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REVIEW

Treatment of Childhood Psoriasis with Phototherapy and Photochemotherapy

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Abstract: Phototherapy and photochemotherapy are well-described treatment modalities for psoriasis in adults. Like many other treatments, the experience and long-term safety of their use in children is limited. We conducted a literature search and identified publications reporting the use of phototherapy and photochemotherapy in pediatric populations. This article summarizes the existing literature on this topic. Although many studies report good improvement with these treatment modalities, long-term safety data on their use is lacking for pediatric patients.

Keywords: psoriasis, children, phototherapy, photochemotherapy

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Introduction

Psoriasis is a multifactorial inherited papulosquamous disorder common in pediatrics. It has been estimated that psoriasis affects 1% to 3% of the general population,[1,2] and although its true prevalence in pediatric patients remains to be established, it represents about 4% of all dermatoses in patients less than 16 years of age.[3] Recent data has also shown that prevalence rates increase linearly from 0.2% at the age of 1 year to 1.2% at the age of 18 years.[4] This same study also reported a total rate of psoriasis of 0.71% in patients younger than 18 years, making it a frequent consult in pediatrics, particularly in older pediatric patients.[4] Psoriasis has also been shown to adversely affect quality of life for children.[5]

A step-wise therapeutic approach is generally used in patients with psoriasis. Many patients, especially those with limited disease, respond to topical treatments like steroids or vitamin D derivatives. In moderate and severe cases, topical medications are often insufficient to control the disease. Furthermore, topical medications may be difficult and unsafe to apply over large surface areas. It is in these situations when other treatment modalities such as systemic immunomodulators, biologics, phototherapy, or photochemotherapy may be considered.[6,7]

Very few clinical studies have been carried out in pediatric psoriasis patients and there is a lack of clinical trial data to guide therapeutic decisions in this patient population. Phototherapy and photochemotherapy have traditionally played important roles in the treatment of moderate to severe psoriasis in the pediatric patient, but even this treatment modality has not been well studied. This article reviews the evidence and use of phototherapy and photochemotherapy as treatment options for psoriasis in the pediatric population.

Clinical Findings

The pathogenesis of psoriasis has not been fully elucidated, but its multifactorial nature is widely accepted.[8] It is known that psoriasis is a chronic disease, which is immunologically mediated and leads to inflammatory skin lesions. Immunologic and environmental factors in a genetically predisposed host appear to be main factors that lead to psoriasis.[9] Evidence also suggests that triggers such as streptococcus infections, cold, stress and certain drugs (eg, systemic corticosteriods) may either precipitate or worsen the disease in children.[10,11]

At the skin level, a hyperproliferation and altered differentiation of epidermal keratinocytes, in addition to inflammation of the epidermis and dermis, are typical findings for this condition and account for the clinical skin findings.[8]

Pediatric psoriasis patients will often present similarly to adult psoriasis patients. The disease in children, however, is more pruritic and the lesions are thinner, softer and less scaly in comparison to adults. Clinical variants such as erythroderma, arthropathy and localized and generalized pustular psoriasis are rare.[8] Facial psoriasis is also more commonly characteristic of pediatric psoriasis, unlike adult psoriasis. However, clinical findings in the pediatric population may evolve with time. Plaque psoriasis has been reported as the most frequent form of psoriasis in children, followed by psoriatic diaper rash with dissemination, scalp psoriasis, anogenital disease and guttate psoriasis.[12] Other less frequent presentations in children include nail psoriasis and pustular psoriasis. Pediatric psoriasis is associated with other co-morbidities such as allergic contact dermatitis, eczema, vitiligo and alopecia areata.[8]

Understanding Phototherapy and Photochemotherapy

Radiation within the ultraviolet (UV) spectrum can be divided by wavelength into UVA (320–440 nm), UVB (290–320 nm) and UVC (200–290 nm). UVA can further be divided into UVA-I (340–400 nm) and UVA-II (320–340 nm). The term narrow-band UVB refers to UVB light with a wavelength of 311–313 nm.[13]

All of UVC and about 90% of UVB are naturally absorbed by the earth's atmosphere, so the UV radiation that reaches earth is mostly UVA (95%). The amount of energy produced by ultraviolet radiation is inversely proportional to its wavelength. This means that the shorter the wavelength, the more energy it possesses. UVB possesses more energy than UVA but UVA, by virtue of its longer wavelength, penetrates both the epidermis and dermis, while UVB only reaches the epidermis.[14]

Phototherapy is defined as the use of UV radiation in the treatment of skin disease.[13] Photochemotherapy, on the other hand, uses a combination of a photosensitizer,

such as psoralens, and ultraviolet radiation. Psoralens are furocoumarins that have UV absorbance. There are several available psoralens: 8-methoxypsoralen, 5-methoxypsoralen and 4,5,8-trimethoxypsoralen. These psoralens can be used orally or topically as ointments, creams, lotions and baths. Topical or bath psoralens have the advantage of less gastrointestinal side effects.[14] The photosensitization with topical psoralens also typically persists for a much shorter period of time than oral psoralens.

Xenon chloride gas excimer has more recently become available as a source of delivery of light therapy. The xenon chloride gas excimer delivers larger fluences of UVB light (308 nm) that can be used on limited cutaneous lesions, decreasing the body surface area exposed to ultraviolet radiation. This theoretically decreases the carcinogenic potential of phototherapy. There are 2 delivery systems for this type of light, which include laser technology (excimer laser) and non-laser technology (excimer light).[15]

Mechanism of Action, Metabolism zand Pharmacokinetic Profile of Phototherapy

Phototherapy has anti-inflammatory, anti-proliferative and immunosuppressant properties and its therapeutic success is likely due to a combination of these roles. Light has been shown to induce a shift from a T cell helper 1 (Th1) to a T cell helper 2 (Th2) immunologic response. It induces lymphocyte apoptosis and decreases the secretion of IL-10 and suppresses Interleukine 17 (IL-17) and Interleukine 23 (IL-23) pathways.[16] Specifically relevant in psoriasis, NB-UVB has been shown to inhibit T cell helper 17 (Th17), known to play a role in the pathogenesis of this condition.[17] It has been shown that NB-UVB inhibits the local innate inflammatory response to double-stranded ribonucleic acid (RNA) that has increased expression and activity in psoriasis lesions and is thought to play a role in maintenance of psoriatic inflammation.[18]

Another immunomodulatory effect of light therapy is inhibition of antigen-presenting cells, leading to decreased antigen presentation. It also leads to the induction of regulatory T cells. Light increases the expression of immunosuppressive cis-uroeanic acid in the skin, which leads to suppression of the cellular immune response and inhibition of antigen presenting function of Langerhans cells.[14,19]

Anti-proliferative effects that have been attributed to phototherapy include inhibition of epidermal proliferation, apoptosis of keratinocytes and apoptosis of pathogenically-relevant cells. It has been shown that apoptosis that takes place in lesional epidermis primarily takes place in keratinocytes, making light therapy particularly useful in psoriasis.[20] NB-UVB has been shown to re-induce production of GATA 3, which is a transcription factor identified to be significantly downregulated in psoriatic skin. GATA 3 serves as a switch in both epidermal and T helper cell differentiation and plays a key role in keratinocyte hyperproliferation and skin barrier dysfunction.[21]

Light therapy enhances melanocyte proliferation, making it clinically relevant for conditions such as vitiligo. It has also been shown to decrease release of histamine from basophils and mast cells, which makes it useful in the treatment of atopic dermatitis and urticaria pigmentosa.[19]

A recent publication presented data on 18 patients with psoriasis, 18 patients with atopic dermatitis, and 15 healthy individuals showed that NB-UVB increased vitamin D levels and improved skin lesions.[22] They also found that NB-UVB increased cathelicidin and decreased human beta-defensin expression; both antimicrobial peptides were regulated by vitamin D, and were thought to be increased in psoriatic skin.[22,23]

When light is combined with psoralens, the psoralens photoconjugate to the DNA and subsequently suppress DNA synthesis and cell proliferation. The addition of psoralen also generates reactive oxygen species that cause mitochondrial dysfunction and lead to apoptosis of Langerhans cells, keratinocytes and lymphocytes, leading to the control of skin disease.[14]

Clinical Studies

Several studies have been published reporting the use of phototherapy in pediatric psoriasis. Most publications have been on the use of narrow band UVB (NB-UVB), but there are a few reports on the use of broad band UVB (BB-UVB) and Psoralen + UVA (PUVA).

The latest article on this topic gathers the largest group of pediatric patients treated with NB-UVB. Pavlovsky et al present 88 patients with psoriasis, with a mean age 12 ± 4 years. These patients were treated for 3.1 ± 2.26 months and received a mean cumulative dose of 46.5 J/cm^2. They describe a partial response (<75% improvement) in 6 patients (8%), a good

response (at least 75% improvement) in 33 patients (41%) and clearance in 40 patients (51%). Overall, 92% of children with psoriasis in this study improved more than 75% with NB-UVB.[24]

Another recent article by Zamberk et al[25] reports on data regarding the use of NB-UVB in pediatric psoriasis. They describe results in 20 pediatric patients, with a mean age 13 years (range 5–17). These patients presented mostly plaque psoriasis (80%) and the remaining had guttate psoriasis (20%). More than 90% improvement in their PASI scores was seen in 52.17% of patients and 70% presented remission in approximately 8 months.

Another publication regarding phototherapy use in children reported 116 children that received NB-UVB.[26] The mean age of these patients was 11 years (range 2.6–15.9) and the majority of the patients had Fitzpatrick skin phototype II. They divided the patients into responders and non-responders, and found that patients with psoriasis responded better than those with atopic dermatitis. Out of this cohort, 38 patients (33%) had a diagnosis of psoriasis. These patients received a mean of treatments of 27.8 (range 4–76), a mean cumulative dose of 20370 mJ/cm^2, and a mean maximum dose per treatment of 1388 mJ/cm^2. There was a 90% response to treatment (response was defined as more than 75% improvement or clearance).

Ersoy-Evans et al[27] reported their experience with NB-UVB in children. They presented 28 patients with psoriasis, with a mean age 12 ± 2.5 years, and 26 of them (92.9%) improved by more than 75%. They found that patients with plaque type psoriasis required more treatment sessions compared to those with guttate type (mean number of treatments of 36 for plaque type versus 16 for guttate type).

2 other publications, 1 by Jain et al[28] and another by Jury et al[29] also presented data on the use of NB-UVB. Jain et al presented 20 patients with psoriasis that had more than 20% BSA involvement. All these patients had skin type IV and age ranged from 6 to 14 years. They used NB-UVB twice weekly in non-consecutive days with an initial dose of 50 mJ and increments of 10% at each session. They found that at the end of 12 weeks, 12 (60%) patients showed an excellent response defined as 90% or more reduction in the PASI score, 3 (15%) had a good response (70%–90% reduction of PASI score), 1 (5%) had a moderate response (50%–70% reduction of PASI score) and 2 (10%) showed no response (less than 50% reduction or worsening of disease). Jury et al[29] also published their data from Scotland. They conducted a retrospective review in children 16 or younger that were treated with NB-UVB. They studied records of 77 children (median age of patients was 12, range 4–16) and 32 (45%) of these had psoriasis. The median number of NB-UVB treatments for patients with psoriasis was 17.5 (range 9–35). By the end of the treatment, 22/35 (63%) of patients had cleared or had minimal residual disease, 3/35 (9%) were not better by the end of the treatment, and information was missing in 10 patients.

In a similar manner, Pasic et al[30] reported data from 20 patients with a mean age of 9.5 (range 6–14) years. They report that 45% (n = 9) of patients had excellent response, 20% (n = 4) had good response, 20% (n = 4) had moderate response and 15% (n = 3) did not improve after these treatments.

In 2008, Jain et al[31] reported data comparing the use of NB-UVB alone versus NB-UVB and mineral oil. In this cohort, mineral oil was applied to half of the body prior to NB-UVB treatment, while the other half received only NB-UVB. They found that after 3 months, there was a significantly greater improvement ($P < 0.05$) in scaling, induration and clearance in the pretreated half when compared to the other half (see Table 1).

Ersoy-Evans et al[27] also report on the use of BB-UVB and PUVA. A total of 30 patients with psoriasis were treated with BB-UVB (see Table 1). The mean age of patients treated with BB-UVB was 11 ± 3.6, and after a mean number of treatments of 28.8 ± 13.3, 93.3% of them (n = 28) had more than 75% improvement. They also report 7 patients with plaque or guttate type, older than 12, that did not respond to NB or BB-UVB. These patients were then treated with PUVA. They found that 83% of patients improved by more than 75% after an average of 28 PUVA treatments.

Kortuem et al reported 65 patients that received daily application of crude coal tar followed by daily UVB for 3 weeks, referred to as Goeckerman treatment (see Table 1).[32] The age of patients in this study ranged from 3 months to 18 years. The mean duration of treatment was 20 days (range 8–37 days) and 82% of patients (n = 53) got wet dressings prior to treatment. They found that 62% of patients (n = 40)

Table 1. Phototherapy and photochemotherapy in pediatrics.

Study and year of publication	# of ptes	Treatment	Age (yr)	Mean # of treatments	Mean cumulative dose (mJ/cm²)	Max dose per Tx (mJ/cm²)	Result
Jain et al[31]	18	NB-UVB + mineral oil vs. NB-UVB alone	Range 5–14	NB-UVB + MO 20.56 ± 3.06 NB-UVB alone 23.78 ± 3.14	NB-UVB + MO 2,956 ± 1070 NB-UVB alone 4,088 ± 1,236	NB-UVB + MO 297 ± 100 NB-UVB alone 395 ± 115	End point of the study: clearance (achieved in all patients). Greater improvement in scaling, induration and clearance in pre-treated half ($P < 0.05$).
Menter et al[34]	31	Goeckerman treatment	Youngest patient 1 yr old (other ages not specified)	12	NA	NA	Maximum clearing of over 90% seen in 64% of patients; 80%–90% clearing in 23% of patients
Borska et al[33]	26	Goeckerman treatment	Range 8–17, mean 13	12–32, average 19	NA	NA	
Kortuem et al[32]	65	Goeckerman treatment	Mean 11.6 (range 3 months to 18 yrs)	20 (range 8–37)	NA	NA	85% of patients had > than 80% clearance of their psoriatic plaques.
Ersoy-Evans et al[27]	30	UVB	11 ± 3.6	28.8 ± 13.3	21,000 ± 15,700	820 (200–8,200)	93.3% of patients (n = 28) had more than 75% improvement
Ersoy-Evans et al[27]	7	PUVA	15 ± 0.7	108 ± 68.5	498,800 ± 377,000	5,200 ± 2,000	>75% improvement in 83% of patients (n = 5)

had 90% or more improvement, 23% (n = 15) had 80%–89% clearance, 8% (n = 5) had 70%–79% clearance, 3% (n = 2) had 60%–69% clearance and 5% (n = 3) had less than 49% clearance. They report that remission was sustained for a mean of 2.6 years. 2 prior publications also reported on the use of this treatment modality in children; 1 reported a statistically significant decrease in PASI scores in 26 patients[33] and the second publication showed a maximum clearing of >90% in 64% of patients (n = 31) with substantial improvement in others.[34]

These studies suggest that NB-UVB phototherapy demonstrates potential benefit in the treatment of plaque and guttate psoriasis in pediatric patients. Further research is required to investigate the long-term side effects. A review of studies utilizing phototherapy and photochemotherapy is outlined in Table 2.

How to Deliver Phototherapy

In some centers, the first step in order to start patients on phototherapy is to determine the minimal erythema dose (MED), defined as the presence of erythema 24 hours after exposure. Once the MED is established, the first NB-UVB treatment is given at 0.7 MED, and then it is increased according to the post-irradiation erythema.[14] Because this process can be very time consuming and exhausting in children, not all centers determine the MED. When the MED is not established, the initial treatment is decided according on the patient's Fitzpatrick skin type, as proposed by the classification of Pathak et al. This classification proposes that for skin types I and II an initial dose of 0.03 J/cm^2 of UV-B is used, and of 0.05 J/cm^2 for skin types III and IV. In a similar manner, for UV-A an initial dose of 1 J/cm^2 is started for skin types I and II and of 1.5 J/cm^2 for skin types III and IV.[35]

Table 2. Reported side-effects from phototherapy and photochemotherapy in pediatric patients.

Study	# of patients	Treatment	Skin type	Side effects
Jury et al	77 (35 with psoriasis)	NB-UVB	NA	30% erythema 5 ptes blistering 1 pte VZV reactivation 2 ptes HSV triggered 5 ptes anxiety*
Jain et al	20	NB-UVB	IV	10% mild erythema 10% worsen, so they withdrew from treatment
Tan et al	116 (38 patients with psoriasis)	NB-UVB	I—6 ptes II—58 ptes III—31 ptes IV—20 ptes	36% brief, minimally symptomatic erythema
Pasic et al	20	NB-UVB	II—7 ptes III—11 ptes IV—2 ptes	No side effects
Jain et al	18	NB-UVB ± mineral oil	IV	No adverse events
Zamberk et al	20	NB-UVB	II—35% III—50% IV—15%	35% erythema
Pavlovsky et al	88	NB-UVB	NA	15% mild erythema 1% pruritus 3% burn Doubtful melanoma in situ
Kortuem et al	65	Goeckerman treatment	NA	42% folliculitis
Ersoy-Evans et al	113	NB-UVB, UVB and PUVA	NA	51.6% erythema (76% patients treated with NB-UVB, 40% with UVB and 33% with PUVA) 18% pruritus 9% burning

Note: *Not all side effects were specified by underlying diagnosis, but 2 of the patients that presented blistering had hydroa vacciniforme and both of the patients with HSV had AD.

Once treatment is started, increments on the treatment dose are carried out in each session. Increments of 10%–20% increase from the last the treatment dose is used until erythema is noted. The dose is then maintained.[25]

Most phototherapy units are designed booths with patients needing remain inside until the treatment is delivered. The tight space in the booth might be a challenge for pediatric patients. For smaller children, it may be difficult to get them to stay still while inside the booth. In some centers, parents are allowed in the booth for the first treatments to reduce anxiety and ensure that patients learn what to do and not to do inside the booth.[36]

All patients should wear photoprotective eye wear when they receive phototherapy. They also need to have their genitals protected during therapy.[19,37] This is usually done by having patients wear their underwear or other protective garments.

Safety

Phototherapy is generally considered to be a low risk treatment option, particularly in adult populations. However, short and long-term concerns can arise from the use of this treatment modality.[14]

UVB can cause acute phototoxicity, presenting as erythema and blistering after exposure. This can present in the first 4–6 hours after exposure and peaks 12–24 hours after. With the use of PUVA, erythema can start 24–36 hours after the exposure, and peaks 48–72 hours later. PUVA erythema can last for a week or more. It is particularly important if PUVA is used to avoid prolonged sun exposure, wear UVA-absorbing sunglasses outdoors, use a broad spectrum sunscreen and photoprotective clothing the days of the treatments to prevent significant phototoxicity.[19]

Both UVB and PUVA can also lead to tanning, photooncholysis, melanonychia and friction blisters. Patients and parents should be aware of these possible effects.[14]

Long-term safety data of phototherapy and photochemotherapy in children is lacking. Photoaging is a well known side effect of this treatment, but its relevance for children has not been established.[37] The use of PUVA is known to cause lentigines in adults in exposed and unexposed skin.[38] The risk of non-melanoma skin cancers is dose-dependent in patients that receive PUVA. For NB-UVB, and association with non-melanoma skin cancers has not been determined.

Wearing proper protective eyewear when exposed to the light treatment is of particular importance for the prevention of UVB-induced keratitis and PUVA induced cataracts.[19]

Absolute contraindications of phototherapy include xeroderma pigmentosum, systemic lupus erythematosus and basal cell nevus syndrome. Relative contraindications include previous history of skin cancer, treatment of genital area, photosensitive disorders, contact photosensitive substances and photosentitizing medications. For the use of PUVA, absolute contraindications include xeroderma pigmentosum, systemic lupus erythematosus, basal cell nevus syndrome, photosensitive disorders, age <10 years, pregnancy, breastfeeding and history of melanoma.[14,19]

Side Effects

Side effects from phototherapy can be divided into short and long-term. Short-term side effects from phototherapy are usually mild and most of the time they are caused by overdosage. These include xerosis, erythema, pruritus, blistering and photoactivation of herpes virus. Long-term side effects include premature photoaging and carcinogenesis. Increased incidence of wrinkling, actinic keratoses, lentigines, telangiectasia, basal and squamous cell carcinomas have been associated with this treatment.[39]

In the pediatric population, short-term side effects have been well described. Table 2 summarizes the side effects reported in the literature. Long-term side effects are not well-documented. There is need for long-term follow up of these patients in order to clarify associations with adverse effects. It is known that radiation received from UBV phototherapy is cumulative with chronic sun exposure, and sun exposure has been linked to skin cancer. There is one report of a child treated from age 18 months to 8 yrs with methoxsalen and UVA (PUVA) for refractory psoriasis that developed two basal cell carcinomas (BCC) before the age of 21, suggesting that exposure to PUVA in childhood may increase the risk of developing BCC.[40]

Patient Preference

Time commitment for patients and families is a challenge in this treatment modality. Phototherapy may

be inconvenient and difficult to use in the pediatric population. Accessibility is often an issue.[37] These concerns may preclude the use of phototherapy in this population.

Who Should Receive Phototherapy?

Phototherapy can be considered in older pediatric patients with psoriasis that have failed topical treatment. Those with moderate to severe psoriasis, with more than 15%–20% BSA involvement and focal debilitating palmo-plantar psoriasis will particularly benefit from this treatment modality.[41]

Phototherapy plays an important role in patients who cannot receive systemic therapy for their moderate to severe psoriasis. Out of the different modalities of phototherapy, NB-UVB may be particularly useful in pediatrics, since it presents milder side effects and has been shown to be effective especially for guttate psoriasis and thin plaque disease. It has replaced broad band BB as first line therapeutic option since NB offers more rapid clearance of psoriatic plaques with fewer treatments in comparison to BB.[42]

Conclusions

It is clear that early recognition and management of pediatric psoriasis is fundamental in order to prevent psychosocial and physical sequelae that can result from the disease.[8,43] Although long-term safety data on the use of phototherapy and photochemotherapy is lacking for pediatric patients, these treatment modalities continue to play an important role in the management of selected children with psoriasis.

Author Contributions

Conceived and designed the experiments: ILC. Analyzed the data: ILC. Wrote the first draft of the manuscript: ILC, PL. Contributed to the writing of the manuscript: ILC, PL. Agree with manuscript results and conclusions: ILC, SR, PL. Jointly developed the structure and arguments for the paper: ILC, SR, PL. Made critical revisions and approved final version: ILC, SR, PL. All authors reviewed and approved of the final manuscript.

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