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Phototherapy

Fototerapi

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Abstract

Considering its effects, side effects, and contraindications, phototherapy is a treatment option that can be used in patients who do not respond to topical treatments, suffer side effects, or have diffuse lesions. By showing antiproliferative, immunomodulatory, and anti-inflammatory actions, phototherapy may help heal psoriatic lesions. Phototherapy can be administered as narrow-band UVB or PUVA. It can be combined with other anti-psoriatic therapies. Since it may increase the risk of non-melanoma skin cancer, its use should be limited to a certain number of sessions, and any maintenance treatment involving phototherapy should be avoided.
Keywords: Phototherapy, narrow-band UVB, PUVA

Öz

Topikal tedaviye yanıt alınamayan, yan etki gözlenen veya yaygın lezyonları olan hastalarda fototerapi etki, yan etki ve kontrendikasyonlarda dikkate alınarak uygulanabilen bir tedavi seçeneğidir. Fototerapi anti-proliferatif, immünomodülatör ve anti-inflamatuar etki göstererek psoriasis lezyonlarının iyileşmesini sağlar. Fototerapi dar bant-UVB veya PUVA şeklinde uygulanabilir. Diğer anti-psoriatik tedaviler ile kombine edilebilir. Non-melanom deri kanseri riskinde artışa yol açabildiğinden kullanımı belirli seanslarla sınırlı olmalı ve idame tedavisinden kaçınılmalıdır.
Anahtar Kelimeler: Fototerapi, dar bant-UVB, PUVA

Definition, principles and mechanisms

Ultraviolet (UV) irradiation is part of the electromagnetic spectrum. UV irradiation is functionally divided into three groups, UVA (320-380 nm), UVB (280-320 nm) and UVC (100-280 nm). UVA range is studied in two groups, (340-400 nm) and UVA2 (320-340 nm). When considering UVB for phototherapy, it can be methodologically divided into two groups, wide-band UVB in the range of 280-320 nm and limited narrow-band UVB at 311 nm[1]. Due to its short wavelength, UVB is quickly absorbed by the epidermis, but a small portion of it (15%) penetrates the papillary dermis. The energy of UVA is absorbed much slower due to its long wavelength, and for this reason, it can penetrate deeper layers of the dermis[1].

Phototherapy allows designing personalized treatment options in psoriasis and its basic mechanisms of action are seen in Figure 1[1-3].

Efficacy and treatment modality

Phototherapy is a treatment option used after considering its side effects and contraindications in patients who do not respond to topical therapies, who experience topical therapy side effects, or who are not eligible for a topical therapy due to diffuse lesions. Patients for whom a decision has been made to use phototherapy should also be assessed in terms of compliance to treatment such as travel to and from the phototherapy centre.

Phototherapy treatment algorithm and efficacy based on the clinical aspects of psoriasis is seen in Figure 2.

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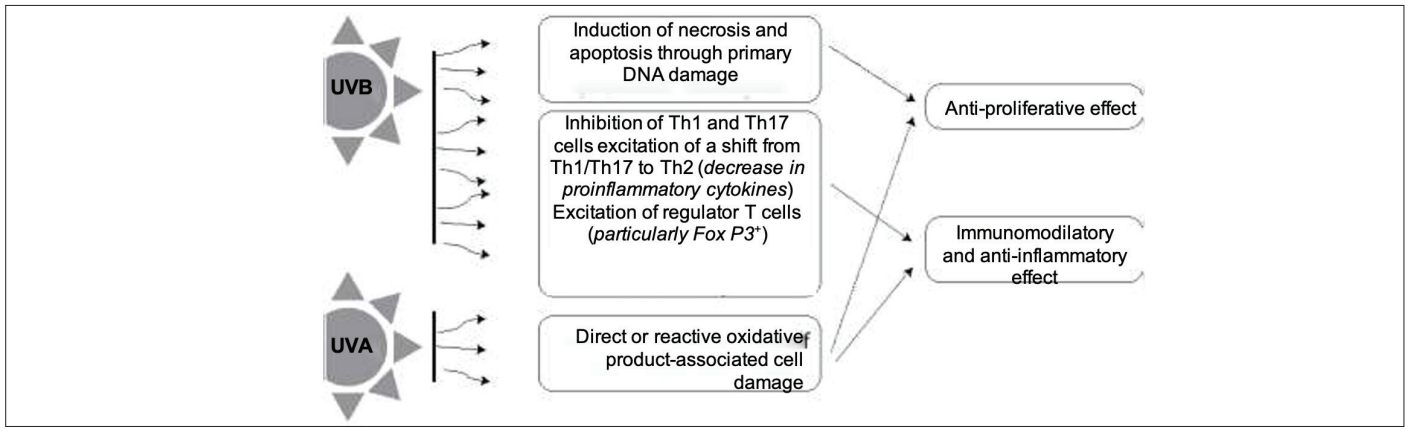

Figure 1. Basic mechanisms of action in phototherapy

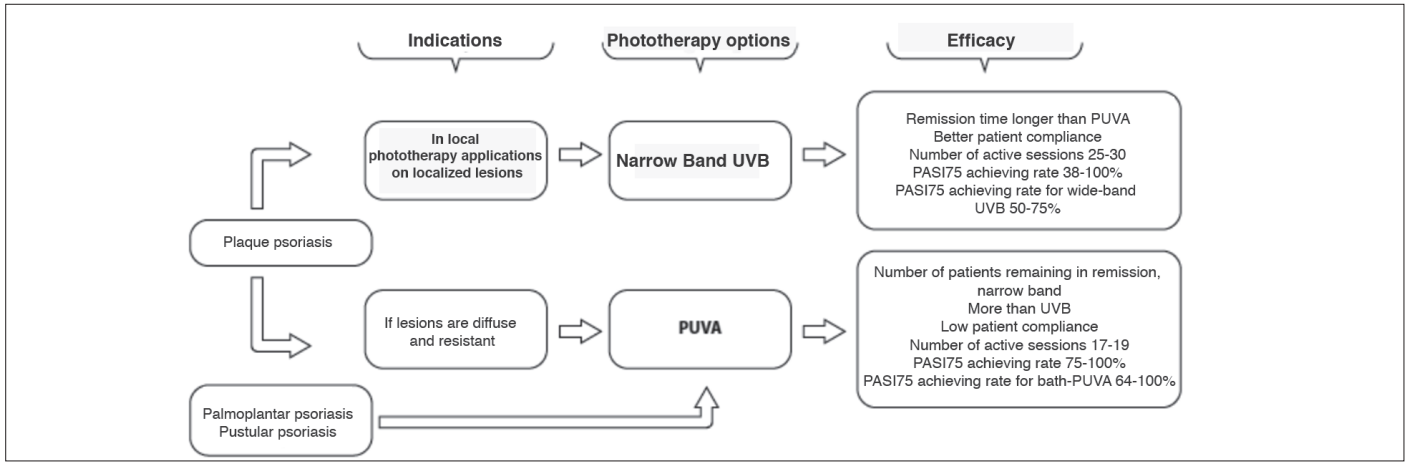

Figure 2. Phototherapy algorithm in psoriasis

UVB therapy may be carried out in two different ways, wide and narrow band. Narrow-band UVB phototherapy with a wavelength of 311 nm is the most widely used phototherapy option in psoriasis due to being both therapeutic and cost-effective[1,4,5]. However, new practices such as 312 nm narrow-band UVB therapy for localized lesions have also been included in the treatment options[3].

In daily practice, narrow-band UVB is used much more frequently than wide-band UVB. Narrow-band UVB therapy is more effective in generalized plaque psoriasis than wide-band UVB[6-8]. Narrow-band UVB phototherapy is also preferred in daily practice for being safer than PUVA[9]. PUVA can be recommended for the chronic phase of generalized pustular psoriasis. Narrow-band UVB may be recommended either in combination with the first option medication or after the first option medication[10].

Phototherapy is not recommended for maintenance treatment as sufficient data is not available. However, when deciding on maintenance treatment, a patient-oriented approach based on the side effects of other therapies, complications and contraindications is essential[2,11-14].

Narrow-band UVB is usually a first phototherapeutic option in patients with psoriasis. If more than 10% of the body surface area is involved, a narrow-band UVB phototherapy should be considered[15].

PUVA is the second choice if there is nonresponse to the treatment, a fast relapse occurs after the treatment, the PASI is high or there is resistance. Nonresponse to a narrow-band phototherapy is not indicative of also nonresponse to a PUVA therapy[16].

In cases where the PASI is high and there is little or no response to a nbUVB therapy, PUVA may be employed as an induction therapy[12]. Topical or bath PUVA may be appropriate to avoid systemic toxicity. Topical PUVA may be as effective as oral PUVA with a total dose 2-6 times less[17-19]. An 8-MOP bath and oral PUVA is more preferable to a TMP bath PUVA[20-23].

The indications of PUVA therapy for different types of psoriasis are given in Table 1. PUVA is very effective in psoriasis, but DNA damage caused by it and its carcinogenic potential are the major disadvantages. Therefore, its indication for a particular use should be specified clearly[1]. Systemic conventional and biological agent therapies are known to have cardiovascular disease preventing effects in psoriasis patients[24-26]. For this reason, a cardiovascular risk assessment and a patient-oriented treatment plan is recommended in patients for whom phototherapy is planned.

Table 1. PUVA indications by types of psoriasis

Types of psoriasis	Systemic PUVA	Bath PUVA	Hand/foot PUVA
Psoriasis vulgaris	+	+	-
Palmoplantar psoriasis	-	-	+

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Procedure, dosage and treatment scheme

Patients should be provided general information before phototherapy and their age, personal ultraviolet sensitivity, whether they can stay in the ultraviolet cabin, their previous ultraviolet sessions and responses received, and cumulative doses should be evaluated. Male patients should be warned about protecting their genital regions during the therapy. All patients should go through a whole skin examination and clinical effectiveness and treatment compliance should be reviewed every 2-3 months after commencing the therapy[2,14,17].

The minimal erythema dose (MED) is the lowest irradiation dose that causes a noticeable pink erythema and is measured in mJ/cm^2. Use of drugs such as nonsteroidal anti-inflammatory drugs, calcium channel inhibitors and phenothiazines may affect the minimal erythema dosage[12,27].

To test photosensitivity, UVB irradiation is emitted with increments of 10 mJ/cm^2 or √2 (1.41) on small circular areas 1 (one) cm in diameter (generally 6-8 sites) on the lower part of the back or on the hips. Since UVB-associated peak erythema emerges in 12-15 hours, the testing should be evaluated 20±4 hours after the irradiation. The initial therapeutic dose of UVB may be 35-70% of the MED to mitigate the risk of burning[2].

It is also possible to adjust the treatment dose based on the skin type, which may be more helpful in practice. Efficacy is similar in both methods[14,28-31]. Although the initial dose is usually 150-400 mJ/cm^2 on the average, initial doses recommended for respective skin types may vary (Table 2)[15].

Table 2. UVB initial doses recommended for skin types

Fitzpatrick skin type	Skin colour and characteristics	Dose (mJ/cm^2)
I	White, very light-coloured skin, ginger/ blonde hair, blue eyes, freckles; always burns	100-200
II	White, light-coloured skin, ginger/ blonde hair, blue/green/hazel eyes; generally burns, difficulty in tanning	200-300
III	Fair skin, light-coloured eyes or hair; occasional mild burns, gradual tanning	300-400
IV	Brown, typical Mediterranean skin tone; rarely burns, easy tanning	400-500
V	Dark brown, Middle Eastern skin types; very rarely burns, very easy tanning	500-600

The procedure should be repeated 2-3 times weekly for an effective treatment[12]. Since the highest level of erythema occurs in less than 24 hours, the increments can be made after each successful therapy. The purpose of dose increments is to ensure a minimal detectable erythema as a clinical dose indicator[2]. Treatment in a suberi-thermogenic dose is also effective, but the length of treatment is prolonged. While the number of sessions is 15-20 in an erythemogenic dose, the average number of sessions in a suberythemogenic dose is 25[12].

The ideal dose increment for each session is 10-20% as shown in studies[32,33]. If the erythema on the skin fades away in less than 24 hours after the therapy, the dose may be increased. If erythema remains for 24-48 hours, a natural or artificial UV exposure should be avoided. In that case, the dose increments may be limited to 10%. If erythema exceeds 48 hours, the therapy should be cancelled for that day, returning to the latest low dose that did not cause erythema[34,35].

If a maintenance therapy is indicated with a patient-oriented approach, the procedure can be repeated in the latest dose that allowed clearance twice a week for the first four weeks and once a week for the following four weeks. In a patient for whom a longer maintenance therapy is planned, the last dose should be decreased by 25% and the patient should receive treatment every 1-2 weeks[34].

The maximum doses that can be reached in a nbUVB phototherapy are different; 2,000 mJ/cm^2 for skin types I and II, 3,000 mJ/cm^2 for skin types III and IV, and 5,000 mJ/cm^2 for skin types V and VI. The maximum dose in the facial region should not exceed 1 J/cm^2, regardless of the skin type[17,31,34,35].

If a patient receiving a nbUVB therapy missed 4-7 sessions, the treatment can be continued from the latest dose used, if missed 1-2 weeks, by decreasing the dose 25%, if missed 2-3 weeks, by decreasing the dose 50% and if missed 3-4 weeks, by starting from the beginning. The treatment should be started anew in any case when four weeks is exceeded. If an erythematous reaction occurs as a result of dose increase, the dose will be decreased by 50% and the following dose increments will be limited to 10%[17,36].

The efficacy of treatment should be evaluated every 4-6 weeks. Patients who received more than 350 narrow-band UVB therapies should have a routine skin carcinoma examination every year throughout their lifetime[18].

Various procedural methods can be used in PUVA therapies. These methods are summarized in Table 3[17,18].

Table 3. Procedural methods in PUVA

Oral PUVA (Oral 8-MOP 0.6-0.8 mg/kg; maximum 40 mg 1.5 hours before the procedure)
Bath PUVA (8-MOP 0.5-1 mg/L; 30 min. before the procedure in broad lesions)
Immersion PUVA (8-MOP 0.5-1 mg/L in water; 30 min. before the procedure in hand and foot lesions)
Cream PUVA (8-MOP 0.0006-0.0005% in lotion or ointment; in cold cream; 30 minute before the procedure in hand and foot lesions)

The basic features of PUVA therapy in psoriasis based on skin types is given in Table 4[19,37].

Table 4. Basic features of PUVA therapy in psoriasis based on skin types

Number of weekly therapies	2-3
UVA dose increments	Fixed
Recovery rate (average)	88%
Number of therapies (average)	25
Recovery time (average)	12.7 weeks
Cumulative UVA dose (average)	245 J/cm^2

A PUVA treatment regimen based on skin types is given in Table 5[17].

Table 5. PUVA treatment regimen based on skin types

Skin type	Initial dose (J/cm²)	Dose increment (J/cm²)	Highest dose (J/cm²)
I	0.5	0.5	8
II	1	0.5	8
III	1.5	1	12
IV	2	1	12
V	2.5	1.5	20

Patients relatively eligible for a topical PUVA therapy are shown in Table 6[18,38].

Table 6. Patients relatively eligible for a topical PUVA therapy

Those with a gastrointestinal system pathology
Patients with cataract
Patients having a compliance problem in protecting their eyes
Those using drugs interacting with psoralen such as warfarin
Patients with localized disease such as hand and foot psoriasis (immersion or cream PUVA)
Children and adults with broad lesions (bath PUVA)

Considering its long-term side effects, maintenance treatment with PUVA is not recommended[2].

Combination therapies

Patient satisfaction is higher when conventional systemic therapies are combined with phototherapy[39]. Combinations of UVB with topical or systemic therapies are summarized in Table 7[15,17,18,34,40-45].

Table 7. UVB phototherapy combined with topical or systemic drugs

Combinations	Combination details
Topically applied combinations	
Emollients	Applications in thick layers impair UVB passage and decrease efficacy. When applied in a thin layer before the therapy, decreases occurrence of erythema. Recommended for patients in whom erythema affects the treatment protocol.
Topical steroids	May reduce time to respond. Significant clinical improvement is not expected. May lead to high rate of relapse. Not recommended for this reason (or recommended when rapid effect is desired)???
Calcipotriol	Applied two hours before or after the UVB therapy. Its contribution to the treatment is debatable. Weakly recommended.
Anthralin or coal tar	Effective but poor patient compliance. Should not be applied before a phototherapy. Recommended.
Tazarotene	Effective and cumulative UVB dose decreases. Recommended.
8-methoxypsoralen	Sufficient data not available. Not recommended.
PUVA	Fewer sessions and lower cumulative dose when combined with narrow-band UVB. Sufficient safety evidence not available. Not recommended.
Systemically administered combinations	
Acitretin	May be preferred as a patient-oriented approach in patients at relatively more risk of skin cancer. May be an alternative to PUVA in thick plaques. To be started at 10-25 mg/day (0.3-0.5 mg/kg/day) two weeks before commencing phototherapy. The starting dose of UVB should be reduced by 30%. Strongly recommended.
Methotrexate	To be started at 15 mg/week four weeks before commencing phototherapy. When remission is reached, methotrexate is to be phased out. UVB may be maintained if necessary. A synergistic effect occurs. Cumulative UVB dose decreases. Recommended.
Cyclosporine	Increased risk of squamous cell carcinoma. Not recommended.
Biological agents	High level evidence for etanercept, limited evidence for the others. Etanercept 25-50 mg twice a week and narrow-band UVB phototherapy 2-3 times a week. There is limited information on adalimumab and ustekinumab in combination with narrow-band UVB; it may enable fast clinical recovery and a reduction in narrow-band UVB dose. There is no apparent evidence on its carcinogenicity developing potential. Its short-term use is recommended in resistant cases.
Apremilast	Eficacy may increase. Safe. Can be recommended.

Its combination therapies may increase the efficacy of PUVA, thereby decreasing side effects. Table 8 summarizes topical or systemic drugs in combination with PUVA.

Table 8. Topical or systemic drugs in combination with PUVA

Topical therapies	Corticosteroids with anthralin and tar is recommended. Also recommended with calcipotriol but patient compliance is poor.
Acitretin	Strongly recommended.
Methotrexate	Not recommended.
Cyclosporine	Not recommended.
Biological agents	Not recommended.

Side effects and toxicity

Table 9 summarizes side effects and toxicity in nbUVB therapy[17].

Table 9. Side effects and toxicity in nbUVB therapy	
Acute side effects and toxicity	Erythema, itching, burning-stinging sensation Herpes simplex reactivation Xerosis Rarely bulla
Chronic side effects and toxicity	Dermatoheliosis Genital tumours in males (in those who received more than 300 therapies without protection) Melasma and folic acid deficiency in pregnant women Carcinogenicity (?)

There is no data on the effect of narrow-band UVB phototherapy on vaccination.

No risk of skin cancer has been seen with wide- and narrow-band UVB therapy when applied less than 100 sessions. Data on patients who had previously received PUVA therapy and whose wide-band UVB therapy exceeded 300 sessions show possibility of a moderate increase in non-melanoma skin cancers[46-48]. Based on this information, lifetime narrow-band UVB therapy should not exceed 350 sessions in patients who had not previously received PUVA therapy.

In those who received more than 350 sessions of PUVA therapy, the risk of basal-cell carcinoma is at the highest level and the risk of squamous-cell carcinoma continues after the discontinuation of the therapy. If the number of sessions is between 100 and 150, the risk is lower but still exists. Although the risk of melanoma has been reported to increase in those who received more than 250 sessions of PUVA therapy in the U.S., this data has not been confirmed in Europe. With less than 100 sessions of bath PUVA, there will not be an increase in the risk of skin carcinoma[46,49]. A lifetime PUVA therapy should not exceed 200 sessions[17].

Considering its mechanism of action, it should be noted that it may be more carcinogenic than narrow-band phototherapy. Especially when used in combination with drugs such as cyclosporine, this risk increases considerably.

The short-term side effects of PUVA therapy are similar to those of UVB therapy. The side effects and toxicity of PUVA are given in Table 10[2,17,40,50,51].

Table 10. Side effects of PUVA	
Acute side effects and toxicity	Erythema Oedema Burns Itching Bullae formation Pain Maculopapular rashes Provocation of photodermatoses Phototoxic reaction Photoonycholysis Nausea-vomiting and dizziness (a switch to 5-MOP or topical PUVA therapy may be appropriate) Folliculitis Subungual haemorrhage Nail pigmentation
Chronic side effects and toxicity	Cataract development (UV absorbing eyeglasses should be used for 12 hours after receiving psoralens) Actinic keratosis Lentigo Photoaging Dermatoheliosis Development of skin carcinoma (risk of basal-cell carcinoma after 100 sessions and melanoma after 200 sessions) Genital region carcinomas in males

Contraindications

The contraindications of UVB phototherapy are given in Table 11[17].

Table 11. Contraindications of UVB phototherapy	
Absolute contraindications	Xeroderma pigmentosum Lupus erythematosus Other photosensitive diseases
Relative contraindications	Skin types I and II Use of photosensitive drugs Prior ionised ray (grenz rays, X-ray) therapy A history of arsenic intake A personal or family history of melanoma

Table 12 shows the contraindications of PUVA[14,18].

Table 12. Contraindications of PUVA	
Absolute contraindications	Age less than 10 years Xeroderma pigmentosum Gorlin's syndrome Hereditary dysplastic nevus syndrome Systemic erythematous lupus Dermatomyositis Trichothiodystrophy Bloom syndrome Cockayne syndrome A history of melanoma Pregnancy Lactation
Relative contraindications	Age less than 12 years Previous or current non-melanoma skin carcinoma Exposure to arsenic and ionised radiation Presence of premalignant lesions Accompanying immunosuppressive treatment Porphyria Cataracts Bullous pemphigoid Previous or accompanying methotrexate therapy Major hepatic dysfunction Use of cyclosporine Presence of dysplastic nevus Skin type I Claustrophobia

Phototherapy in pregnancy and lactation

Narrow-band UVB phototherapy is safe and effective in pregnancy and lactation[15]. Narrow- and wide-band phototherapies are equally safe during lactation[52].

PUVA is absolutely contraindicated in these periods.

Phototherapy in childhood

Recurring sunburns and UV exposure increase the risk of developing melanoma 3-4 fold in children younger than 12 years. Although no studies are available clearly demonstrating the effect of phototherapy on skin carcinoma, the use of phototherapy in children older than 12 years depending on the course of psoriasis and in the presence of contraindications for other treatment options, narrow-band UVB phototherapy may be decided for children younger than 12 years (not younger than 8 years) in a patient-oriented manner. PUVA therapy is absolutely contraindicated for ages less than 10 years and relatively contraindicated for ages less than 12 years[53,54].

In children, the total dose should be kept as low as possible and phototherapy should not be considered as a first line treatment option. Children who were administered UVB phototherapy should be under long-term follow-up for the risk of carcinogenicity[53,55]. To improve treatment compliance in children, they should be informed in detail considering their age and family status about the benefits and risks and should be familiarized with the unit where the phototherapy will be carried out.

PUVA therapy can be administered only to children older than 12 who have broad lesions and did not respond to a nbUVB or wide-band phototherapy[56]. In any case, a narrow-band UVB therapy should be the first phototherapy option in childhood[57].

Phototherapy in geriatric period

Although there is no protocol specifically developed for the older population, narrow- or wide-band phototherapy may be used effectively and safely[58]. Due to multiple drug use in older population, UVB should be considered instead of PUVA[53].

Phototherapy in persons infected with HIV

In the light of available data, UVB and PUVA therapies are agreed to be safe in HIV-positive patients[2].

UVB phototherapy at home

Although UVB therapies applied at home or in a hospital do not differ in terms of effectiveness, patient compliance with treatment is higher in home phototherapy. Therefore, home UVB phototherapy may be used safely in selected patients if patient follow-up is implemented properly[59,60].

Targeted phototherapy

Protecting the skin areas without lesions, targeted phototherapy may be used on the scalp and palmoplantar region and in cases where less than 10% of the body surface area is involved but that are resistant to treatment[15]. The initial dose is determined based on the skin type or MED and the therapy is administered three days a week. The phototoxic and carcinogenic risk is expected to be lower. Devices with a 308 nm excimer laser, 308 nm excimer nonlaser and targeted narrow-band (311-313 nm) UVB irradiation are used. Due to presence of various types of devices, it is difficult to establish a standardised treatment dose. The number of studies with high evidence levels is limited in targeted phototherapy. The effectiveness of a 308 nm Excimer laser is higher than those of the other two devices. A recovery more than 80% may be achieved as a result of a therapy repeated 7-13 times. The efficacy in palmoplanar lesions is less than 60%[61-64].

Their combination with topical therapies may increase the efficacy[65]. They are also safe in children[61]. Efficacy may be increased by adding targeted phototherapy to long-term systemic therapies[66]. The major side effects of a targeted phototherapy are erythema, bulla formation and hyperpigmentation[18,40].

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