Artigo Original

Fotoquimioterapia Sistémica no Tratamento de Psoríase na Adolescência

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RESUMO – **Introdução**: A eficácia e segurança da radiação UVB no tratamento da psoríase infantil e da adolescência encontra-se bem descrita na literatura. Contudo, existem poucos dados no que concerne à utilização de psoraleno e UVA (PUVA) nesta faixa etária. O objectivo do presente trabalho é avaliar a eficácia e segurança a curto prazo da terapêutica com PUVA numa população de adolescentes com psoríase. **Métodos**: Revisão e análise retrospectiva dos dados clínicos relativos aos doentes com psoríase com idade entre 13 e 17 anos. A população analisada incluiu 20 doentes, dezoito com psoríase em placas moderada a grave e dois com psoríase *gutata*. **Resultados**: Nove doentes foram tratados com apenas um ciclo de PUVA, e os restantes com dois. Foram associadas terapêuticas sistémicas em 52%. A taxa de resposta total foi de 86,2%, com uma média global de 16,7 tratamentos de PUVA e uma dose cumulativa total média de 174,0 J/cm^2. O tempo até recidiva foi de 4,3 meses, e em 2 doentes (10%) não houve recidiva durante um ano de seguimento. Observaram-se efeitos secundários em 3 doentes (15%), nomeadamente náuseas e eritema cutâneo. **Conclusões**: A fotoquimioterapia demonstrou boa eficácia na nossa população de adolescentes. Os efeitos secundários foram reduzidos e não motivaram suspensão da terapêutica. O potencial carcinogénico da radiação UVA poderá ser uma limitação importante desta modalidade terapêutica, pelo que são necessários mais estudos que avaliem a sua segurança a longo prazo.
PALAVRAS-CHAVE – Fototerapia; Psoríase; Adolescente.

Systemic Photochemotherapy in the Treatment of Adolescent Psoriasis

ABSTRACT – ***Introduction:*** *Ultraviolet-B radiation is known to be effective and safe in childhood and adolescent psoriasis, but little has been published on the combined use of psoralen with ultraviolet-A radiation. The aim of this work is to assess the efficacy and short-term safety of systemic photochemotherapy in an adolescent population.* ***Methods:*** *Relevant clinical data on psoriatic patients aged 13 to 17 was retrospectively collected and analyzed. The sample population included twenty patients, eighteen with moderate to severe plaque-type psoriasis and two with guttate psoriasis.* ***Results:*** *Nine patients were treated with one single cycle and the remaining eleven with two cycles, in association with systemic therapies in 52%. Total improvement rate was 86.2%, with an average of 16.7 treatments per patient and a mean total cumulative dose of 174.0 J/cm^2. The mean time for disease relapse was 4.3 months and two patients (10%) did not experience relapse during one-year follow-up. Side effects occurred in three patients (15%), namely nausea and erythema.* ***Conclusions:*** *Photochemotherapy showed to be highly effective in our adolescent population. Side effects were minor and none led to therapy discontinuation. Carcinogenic potential of ultraviolet-A radiation might be an important limitation. Further studies are warranted to access long-term safety of photochemotherapy.*
KEY-WORDS – *Phototherapy; Psoriasis; Adolescent.*

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INTRODUCTION

Psoriasis is a chronic burdensome skin condition commonly affecting under 18-years-old individuals.[1] Facial involvement and pruritus occur more frequently in this age group.[2]

Extensive childhood and adolescent psoriasis treatment is often challenging due to disease's potential impact in psychological development and the need to avoid systemic agents' toxicity.[3] Treatment efficacy and potential side effects have to be considered when selecting therapeutic modality in this context.

Several phototherapeutic options are available, such as narrowband UVB (nb-UVB), broadband UVB (bb-UVB), systemic and topic psoralen-UVA photochemotherapy (PUVA and topic PUVA, respectively) or excimer laser therapy. Treatment is selected on a case-to-case basis according to diagnosis, disease severity, skin phototype and age.[4]

UVA with longer wavelengths penetrate deeper into the skin and are recommended for the treatment of very thick psoriatic plaques.[4,5] In adults, PUVA therapy is known to be more effective than nb-UVB, with reported efficacy rates of 80% vs 70%.[5] Treatment protocol includes 2 to 3 weekly sessions, starting at 75% of the minimal phototoxic dose (MPD) for UVA or according to skin phototype. Between one to two hours before radiation exposure, 8-methoxypsoralen (8-MOP) dosed at 0.5-0.6 mg/kg is administered orally. The radiation dose is increased by 10 to 20% in each session if no erythema occurs, until a maximum of 6 J/cm^2 per treatment.[6]

PUVA is not routinely used in patients younger than 12 years due to its carcinogenic potential, well-known side effects (e.g. nausea, vomiting, ocular toxicity, headaches, phototoxicity, hepatotoxicity) and the need of sun protection measures in the 24 hours after 8-MOP ingestion.[4] Recent evidence-based recommendations have concluded that there is no increased risk of PUVA-associated cataract provided that ocular protection measures are followed.[5]

Available evidence supports nb-UVB effectiveness and safety to treat childhood psoriasis. Eleven studies[7-17] enrolling 295 children reported efficacy rates of 60-92.9%, without severe short-term side effects.

Nonetheless, little has been published on the use of systemic PUVA in under 18-years-old patients. To the best of our knowledge, only one series including seven adolescents (average age of 15 ± 0.7 years) has been published.[10] Three patients had guttate psoriasis, three plaque-type psoriasis and one had both. A response rate of 83.3% was achieved at an average of 28 treatments and a total dose of 498.8 ± 377.0 J/cm^2. More recently, de Jager and co-workers[18] reviewed three cases of children treated with systemic PUVA. One patient with plaque-type psoriasis had a complete response after 18 PUVA treatments.[19] The other two, with erythema annulare centrifugum-type psoriasis cleared with 15 and 21 treatments.[20] No severe side effects were observed.

Little data is available regarding the use of topical PUVA to treat childhood psoriasis. In younger children, the absence of systemic side effects and the shorter duration of photosensitization favor the use of this PUVA modality, 15 however topical PUVA is time consuming and less convenient[4]; thus other treatment options are generally preferred. To date, only one case of childhood psoriasis treated with topical PUVA has been reported.[18]

The aim of this observational retrospective study is to assess PUVA efficacy and short-term safety in the treatment of moderate to severe psoriasis in an adolescent population.

METHODS

Psoriatic patients aged 12 to 17 who had been treated with systemic photochemotherapy in our department over a 17-year-period (January 1997 to December 2013) were included. Data was retrospectively collected from phototherapy charts and clinical records. Patients who had previously received phototherapy of any kind were excluded.

Treatment was administered twice weekly on non-consecutive days, according to a standardized protocol, using a *Waldmann* UV8001K cubicle with 27 UVA and 13 UVB fluorescent lamps (*Waldmann Lichttechnik Gmbtt, Schwenningen, Germany*):

- Oral 8-MOP was given at 0.6 mg/kg 120 minutes prior to UVA exposure.
- The initial radiation dose was 1.5 and 2 J/cm2, respectively for phototype II and III.
- Dose was subsequently increased by 0.5 J/cm2, to a maximum dose of 5 J/cm2.
- Incremental increases were decided every session depending on the presence or absence of erythema and pigmentary response. MPD was not calculated routinely.
- Face and genitals were protected during treatment unless there were significant lesions on those areas.
- All patients wore UV protection sunglasses during treatment and in the following 24 hours whenever outdoors.
- Ophthalmology consultation was not routinely recommended.

Studied variables included age, gender, phototype, type of psoriasis, time since diagnosis, family history of psoriasis, co-morbidities, initial Psoriasis Area Severity Index (PASI), number of phototherapy cycles, number of sessions and dose per cycle, cumulative dose, adverse events, final PASI and time to relapse.

Main clinical outcome was PASI score decrease. Patients who improved >75%, between 50 and 75%, and less than 50% of initial PASI score were considered good, moderate and non-responders to treatment, respectively.

Statistical analysis was performed with Excel and RStudio using Chi-squared test, Fisher's exact test and Kruskal-Wallis test. Statistical significance was defined as $p < 0.05$.

RESULTS

Twenty patients were included. Table 1 outlines their characterization according to demographic and clinical variables.

Overall, the 20 patients included underwent 29 PUVA cycles, as summarized in Table 2.

Overall, the average number of treatments per patient was 16.7 and the mean total cumulative dose was 174.0 J/cm^2. In

Table 1 - Characterization of the 20 patients treated with PUVA

Gender	Female: 15 (75%)
	Male: 5 (25%)
Age in years (mean ± SD; range)	15.7±1.4; 13-17
Skin phototype	II: 7 (35%)
	III: 13 (65%)
Psoriasis type	Plaque: 16 (80%) *
	Guttate: 4 (20%) **
Time since diagnosis (mean, years)	5 ± 4.1
Previous therapies	Topical corticosteroids: 20 (100%)
	Systemic retinoids: 10 (50%)
	Cyclosporine A: 1 (5%)
PASI score (mean)	15.7 ± 3.2
Number of PUVA cycles	One: 11 patients (55%) 2 males and 9 females
	Two: 9 patients (45%) 3 males and 6 females
Number of phototherapy cycles (including nb and bb UVB) (mean)	1.9 ±1.1

*one patient had also concomitant palmoplantar involvement; ** none had personal history of upper respiratory streptococcal infection; SD, standard deviation

25 out of 29 PUVA cycles (86.2%), an improvement of at least 75% of initial PASI score was observed. One patient failed to achieve a 50% PASI improvement despite 19 treatments (total cycle dose 81.5 J/cm^2). The remaining three patients withdrew the treatment after a mean of 4.3 PUVA sessions, all for non-clinical reasons. Side effects occurred in three cases (15%), namely nausea in two of them and erythema in one patient. None led to interruption or discontinuation of treatment.

The mean disease relapse time was 4.3 months, varying from 1 to 9 months. Two patients did not experience relapse during one-year follow-up after one single PUVA cycle (dose 89 and 174 J/cm^2, respectively). One of them had been diagnosed one year before with guttate-type psoriasis and the other had 2-year evolving plaque-type psoriasis.

Systemic therapies were associated during 15 out of 29 PUVA cycles (52%). When comparing these 15 cycles with those 14 PUVA courses without concomitant systemic medications, a higher average number of treatments per cycle (19.9 *vs* 12.8) and a higher mean dose (107.9 *vs* 93.6 J/cm^2) were needed to clear patients with an associated systemic medication and the rate of improvement was lower (80% vs 85.7%,). Those differences were not statistically significant.

The need for those therapies was correlated with higher disease severity and higher number of treatments ($p = 0.022$) on the first cycle and, on the second cycle, there was also a positive association with male gender ($p = 0.025$) and family history of psoriasis ($p=0.024$). Conversely, significantly fewer systemic therapies were prescribed to patients with guttate psoriasis ($p = 0.016$).

No significant correlation between age, phototype, duration of the disease or previous systemic therapies and radiation dose, duration of treatment or time to relapse was identified.

DISCUSSION

According to our data, photochemotherapy is a highly effective therapeutic approach for moderate to severe cases of adolescent psoriasis. We observed an overall improvement rate of 86.2%. A similar efficacy rate (83.3%) was reported in the only published series of PUVA-treated psoriatic adolescents10, although a higher average number of treatments (28±22.8 *vs* 16.7±7.5 treatments, respectively), as well as a higher total cumulative dose (498.8±377 *vs* 174±142.5 J/cm^2) were

Table 2 - Relevant information on PUVA therapy performed over the studied period

	Number of treatments (mean, SD)	Dose in J/cm^2 (mean, SD)	Duration in months (mean, SD)	PASI 75 improvement (n; %)	Non responders (n)	Withdrawal (n; %)	Associated systemic therapies	Time to relapse in months (mean, SD)
First cycle (n = 20)	17.2 ± 5.8	111.0 ± 60.9	2.9 ± 1.3	18; 90%	1	1; 5%	10 (50%) retinoid*; 1 (5%) CyA**	3.6 ± 3.0***
Second cycle (n = 9)	15.6 ± 10.6	123.6 ± 118.6	2.8 ± 2.5	7; 77.8%	0	2; 22.2%	4 (44%) retinoid*	7.5 ± 4.9***
Total (29 cycles)	16.7 ± 7.5	Total cumulative dose: 174.0 ± 142.5	2.9 ± 2.5	25; 86.2%	1	3; 10.4%	15 (52%)	4.3 ± 3.6***

* Acitretin was prescribed to 2 male patients on the first cycle; the remaining retinoids correspond to isotretinoin;** CyA was being tapered with fast relapse when the patient was proposed to phototherapy, with overlap of both therapies in a short period; *** no available follow-up information for 7 patients on the first cycle and 5 on the second; SD, standard deviation

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reported[10]. Nevertheless in the previously published series no systemic therapies were associated with PUVA, as was the case for some of our patients.

Published series of nb-UVB-treated psoriatic children reported an average of 19-25.[8] treatments per cycle, which is also higher than our numbers. The response rates on those series ranged between 65-92.9%.[10,15] On the other hand, Archier and co-workers[21] concluded on a recent systematic review that PUVA seems to clear adult psoriasis more reliably and with fewer sessions than UVB treatment. In childhood, available data seems to point towards a similar conclusion; however, further investigation is needed to confirm this hypothesis.

The response rate to PUVA therapy in the present study was similar or even higher than that reported for other systemic treatments (80-91.7% to metothrexate18 and 68% to etanercept).[22] Advantages of PUVA are the lack of the systemic immunosuppression associated with systemic treatments and the favorable safety profile. In our patients, only minor side effects occurred, none of which leading to therapeutic discontinuation.

Time to relapse was relatively short in our patients when compared to that reported for nb-UVB[7] (4.3 *vs* 20 months). It is worth highlighting that two adolescents had no relapse of the disease within one-year follow-up and were not considered when calculating mean time to relapse. Furthermore, five of the remaining 18 patients (27.8%) are currently being treated with biologic agents, hence reflecting the persistence and severity of their disease, which might explain the short time to relapseobserved in our study.

Systemic therapies were associated in about half of the performed PUVA cycles. Those patients were treated with oral medications as first line systemic therapy but did not achieve a satisfactory clinical response. Photochemotherapy was then started and ongoing medications were maintained due to disease severity, being reduced as clinical response with the combined approach was achieved. The potential harm caused by associating systemic therapies may be counterbalanced by lower time under those medications and lower administered radiation dose, with a favorable risk-benefit relationship usually reported. Nevertheless, the higher severity of patients with associated systemic therapies that were included in our study could not show the advantage of a reduced exposure to UVA.

Actually, these associated therapies tend to be used in cases of more severe disease and potentially requiring a higher number of treatments per cycle, therefore justifying its use. Likewise, patients who needed an associated systemic therapy on the second PUVA cycle were more likely to be male and have positive family history of the disease. These features have also been linked to psoriasis severity.[23,24] thus explaining the need of a more intensive treatment approach.

The potentially associated carcinogenic risk is another concern of using phototherapy to treat young patients, particularly if considering the clear dose-effect relationship[25] and the long-life expectancy of this group. Moreover, psoriasis is a chronic disease and most patients will be likely to require other treatments in their lifetime. For this reason, a high radiation dose in young patients should be avoided as it might limit future therapeutic approaches. Treatment with more than 200 PUVA sessions or with over 2000 J/cm^2 has been reported to significantly increase carcinogenic risk in adulthood.[25] Nevertheless, these numbers are significantly higher than those of our case studies.

Additionally, association of systemic retinoids to PUVA therapy is known to lower carcinogenic risk,[5] and these drugs were prescribed to about half of the patients in our study. However, retinoids cannot prevent nevi stimulation induced by radiation, which is also a concern for young patients.

Although retrospective design, sample size and the lack of assessment for long-term oncogenic risk are limitations of our study, this is currently the largest series of data on under 18-years-old psoriatic patients treated with PUVA. Concomitant systemic therapies, used in more severe cases, also limit the assessment of PUVA efficacy alone.

CONCLUSIONS

In view of the reported effectiveness and short-term safety of photochemotherapy in our adolescent population, it may be a valid therapeutic approach in cases of extensive disease, thick plaques or refractivity to other therapeutic modalities. Nonetheless, the withdrawal rate (10.4%, all cases for reasons other than clinical) and school absenteeism might limit the use of this therapeutic option in this group.

Further studies are warranted to confirm PUVA efficacy and short-time safety in children and adolescents with psoriasis, as monotherapy or in combination with other systemic medications, as well as to access its long-term safety concerning skin cancer and nevi stimulation.

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