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Phototherapy arsenal in the treatment of psoriasis

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An essential method of treatment for psoriasis vulgaris in the twenty-first century will remain the option for UVB light therapy and photochemotherapy. During the last half of the twentieth century, the use of UVB therapy was one of the mainstays of treatment for psoriasis. During the last quarter century, photochemotherapy in the form of psoralen plus UVA (PUVA) emerged as one of the most effective modalities of treatment for psoriasis. Accompanying the advent of the most recent era of psoriasis with targeted biologic therapies has been a decline in the frequency of phototherapy. This does not diminish its known clinical effects and, because of a better understanding of photobiology, the therapeutic approach to treatment of psoriasis with UV light has a common basis for treatment of psoriasis along with and in combination with new biologic agents [1].

Individuals affected with psoriasis vulgaris know the natural effect of sunlight can improve psoriasis in most cases. This use of limited amounts of natural sunlight will continue as a practical approach to treatment of psoriasis for patients. Refinement of the delivery and methods for the most effective wavelengths of UV light in treating psoriasis will continue into the twenty-first century. This is evidenced by the continued prevalence of the availability of narrowband UVB, which has been recognized as more effective than broadband UVB, in addition to the devices that deliver the most effective range of UV light to the skin in a localized manner. The efficacy of PUVA for the treatment of psoriasis has not been surpassed by any other form of phototherapy. It still plays a significant role, especially in extensive resistant psoriasis, and can be used with precautions and limitation of total dose with excellent response. The long-term experience with the use of photochemotherapy has been important in helping to understand potential risks and side effects for that modality. It is similar to other psoriasis treatments in that caution must be used when PUVA and other forms of photochemotherapy are used.

Natural phototherapy

Natural sunlight for treatment of psoriasis has been used throughout the ages, even before the advent of Westernized medicine. It is common knowledge, evidenced by experience and observation, that a vacation to more southern latitudes or to areas of recreation, such as beaches, tends to help patients with psoriasis and in many cases contributes part of an annual practice to help clear up limited thin plaque-type psoriasis. The closer one is to the equator and the lower the latitude, there is more energy in the terrestrial light in UVB range. This is caused by the angle of incidence of the sun to the earth's surface.

As such, there are special geographic locations in the world today that further enhance the effects of UV light and are frequently used as a therapeutic approach to treatment. Specifically, the UV light that reaches the earth's surface at the Dead Sea, which is below sea level, is unique in its spectrum [2]. Because the Dead Sea is below sea level, the terrestrial light at this location has less of the 290 to 300 nm wavelengths of light. This slight shift in the spectrum more toward the mid range of UVB enhances the ability for a person to incur less sunburning and obtain more therapeutic UVB as it relates to treatment of psoriasis. This is very beneficial because of the known enhanced effects of wavelengths closer to

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310 to 315 nm. One can consider the Dead Sea to be more of a natural location for therapeutic UVB unique in the world. Use of this therapeutic spa and scientific investigations that have been ongoing for decades at the Dead Sea attest to this being a very special place to receive UV light in combination with the specialized salts found in the Dead Sea. The remissions obtained and the clearing percentage for persons attending the spa for 2 to 4 weeks has not been achieved at any other natural therapeutic resort for treatment of psoriasis.

Artificial UVB

A mainstay of therapy for psoriasis during the mid-portion of the twentieth century was the use of UVB produced by an artificial light source, either alone or in combination with other agents. The refinement of this modality of therapy using either a discontinuous spectrum from hot quartz lamps or the use of fluorescent tubes has gradually evolved and facilitated ease of use in an office-based setting. The current mainstay of therapy for office-based UV light is the fluorescent tube. The fluorescent tube has the benefit of ease of mass production and depending on the phosphor used to line the inner surface of the fluorescent tube, can also have more specific emissions spectrum. The broad-spectrum fluorescent tubes remain important and contain a relatively wide range of UV light. They contain higher-energy, lower-frequency UV light, and carry a greater potential for a sunburning-type reaction and erythemogenic response.

The availability of narrowband UVB on a commercial scale was made possible because of the specialized lamps produced by Phillips having the narrow spectrum between 300 and 313 nm. Because of their specialized use, however, the production of these lamps has not been a major emphasis by this company. The lamps have a relatively shorter working life of 500 to 1000 hours of operation as compared with the more durable broader-spectrum UVB lamps that can maintain fairly consistent output with thousands of hours. This fact requires that the narrowband UVB lamps be replaced more often because their fluence diminishes with less use as compared with broad-spectrum UVB lamps.

Traditional broadband UVB therapy

The use of conventional broadband UV light therapy is dependent on an induction phase during the initial response with thinning of the psoriatic plaques and then a variable duration of approximately 15 to 25 treatments before full therapeutic efficacy. The most efficient approach to treatment with any UVB protocol for the practitioner is first to determine the minimal erythema dose (MED), which is dependent on the response a person experiences to that particular light unit. The determination of the MED shows a dose response and allows for more precise and more aggressive therapy with UVB, which facilitates more rapid clearing and better final results.

Investigation comparing erythemogenic and suberythemogenic UVB delivery demonstrates that the more aggressive monotherapy with broadband UVB produces a quicker response rate and a better overall response. With that type of approach, however, patients may experience mild discomfort because of the pink erythema that is consistently produced by the advancement of therapy on a daily basis. Patients can improve while undergoing broadband UVB light therapy without having to incur the maximal MED on each visit [3]. It is customary to obtain a MED and proceed by starting at 70% to 75% MED and increasing by up to 50% of the MED each visit.

Aggressive treatment with UVB therapy is possible because the maximal erythema reaction of the effects of UVB on the skin is seen between 12 and 18 hours. Patients demonstrate the reaction on their return even if treatments are given on consecutive days. Such an aggressive treatment protocol customarily uses an average of 15 to 25 treatments during the course of therapy to achieve maximal benefit. Protocols and approaches to treatment may vary from region to region and a more simplified and slightly less aggressive approach to treatment for broadband UVB is set forth in Box 1.

Narrowband UVB

Narrowband UVB has finally achieved general recognition in North America as advancement in the further refinement of UV therapy for treatment of

Box 1. Broad band UVB protocol by Minimal Erythma Dose (MED)

1) Obtain MED using the following doses (mj/cm^2): 20, 40, 60, 80, 100, 120
2) Start at 70% of MED
3) Increase by 20% of MED each treatment
4) Treatment frequency of 3–5X/week

psoriasis. Before the availability of narrowband UVB in North America in 1998, Europeans had been using narrowband UVB with regularity and good success. The original reports reflecting the efficacy and preference of narrowband UVB emerged in the mid-1990s. Comparison trials with right- and left-sided controls on the same individual demonstrated that narrowband UVB is more effective than broadband UVB and eliminated the need to produce erythema at each visit [4–6].

Delivery of broadband UVB is best initiated with determination of the MED, as with any UVB treatment. This is especially important because the dosimetry between the broadband and narrowband is different and to be able to have a dosage measured in millijoule per square centimeter, one needs to have the proper photometers or accurate readings of the irradiance from the lamps themselves provided by the manufacturer. This information enables one to deliver incremental doses just below the range known to cause erythema for the Fitzpatrick's skin type determination of patients being treated. This is important because the more limited wavelengths of the narrowband spectrum emitted by these specialized fluorescent tubes require a much higher energy because of the absence of the more erythemogenic shorter wavelengths from 310 nm and below. The dosage range for the determination of MED by skin type is included in Box 2. There can certainly be production of erythema using narrowband UVB, and this is also on a reproducible dose response curve in an individual.

As with any erythema dose response within the UV range, the higher the skin type, the higher the average mean of the millijoule per square centimeter is needed to produce erythema. Each skin type has a broader range for MED with narrowband UVB than with broadband UVB, which further illustrates the importance of determining MED before initiation of a treatment protocol.

A series of experiments done in the 1990s to maximize therapeutic benefits of narrowband UVB shows therapy done three times weekly is essentially as effective as broadband UVB done five times per week and is certainly more convenient for the patient [7]. A more aggressive approach that maximizes the erythemogenic potential of narrowband UVB does not offer substantial benefit over trying to maximize the amount of erythema produced at each visit. The less aggressive approach is certainly preferred by the patients receiving treatment.

Box 2. Dose range for MED testing for narrow band UVB

- Six test sites of 1.5 cm^2 each
- For skin types I–III (mj/cm^2): 400, 600, 800, 1000, 1200, 1400
- For skin types IV–VI (mj/cm^2): 600, 800, 1000, 1200, 1400, 1600

Box 3. Narrow band UVB protocol by Minimal Erythma Dose (MED)

1) Obtain MED
2) Start at 50% of MED
3) Increase by 10% of MED each treatment
4) Treatment frequency of 3–4X/week

The use of lubricants that help transmit UV light on top of the skin's surface and decreases reflectance from the psoriatic scale is also considered standard therapy. The protocol for the use of narrowband UVB in an office-based setting is outlined in Box 3. There is some variability of the starting dose of narrowband UVB, either at a more conservative 50% or slightly more aggressive 70% of the MED. The onset of erythema following narrowband UVB occurs within 8 to 24 hours.

One of the practical advantages of using limited narrowband UVB wavelengths delivered to the skin surface is that phototoxic or photoallergic drug reactions do not occur as frequently as with the broader-spectrum broadband UV, and with UVA light used with photochemotherapy. There have been reports of photoallergic reactions in patients who are receiving narrowband UVB, but the occurrence of drug reactions while receiving narrowband UVB is uncommon.

Localized UVB

The traditional use of localized delivery of UV light for treatment of hands and feet has been facilitated by the availability of 2- to 3-ft fluorescent tubes with broadband wavelength. Similar systems are used for localized bath PUVA therapy with irradiation or systemic PUVA with irradiation of just the hands and feet. The use of UVB for hyperkeratotic thick plaques on the distal extremities has limited response, and combination therapy with a systemic retinoid is frequently used to enhance the efficacy of the treatments. There is more success with the use of systemic administration of psoralen with localized delivery of UVA to the hand and feet but this approach also is enhanced with addition of systemic retinoids to

decrease the thickness of the plaques before and during phototherapy.

The application of localized delivery of laser light near the optimal wavelength for maximal efficiency in the treatment of psoriasis led to clinical investigations regarding the excimer laser for treatment of psoriasis [8]. Because noninvolved skin is left unirradiated, this offers the opportunity to test for the optimal method of delivery and dose for treatment of psoriasis without involving the surrounding skin. Using multiples of the MED when treating psoriasis has been found to enhance the benefits and therapeutic response to laser light. The durability of the clearing was also correlated with the more aggressive treatment using 4x, 6x, and 8x multiples of the MED. As expected, using multiples of the MED produced very pronounced effects of marked erythema and blistering at the sites of delivery, although scarring at the sites was not observed. Another aspect of this approach to treatment is the reduction in the number of treatments needed to achieve the response [9]. Generally 8 to 10 treatments can attain clearing of plaques. Continued experience with this method of treatment using multiples of the MED with localized treatment makes it obvious that certain locations tolerate a higher dose of UV light, such as the knees and elbows. In those locations multiples of 6 to 8x MED should be used as compared with 4 to 6x MED on more sensitive non-UV hardened skin, such as the intertriginous skin or buttocks.

The same principles used with the laser-generated coherent light at 308 nm have been applied to the localized delivery of broader band UVB generated by a filamentous light source delivered through optics to a small spot target area. Less complicated technology using a high-intensity lamp as the light source has been developed and brought to the market for treatment of psoriasis and other photoresponsive dermatoses. The two main devices are being marketed through Lumenis and Theralight corporations. There are differences between the coherent light at 308 nm from the excimer laser and the range of the UVB delivered by the other localized delivery systems for UVB. Both light units have the same filamentous light source, but the Lumenis system, B Clear, transmits the light through a fiberoptic cable to a very functional handheld delivery, whereas the Theralight unit uses a liquid medium in a flexible cable to a cylindrical pencil-grip type handpiece. The Theralight system has the ability also to switch to a low-fluence UVA if localized PUVA is a consideration for therapy.

Basic principles of localized delivery of UVB are the same as with the excimer laser. First, an MED needs to be obtained; then, choices for the multiple of the MED to be used for the site to be treated are selected by the clinician. The actual setting on the device is very easy to determine on the Lumenis system, which gives a numerical reading of the actual dose to be delivered. The Theralight system requires reference to a chart to set the machine, but follows the same principles of the multiples of the MED. Once a phototherapist becomes accustomed to the use of any of the devices the actual operation becomes routine.

Photochemotherapy

The development of photochemotherapy for treatment of psoriasis comprises a major advance in therapy and efficacy of treatments for psoriasis worldwide. For centuries it was known that agents with photosensitizing compounds in the class of psoralen drugs could be used for treating vitiligo and other skin disorders. The discovery, however, that the ingestion of certain psoralen molecules when combined with UV light has dramatic effects on psoriasis improved the effective available treatments further. These advances were championed primarily in the United States by Fitzpatrick and Parrish but also were recognized by European colleagues who developed the use and protocols for delivery of PUVA [10]. This therapy generated intense clinical research during the late 1960s and early 1970s.

One reason that photochemotherapy is so important is that the duration of remission following clearing with PUVA is more durable than with UVB light. Refinements of photochemotherapy and improvements in the bioavailability of the chemical after ingestion help make this therapy one of the standard treatment options in the arsenal for treatment of psoriasis. Specifically in North America, 8-methoxypsoralen has been the psoralen used for PUVA therapy. In Europe this has also been a mainstay but there has been more use in the recent decade of 5-methoxypsoralen, which has therapeutic efficacy and fewer gastrointestinal side effects [11].

As with the acceptance of UVB therapy for treatment of psoriasis, the adoption and development of photochemotherapy occurred because of the observed beneficial therapeutic effect on people with psoriasis. The exact mechanisms of the psoralen molecule as it relates to treatment of psoriasis have not been entirely clear. In fact, further insights are gained into the mechanism of action for both UV light and photochemotherapy because of a better understanding of the pathogenesis of psoriasis. The known effects of photochemotherapy are dependent on both the availability of the psoralen molecule at the site of action

and stimulation by wavelengths of UV light within its absorption peaks. It is known that the psoralen molecule intercalates between DNA base pairs through a concentration gradient. There is no biochemical interaction between the psoralen molecule and DNA itself without activation or absorption of photons of UV light. If there is absorption of photons of UV light there is a photochemical reaction with the psoralen molecule and a pyrimidine base and DNA cross-links can occur. For a true cyclobutane ring to form another photochemical reaction must occur. If a cross-link does form, this is one of the theoretical reasons for increased development of squamous cell carcinomas with repetitive therapy over years.

A second mechanism of action of PUVA therapy on inflammatory skin disorders is oxygen-dependent photochemical reactions (ie, reactive oxygen species are formed when the psoralen molecule absorbs photons in the presence of oxygen). This type of oxygen-dependent reaction causes membrane and cell damage and may be central to the observable effects of UV light on the skin. It seems that antigen-presenting cells and T lymphocytes are more susceptible to these oxygen-dependent reactions than keratinocytes, and the underlying mechanism of action of psoriasis photochemotherapy may be inhibition of immune activation and immune recruitment of additional T cells into the skin [12].

Taking this one step further one could speculate that long-term remissions induced by PUVA may be caused by depopulating the epidermis of antigen-presenting cells, natural killer T cells, and cutaneous lymphocyte antigen (CLA)-positive lymphocytes. These effects decrease the recruitment of additional cells and reduce the stimulus for the ongoing psoriasis reaction instead of just interfering with the activation of lymphocytes or cytokine messaging. A short-term remission is expected if message interference occurred. A long-term remission is expected if the cells stimulating the reaction of T lymphocytes and immune competent cells in the epidermis and dermis are reduced in number or eliminated.

The use of PUVA gained more widespread availability throughout the last quarter of the twentieth century in North America. It is still a vital tool in therapy, but the availability of PUVA has declined over the past decade for two main reasons. First, other therapies have become available that are potent and modify the immune system. Examples are the known effect of the cyclosporine class of drugs and more recently the biologic protein medications that show efficacy without the need for specialized equipment and specialized personnel. The second reason is the 30 years of experience with PUVA and the known increased risk of squamous cell carcinoma that occurs especially in fair-skinned individuals with greater than 250 treatments over time [13]. There have been reports also of increased risk of melanoma in this special population by following over three decades a cohort of patients registered in North America [14]. This group of patients has confounding factors, such as other treatments for psoriasis including systemic immunosuppressive therapy and the fact that the early protocols for PUVA used high-dose PUVA, which is not done to such a degree today. Nonetheless, now that these important observations and statistical analysis of a specialized group of patients have been done, clinicians are better able to use this tool in a way that is safer and with parameters that help ensure the overall well-being of patients. Precautions and limitations of the use of PUVA over time are listed in Box 4.

The delivery of PUVA is more complicated than UVB therapy even though both must have ocular protection to prevent corneal burns in the case of UVB and lens and retinal changes more specifically with the use of PUVA. PUVA requires additional protection from any other sources of UVA light for 18 to 24 hours following treatment. In my opinion, PUVA has been a great success story in preventive medicine over time because of the awareness of the potential for ocular side effects and the institution of standardized protocols and mechanisms for proper eye protection following a treatment.

A manageable but frequent side effect of psoralen is caused by the nausea that the psoralen compound commonly produces especially with the use of 8-methoxypsoralen. There is a dose-response relationship with the degree of nausea that occurs and peak blood levels of the psoralen compound that occasionally is so pronounced that patients withdraw from therapy. Management of the nausea is to take the psoralen exactly the same way at the same time of day, preferably in the afternoon, and to have a small bit of food with the psoralen dose [15]. A slight reduction in the dose can also be attempted; however,

Box 4. Precautions in selection of PUVA patients

- Skin types I and II
- Previous history of skin cancer
- Previous or current immunosuppressive therapy
- Cumulative number of previous PUVA treatment >200

Box 5. PUVA protocol by skin type

1) Dose of 8-MOP = 0.5 mg/kg
2) Ingest psoralen 1.5 hours prior to treatment
3) Take psoralen at same time of day with liquid
4) If nausea take psoralen with some food
5) Dose of UVA
   Skin type I–III Initial = 2 J/cm^2
   Skin type IV–VI Initial = 4 J/cm^2
   Increase by 1 J/cm^2 each treatment
6) Frequency of treatments 3X/week

care must be taken not to reduce the dose below the therapeutic range.

There is variability from person to person in the gastrointestinal absorption of the psoralen molecule. The range for dosing and the timing of dosing should remain constant for each individual throughout their particular course of therapy. Although protocols vary between regions of the country and between continents, one of the standard protocols is included in Box 5. Different psoralen molecules have been used in Europe primarily to reduce the gastrointestinal side effects while maintaining efficacy. The most widely used psoralen molecule besides 8-methoxypsoralen is 5-methoxypsoralen. It still has potential to form cyclobutane rings and with excessive long-term use is also expected to increase the risk of squamous cell carcinoma. The efficacy of 5-methoxypsoralen is approximately that of 8-methoxypsoralen, however, with much fewer complaints of gastrointestinal side effects [16]. The 5-methoxypsoralen is not available in the United States as a commercial product, however, and requires clinical trials to demonstrate its efficacy before approval by the Food and Drug Administration.

Combination therapy

Phototherapy historically has been used, especially in this modern era, in combination with both topical and systemic agents. In fact, it is unusual not to have some sort of combination therapy in the form of concomitant topical agents while the patient is undergoing induction and treatment with either UVB modalities or PUVA. There are myriad combinations that have been used, with some known to enhance the therapeutic effect while reducing the dose and total number of treatments required for response. This section highlights the best and most common combination therapies to use with phototherapy and specifies important nuances in understanding the maximum benefit and the most efficient delivery of the combinations.

Topical agents plus phototherapy

Patients must understand that certain topical agents used with phototherapy may either inhibit the effects of the UV light by blocking UV light at the surface of the skin and not allowing it to penetrate to the proper site of action or inactivate the drug through absorption of UV light. Topical steroids are still the most common treatment for mild plaque-type psoriasis and can be used safely in combination with phototherapy. Although there might be some initial reduction in the thickness and a more rapid initial response for plaque-type psoriasis, continued use of the topical steroids throughout the course of a full therapeutic regimen with UVB does not necessarily add much long-term benefit. When superpotent topical corticosteroids are used, a regimen of using the initial treatment for induction followed by tapering and discontinuation of topical steroids should be used. This is the most effective approach to combination treatment and seems to have the best initial benefit.

Calcipotriene with both UVB and PUVA therapy has also been used. Calcipotriene can enhance phototherapy; however, certain precautions must be taken to ensure that their combined use does not inhibit or alter the calcipotriene molecule. Specifically, if calcipotriene is applied immediately before UV light therapy, inactivation of the molecule may result. To realize the enhanced effect of this topical combination with phototherapy, one should deliver the UV light treatment first and then use the topical agent later that day or at least 2 hours before treatment [17]. This helps ensure the modest benefit that might be obtained with this combination therapy. Topical formulations of retinoids have also been used to help enhance the effects of UV therapy [18]. As with the vitamin D derivatives, application should not immediately precede the delivery of the UV light. Caution should be used when advancing the dose of UVB or PUVA in this circumstance because of the retinoid effect on the plaques of psoriasis.

Systemic retinoids plus UV therapy

The best combination therapy with UV light, whether UVB or PUVA, is with systemic retinoids

[19]. Various systemic retinoids are used in combination with UV light therapy, and numerous studies have demonstrated their positive effects. The treatment rationale for combining retinoids with UV light is to enable reduction of the total energy delivered to the skin and enhance the therapeutic regimen by decreasing the total number of treatments needed.

The approach to such treatment is to initiate therapy with the retinoid for at least 7 to 14 days to establish the retinoid effect on the skin and its modification of psoriatic plaques. The observed effect of retinoids on plaque-type psoriasis is to reduce the thickness of the plaque and help reduce scaling through their inherent mechanisms of helping to normalize differentiation of the keratinocytes. The exact effect of retinoids relates to cellular differentiation through impact on retinoid receptors, both local and circulating. Retinoids probably also have an effect on the immune mechanisms involved with psoriasis. This cumulative effect of the retinoids helps to decrease the thickness of the plaques and the scaling, allowing the UV therapy to be more effective and encounter less blocking and scattering of light at the skin surface. The retinoid effect increases susceptibility to erythema from UVB and makes one more prone to phototoxic effects from PUVA. It is not a direct effect from UV light on the retinoid molecule itself that produces the increased susceptibility to UV treatment. It is the effect on the skin, primarily the epidermis, which enhances the UV light combination.

When using a systemic retinoid 2 weeks before initiation of UV therapy, caution must be used during the initiation and induction period of phototherapy. This is another incidence in which determining the MED before UVB therapy, whether broadband UVB or narrowband UVB, is very helpful because using only skin type to determine the dose is not as accurate, and a starting point has to be estimated without any objective measurement. The dose of the retinoid can be reduced when combined with phototherapy as compared with the dose of retinoid if used only as a monotherapy. A simplified modification of the dosage of retinoid when used in combination with UVB or PUVA is contained in Box 6. Caution must be applied when considering adding a retinoid to a UV treatment program if a patient has already received multiple doses of UV light. The tolerance to UV, whether UVB or PUVA, is decreased within 1 week of introduction of the retinoid and unexpected phototoxic reactions may occur even without increase in the dose of UV light. If a retinoid is to be introduced to an ongoing protocol for phototherapy it is recommended the dose of the UV light be reduced by 50% at the start of retinoid therapy and kept at that level for 2 weeks before increasing the dose of UV light.

Box 6. Retinoids and UV therapy

- Dose of Acitretin and UVB or PUVA 10 or 25 mg/day
- Use the retinoid two weeks prior to initiation of UV therapy
- Obtain MED with UVB treatments
- Select a lower skin type determination when using PUVA
- Adding acitretin to an ongoing phototherapy treatment
  Reduce the dose of UV light therapy by 50%
  Keep the dose of the UV the same for six treatments

Various individual retinoid molecules have been used in combination with phototherapy. Currently, the most used retinoid is acitretin [20–22]. The basic principles for the use of retinoids in conjunction with phototherapy have been applied to the combination of acitretin plus narrowband UVB, although there are no studies that have actually been performed in a prospective manner.

Thirteen-*cis*-retinoic acid (Accutane) can also be used in combination with phototherapy, but requires adhering to the general precautions needed for all the retinoids and their use. This is especially true with regard to informed consent and the special precautions necessary for avoidance of pregnancy. There may be times when 13-*cis*-retinoic acid is preferred over acitretin because of the problems with long-term bioavailability of acitretin metabolites when combined with alcohol. With even minimal ethanol consumption a potential for long-term fat storage of the teratogenic metabolite occurs, which requires prolonged years of strict adherence to contraception.

Other systemic agents and UV therapy

There are other systemic agents that have been tried and used with phototherapy. Particular features of some of the more common systemic agents deserve mention when used in combination. Methotrexate has frequently been used in combination treatment for psoriasis [23,24]. Short-term UV light therapy may be particularly helpful in aborting psoriasis flares, which can then be brought under control with long-term use of methotrexate with appropriate monitoring. Methotrexate by itself does not inhibit the

efficacy of UV treatments. In fact, if methotrexate is used before UV light, some of the same plaque-thinning benefits realized by retinoids can occur, helping with the induction of UV light response. It is more common, however, to have UV light used as an adjunct to long-term methotrexate treatments. Early studies show that the combination can be very helpful with application of routine broadband UVB. One must prevent a generalized phototoxic reaction with excessive UV light therapy during the course of treatment. This is true whether a therapeutic use of UV light is used or a patient sustains a sunburn reaction from natural sunlight. This situation can provoke what is known as a "recall reaction" with methotrexate and normal doses of light subsequent to the burn. Although it is an infrequent and unexpected side effect, if the recall reaction occurs, it may be as a result of normal doses of therapeutic UV light.

The combination of methotrexate and PUVA has also been used. This alternative is not considered a very common treatment choice because of the increased incidence of squamous cell carcinoma known to occur with long-term PUVA therapy with the additional relative immunosuppression of methotrexate. Short-term it can be used with caution for very resistant cases having significant plaque-type psoriasis. This is another instance in which methotrexate can be used during the pretreatment phase and then tapered before induction with PUVA. The appropriate procedure is to limit methotrexate use to the 1 or 2 months before induction and maintenance with PUVA.

Another conventional therapy used for resistant plaque-type psoriasis is cyclosporine. Combination therapies with cyclosporine should be used very cautiously because the particular combination of cyclosporine and PUVA therapy, if used long-term, leads to increased risk of squamous cell carcinoma over and above the risk inherent in PUVA itself [25]. Whether broadband or narrowband, UVB combination therapy with cyclosporine generally should not be used in the long-term. If there are resistant plaques, possibly just a short-term course of UV light therapy should be considered. Of particular concern here is historical use of PUVA, especially in patients who had long-term maintenance with PUVA therapy before the advent of the use of cyclosporine. In this instance, even use of cyclosporine post-PUVA carries increased risk of developing or facilitating squamous cell carcinomas years posttherapy as demonstrated by the results of long-term follow-up of the PUVA cohort. Patients having a history of years of PUVA treatment should be considered to have a relative contraindication for any follow-up with cyclosporine.

Biologics in combination with UV light

Over the next 2 to 5 years more information about use of biologic agents with UV light therapy, particularly narrowband UVB, will be available. The regulations regarding phase 2 and phase 3 clinical trials require that phototherapy be excluded as concomitant therapy during the clinical trials determining the dosage, frequency, efficacy, and safety of the biologic agents that have become part of treatment for psoriasis over the last 2 years. Small pilot studies are now starting to appear concerning UV combination treatments with alefacept and etanercept. These initial reports are few and do not define the nuances of phototherapy, which may be important for the most effective and efficient delivery of UVB therapy. The important factors are whether or not there is change in the MED with concomitant use of the biologic treatment and if there is any actual significant enhancement of effect in conjunction with UVB therapy. The general principles underlying combination therapy with UV therapy are to decrease the total dose of millijoule per square centimeter for an individual and to decrease the total number of treatments needed to obtain the desired effect. Subsequent trials will provide further insights concerning these issues.

Theoretically, there could be great advantage to the combination therapy with biologics and UV light. The biologics may have actions that vary from inhibiting circulating T cells from entering the dermis, such as with efalizumab, or decreasing circulating CD4 lymphocytes, as with alefacept. The use of narrowband UVB could compliment these effects through known mechanisms of decreasing CD3 lymphocytes in the epidermis [26], thereby having potential for attacking the cutaneous immune system from the surface of the skin while the biologic agents act on cells in the circulating CLA, $CD45RO^{+}$ lymphocyte pool. Although the frequency of office-based UV light treatment has diminished over the past 5 years in North America there is great potential for short-term intermittent combination therapy for patients who may be on long-term therapy with one of the new biologic agents.

Summary

Ultraviolet light has been the most used and effective treatment of psoriasis over the centuries. The beneficial effects of natural sunlight for clearing of psoriasis on the exposed skin do not depend on technology or insight into the known pathogenesis of the disease. In fact, an understanding of the patho-

genesis was not necessary to recommend one of the traditionally effective treatments of psoriasis with long-term remissions, as was done with the Goeckerman therapy for psoriasis in the mid portion of the twentieth century. Even the current advancements in therapeutics enjoyed today with the advent of the biologics and other immunomodulating systemic agents do not surpass the overall response rate and duration of remission of the previous standard of therapy that was had in the 1950s. Refinements in the delivery of UVB light, the development of photochemotherapy with PUVA, and the more recent focusing of the spectrum of UVB to the most effective region between 310 and 313 nm for narrowband UVB have given clinicians additional options in the arsenal of therapeutics to attack psoriasis. Further refinements of the delivery systems for UVB in the form of lasers and localized delivery through fiberoptics are beneficial in helping to reduce the overall exposure of noninvolved skin and permitting more aggressive doses of UV to the sites of disease while sparing noninvolved skin.

Enhancement of the different modalities of UVB and PUVA has been demonstrated with systemic agents, such as retinoids, but also in combination with immunosuppressive agents for short-term treatment to hasten the initial response to treatment. The advent of the biologic agents in treating psoriasis also introduced the opportunity for combination therapy and the theoretical advantage of managing T cells and antigen-presenting cells in the epidermis with UV light, and activated T cells in the circulation.

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