161] However, because this study used a historical control, it is difficult to draw any meaningful conclusions and further appropriately designed randomized studies comparing

the remission rates of NB-UVB and BB-UVB are needed.

NB-UVB compared with oral PUVA

Several small studies have suggested similar efficacies of NB-UVB and PUVA in the treatment of psoriasis.[162-164] Although one open study of 54 patients demonstrated similar rates of clearing for NB-UVB used twice weekly and oral 8-methoxypsoralen PUVA used twice weekly,[165] another open study of 100 patients demonstrated that oral 8-methoxypsoralen PUVA used twice weekly demonstrated better rates of clearing than NB-UVB used twice weekly.[166] A double-blind, randomized, single-center study that compared NB-UVB with PUVA for the treatment of 93 patients with psoriasis demonstrated that PUVA treatment achieves clearance in more patients with fewer treatment sessions than does NB-UVB and that PUVA results in longer remission times than does NB-UVB.[167] In regard to toxicities, one study evaluated the rates of acute toxicities with NB-UVB and PUVA in 3 neighboring phototherapy units in Wales, United Kingdom, and found low overall rates (0.6% for NB-UVB and 1.3% for oral PUVA).[168]

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Mark Lebwohl, MD: Dr Lebwohl served as consultant, receiving honoraria, for Abbott Laboratories, Actelion Clinical Research, Amgen/Wyeth, Stellas, Biogen, Centocor, Cerexa, Connetics, DermiPsor, Electro Optical Sciences, Galderma, Genentech, GlaxoSmithKline, Graceway, HelixBioMedix, Magen Biosciences, Medicis, NeoStrata, Novartis, Nycomed, Peplin, Pfizer, Pharmaderm, Ranbaxy, Roche, Sanofi-Aventis, Taro Triax, UCB, and Warner Chilcott. Members of Dr Lebwohl's department own patents on short-contact tazarotene, topical genistein, and use of the excimer laser for vitiligo. Member of Dr Lebwohl's department serve as investigators for numerous companies including: Abbott Labs, Actavis, Amgen, aRigen, Astellas, Basilea, Bioform, Celgene, Centocor, Dusa, Galderma, Genentech, Graceway, Longport, Lumenis, Medicis, Novartis, Novo Nordisk, Peplin, Pharmaderm, Provectus, Ranbaxy, Roche, Stiefel, and Wyeth. Dr Lebwohl is a course director for the annual Fall and Winter Clinical Dermatology Conferences and the annual Mount Sinai Winter Symposium, which receive support from numerous dermatology companies.

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