

Phototherapy: Its Main Modalities and Treatment Indications For Dermatology

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Published:

J Turk Acad Dermatol 2019; **13** (3): 19133r1.

This article is available from: <http://www.jtad.org/2019/3/jtad19133r1.pdf>

Keywords: Dermatitis, Psoriasis, Phototherapy, Side Effects, Vitiligo

Abstract

Background: Phototherapy is a very commonly used treatment method in dermatology. The most commonly used phototherapy modalities are narrow band UVB, systemic PUVA, topical PUVA and UVA1, which are discussed in detail in this article. General information about each treatment modality, indications, contraindications, specific protocols and precautions are discussed in each section. Furthermore, acute and chronic side effects of phototherapy and their management are touched upon. Combinations therapies are discussed briefly as well.

The most commonly used phototherapy methods are broadband UVB (290-320 nm), narrowband UVB (311-313 nm), PUVA photochemotherapy, UVA1 (340-400nm), excimer laser (308 nm) and extracorporeal photochemotherapy. Narrowband UVB (nbUVB), PUVA and UVA1 will be discussed in this article in detail.

Introduction

The use of nbUVB is indicated in psoriasis vulgaris, vitiligo, atopic dermatitis, mycosis fungoides, other papulosquamous dermatoses, photodermatoses and pruritic dermatoses. The treatment protocol is determined either according to the Fitzpatrick skin type or according to the minimal erythematous dose (MED) that is determined via testing. MED is the smallest UVB dosage that can cause a pink-red erythema, which can still be visualized 24 hours after treatment. The purpose of dose increments is to obtain the MED. The suberythematogenic doses are effective as well; however, the treatment duration is

shorter with erythematogenic doses. The treatment durations differ for each disease and its severity [1,2].

Narrowband UVB Treatment in Psoriasis

Narrowband UVB is one of the first choices in the treatment of moderate-to-severe psoriasis vulgaris. As nbUVB is a systemic treatment modality, the percentage of affected body surface area should be at least 10%. Acute guttate psoriasis and plaque type psoriasis with minimal infiltration respond to nbUVB the best. nbUVB may cause flares in erythrodermic psoriasis or pustular psoriasis, for that reason it should not be used in these disease

forms unless it is the sole treatment option [3,4] nbUVB is a safe treatment option for children, pregnant and nursing women; it may be combined with topical retinoids [4].

Treatment protocols differ in their calculation of initial UVB dosage. According to the treatment protocol accepted, therapy is either initiated with 50-70% of MED [3,4,5] or 150-600 mj/cm² [3,4] according to the Fitzpatrick skin type. There are detailed protocols for dose increases, missed treatments and maintenance treatments, which is beyond the scope of this article.

Two-to-three treatment sessions are applied per week. The treatment duration needed for disease clearance is shorter, remission period is longer and the cumulative dose is lower with three treatments per week compared to two treatments per week [4] nbUVB treatment is discontinued when full remission is achieved or the disease stops responding to the treatment. Usually clinical remission is achieved at 20-36th session. The patients should be assessed for treatment efficacy with intervals of 2-3 weeks [5].

Narrowband UVB Treatment in Vitiligo

Narrowband UVB is the first treatment choice of phototherapy in vitiligo patients with affected surface area greater than 15-20 %. An international consensus upon the treatment protocol has not been reached. The treatment is given in two to three sessions per week. Patient compliance is better with two times per week; however, regimentation is earlier with three sessions for week. For that reason, many clinics prefer three sessions [6].

The treatment is initiated with 0.1-0.3 j/cm². The UVB dose is increased by 10-20% if no erythema occurs. The same dose is maintained if permanent erythema is observed. If the erythema persists for greater than 24 hours, the dose is decreased by 25%. The treatment is interrupted if tense erythema or bulla occurs [6].

The treatment response is evaluated after 18-36 sessions. A patient with no treatment response should receive at least 48 treatments in order to be classified as a non-responder. Under these conditions, treatment can be stopped. After full remission, maintenance treatment is initiated: two sessions per week

for the first 4 weeks, 1 session per week for the next 4 weeks, 1 session per two weeks for the third and fourth months. The treatment is stopped permanently if there is no relapse [6].

Narrowband UVB Treatment in Atopic Dermatitis

Topical treatments are the first choice in moderate-to-severe chronic atopic dermatitis. For adults and children older than 7 years of age, nbUVB is a second option for the treatment of moderate-to-severe chronic atopic dermatitis. It is as effective as PUVA or moderate dose UVA1. The treatment protocol is similar to that of psoriasis. Two to three sessions are applied per week. At least 30 to 50 sessions is needed for clinical remission. The pruritus subsides earlier than the skin lesions [7].

Maintenance therapy is initiated after clinical response of 95% is achieved. Sessions are applied at the last treatment dose, 1 session per week for the 1st 4 weeks after remission, then 1 session per 2 weeks at a 25% decreased dose for the next few weeks thereafter at the 50% of the highest dose, 1 session per month. nbUVB can be combined with topical corticosteroids and emollients; however, it should never be used with topical calcineurin inhibitors [7].

Narrowband UVB Treatment in Mycosis Fungoides

Narrowband UVB is an effective and well-tolerated treatment modality for early mycosis fungoides (stage 1A, 1B and 2A). The dosing protocol is similar to that of psoriasis: the treatment is initiated with 50-70% of MED and increments of 20% are applied. The treatment is applied 3 times a week on nonconsecutive days. The total treatment duration differs for every patient. It usually takes 3-4 months for the disease to achieve full remission with 3 sessions per week. A short maintenance therapy may be applied as well [8].

Systemic PUVA Treatment

Psoralen is a phototoxic compound that leads to photochemical reactions after absorbing photons. These reactions interact with the cellular components and change their functions. In systemic photochemotherapy, oral

psoralen is used. The indications of PUVA therapy are: Psoriasis, Mycosis Fungoides, Atopic Dermatitis and Vitiligo. The essential components of effective PUVA therapy are the psoralen dose, UVA dose and treatment duration [1,5].

8-Metoxypsoralen (8-MOP) or 5-Metoxypsoralen (5-MOP) is used in systemic PUVA. Psoralen's pregnancy category is C. The psoralen dose is calculated according to the body weight; the maximal dose of 8-MOP is 0.6 mg/kg. The drug should be orally administered 1.5 to 2 hours before treatment along with milk, bread or low-fat foods [3].

The patients should protect themselves from UVA and other UV sources for 16-24 hours until psoralen is cleared from the body. All of the patients should wear protective glasses during and after therapy. All patients, but especially males, should protect their genital organs [1].

According to the European protocol, treatment is initiated with 50-70% of the minimal phototoxic dose (MFD). Two to four sessions are applied per week. The dose increments are personalized; initially 30% of MFD each week and according to the erythema response thereafter. A total of 20 sessions is applied with the cumulative UVA dose of 96 j/cm². The disease clearance rate is 88.8% within an average of 5.7 weeks [5]. In the American Protocol, the initial dose is calculated according to the skin phototype. Two to three sessions are applied a week and the dose increments are not personalized unlike the European protocol. A break of at least 48 hours should be given between sessions. A total of 25 sessions is applied with a cumulative dose of 245 j/cm². The disease clearance rate is 88% within an average of 12.7 weeks [1,3].

PUVA Treatment in Psoriasis

In the treatment of psoriasis, systemic PUVA may be used alone or in combination with other conventional drugs. It is a good treatment option in the patients with widespread chronic plaque type psoriasis, which does not respond to topical treatments or narrow band UVB. It is effective in all psoriasis subtypes but is of primordial importance in guttate and plaque type psoriasis. The initial dose is calculated either according to the skin phototype or according to the MFD [1]. The doses are in-

creased according to the erythema response until a dose of 15 j/cm² is reached; the therapeutic dose should not exceed it [3]. The treatment is applied two to three times a week. Sessions are continued until clinical remission; however a maximum of 30 sessions should not be exceeded per cycle. The total number of sessions received lifetime should not exceed 200 sessions. Maintenance therapy is not recommended [5].

PUVA Treatment in Vitiligo

PUVA treatment is less often preferred compared to nbUVB. The initial UVA dose is 1 j/cm² for all skin phototypes and an increase of 0.5 j/cm² applied. If the European protocol is applied, the initial UVA dose is the 50% of MFD and increments of 10-20% are applied. The maximal UVA dose that can be applied is 5 j/cm² [9]. There is no consensus about the optimal treatment duration. Maintenance therapy is not necessary. PUVA treatment may be combined with topical corticosteroids, topical vitamin D analogs and topical calcineurin inhibitors [1,5].

PUVA Treatment in Atopic Dermatitis

Systemic PUVA may be initiated in chronic atopic dermatitis patients who are not responding to topical corticosteroids, emollients, topical calcineurin inhibitors and nbUVB. Again, the UVA dose is calculated according to the MFD or skin phototype. The Turkish population consists of mainly Fitzpatrick skin type 3-4 patients, for whom the initiating dose of 2 j/cm² is applied with increments of 1 j/cm². The maximal session dose should not exceed 20 j/cm². Two to three sessions are applied per week. There is no consensus upon the optimal treatment duration. Treatment response is usually seen after the 10th session. PUVA may be combined with topical corticosteroids. Maintenance therapy is not required [1,5].

PUVA Treatment in Cutaneous T cell Lymphoma (CTCL)

PUVA therapy is recommended in stages 1B and 2A. It should especially be considered as a treatment modality in plaque type CTCL patients. It is also effective at patch type CTCL; however nbUVB is the treatment of choice in these patients. The initial UVA dose and the increments are determined either according to the skin phototype or MFD. The doses sho-

uld be increased for carefully in erythrodermic patients. Two to three sessions are applied a week. Clinical response can be observed within one month. The three months period following full remission is the consolidation phase. During the consolidation phase the treatment doses and frequencies of induction phase should be applied. Like other diseases discussed above, there is no consensus upon the need of maintenance therapy. PUVA may be combined with interferon alpha-2b or retinoids in non-responders or slow responders [10,11].

Topical PUVA Treatment

There are two forms of topical PUVA: Bath PUVA and Local PUVA. The bath PUVA is applied with diluted psoralen solution. Total body bath PUVA is indicated in generalized chronic plaque type psoriasis, vitiligo and MF. Hand and foot bath PUVA is indicated in chronic hand and foot dermatoses namely hyperkeratotic dishydrotic eczema, palmoplantar psoriasis and palmoplantar pustular psoriasis. Local PUVA is applied with psoralen gel or cream. It is indicated in chronic hand and foot dermatosis, localized vitiligo and alopecia areata [12].

Topical PUVA has several advantages compared to systemic PUVA. First of all, the cutaneous psoralen level is high and the plasma psoralen level is low. As a result, methoxypsoralene exposure is decreased compared to systemic PUVA. Furthermore, free psoralenes are eliminated from the skin quickly. For that reason, the photosensitivity duration is shorter: 2-4 hours. Unlike systemic PUVA, topical PUVA has no gastrointestinal or ocular side effects. The UVA radiation exposure is lower and skin cancer risk is diminished. Moreover, it is more effective than systemic PUVA [12].

In certain situations, topical PUVA is a better option than systemic PUVA. Examples for these situations are hepatic dysfunction, gastrointestinal diseases, absorption disorders, cataracts, pediatric patients, claustrophobic patients, patients using drugs that may interfere with psoralenes (eg warfarin) and patients with minimal compliance to eye protection [13].

Psoriasis Treatment with Local PUVA

0.1% metoxalene gel is applied on the psoriatic plaque. The periphery of the plaque is occluded with Vaseline. UV protection glasses should be used. UVA therapy is initiated 15-30 minutes after the application of the gel. Psoralen should be cleared away with soap and water after treatment and sunscreens with both UVA and UVB filters should be applied. The starting dose is usually 0.5 j/cm² for all skin phototypes and the doses are increased by 0.25-0.5 j/cm² until 4 j/cm² if tolerated. Two sessions are applied a week [1,3].

Vitiligo Treatment with Local PUVA

Similar steps with the psoriasis treatment are applied in vitiligo treatment with topical PUVA as well. The initial UVA dose is 0.25-0.5 j/cm² and the weekly dose increase is 0.12-0.25 j/cm² with a maximum dose of 2 j/cm². The treatment is applied two times a week [1].

Psoriasis Treatment with Hand and Foot Bath PUVA

One ml of 1% metoxalene gel is added to 2 liters of water. The hand and the feet are kept within this mixture for 15 to 30 minutes and dried thereafter. UVA treatment is initiated 30 minutes after the bath. UV protection glasses should be worn during the treatment. After treatment, psoralen is washed away with soap and water and sunscreens with UVA and UVB filters should be applied. Two sessions per week is recommended. The initial UV dose differs for the palms and soles; and the dorsum of hand and feet for each skin phototype. The dose is increased by 0.5 j/cm² in each session however the maximum dose of 2.5 j/cm² should not be exceeded [1].

Vitiligo Treatment with Hand and Foot Bath PUVA

The same steps as in psoriasis treatment with hand and foot bath PUVA are applied. The initial UV doses range from 0.25 to 0.5 j/cm² for each skin phototype. Doses are increased by 0.25 to 0.5 j/cm² until reaching a maximum dose of 2 j/cm². One to two sessions are applied per week [1].

UVA1 Phototherapy

UVA1 ranges from 340-400 nm. Due to its increased wavelength, UVA1 can penetrate until deep dermis or even subcutis. Its erythematogenic effect is lower compared to UVA; thus burn risk as a treatment side effect is lower. There is no need for a photosensitizer agent in UVA1 treatment [14]. The treatment response for UVA1 is better in individuals with Fitzpatrick skin phototypes 1 and 2 compared to those with skin phototypes 3 and 4 [15].

Treatment indications for UVA1 therapy are [16].

- Sclerorising Diseases: Morphea, localized and generalized scleroderma, atherosclerosis, extragenital lichen scleroatrophicus, chronic graft versus host disease and nephrogenic systemic fibrosis
- Atopic Dermatitis
- CTCLs
- Granulomatous Diseases: Necrobiosis lipoidica diabetorum and Grannuloma Annulare
- Prurigo
- Ptyriasis lichenoides acuta et chronica
- Treatment resistant dishydrosis
- Systemic Lupus Erythematosus
- Polymorphous Light Eruption

UVA1 treatment is relatively contraindicated in pediatric patients (<18 years of age). Though, UVA1 treatment may be used in children if there is no treatment alternative. Low to moderate doses of UVA1 may be used without exceeding 40 sessions per year. Similar to adults, children should also be kept away from sunlight after treatment and should routinely be screened for skin cancers [17].

Topical drugs or emollients should not be applied before treatment. The doses are calculated according to the minimal pigmentation dose (MPD) or applied at a constant dose. MED is not used in UVA1 treatment [16].

UVA1 Treatment in Sclerosing Skin Diseases

UVA1 is an effective treatment method for sclerosing skin diseases however it is an insufficient treatment method for pathologies localized in deeper layers. Such diseases are

atrophic lesions, morfea profunda, Parry-Romberg/ Hemifacial Atrophy and eosinophilic fasciitis [16]. Constant doses are preferred more. Low doses of UVA1 range between 10-30 j/cm², medium doses range between 40-70 j/cm² and high doses range between 70-130 j/cm². Three to five sessions are applied per week [18].

Marked improvement in morphea lesions is achieved with 24-30 sessions of UVA1 treatment. The maximum UVA1 session number of an individual per lifetime should not exceed 200 [19]. High dose UVA1 is more effective compared to medium dose UVA1 and medium dose UVA1 is more effective than lower dose UVA1 and nbUVB. The efficacy of low dose UVA1 and nbUVB are similar [18]. If the MPD protocols are applied, the dose is increased 20% per session until pigmentation is achieved. The dose is decreased 10% in the session following minimal pigmentation [20]. There is no consensus upon the need of maintenance therapy [19].

UVA1 Treatment in Atopic Dermatitis

UVA1 is the first treatment choice in adults with severe acute attacks of atopic dermatitis. nbUVB is preferred in chronic cases [21]. UVA1 can be applied at low/medium or high doses. Medium doses of UVA1 is more efficacious than low dose UVA1, UVA and nbUVB; and as efficacious as high dose UVA1 [19]. Remission is achieved at 4 weeks, which is similar to high dose UVA1 therapy. Three to five sessions are applied per week. The average treatment duration is 10 to 15 sessions [22]. nbUVB is recommended for maintenance [21].

UVA1 Treatment in CTCLs

In the treatment of early CTCLs, nbUVB is preferred in stage 1A and PUVA is preferred in stages 1B and 2A. UVA1 penetrates deep into dermis and subcutis, therefore, it is an alternative treatment modality for PUVA in patients with MF and other CTCLs. Thus, UVA1 may be used in the treatment of stage 1A, 1B, plaque, nodular and erythrodermic CTCLs [23]. There is no standardized treatment protocol. The treatment can be applied with constant doses of UVA1 (low, medium or high dose) or at doses calculated with the MPD. Three to five sessions are applied per week. The treatment duration ranges from three to six weeks. Patients may be evaluated

histologically at the end of the treatment cycle [15, 16, 18]. Other diseases in which the CTCL UVA1 protocol is used are lymphomatoid papulosis, pityriasis lichenoides et varioliformis acuta and granulomatous slack skin [19].

Side Effects of Phototherapy

Acute Side Effects

Commonly observed acute side effects of phototherapy are [24].

- Phototoxicity (tense erythema, pruritus, bullous UV burn)
- Headache and vertigo
- GI side effects: nausea, decreased appetite (for oral PUVA treatment)
- Ocular side effects: photokeratitis
- Polymorphous light eruption
- Herpes simplex infection reactivation
- Flares of pre-existing dermatoses

Rarely seen side effects are [24].

- Bronchospasm
- Hepatotoxicity
- Drug fever
- Skin rash
- Photo-onycholysis
- Leg edema
- Hypertrichosis

Chronic Side Effects

The chronic side effects of phototherapy are [24].

- Skin aging
- Wrinkles
- Telangiectasias
- Elastosis
- Skin atrophy
- PUVA lentiginos
- White macules
- Precancerous skin lesions, skin cancer
- Cataract
- Xerosis

Management of complications

If tense erythema, pruritus and bullous UV burn are observed after phototherapy, anti-inflammatory drugs such as aspirin and indometazin may be administered right after the sessions. Topical corticosteroids and emollients can be applied as well. The topical agents are also effective for phototherapy related pruritus. Yet, if the pruritus is severe recalcitrant to topical treatment methods, sessions can be stopped temporarily. Pigmentation may occur due to phototherapy sessions, however, it subsides with treatment cessation or by increasing the intervals between sessions. In order to overcome psoralen induced nausea, psoralen may be taken with food, its dose can be decreased by 10 mg, the dose can be divided into three and taken with 15 minute intervals or an antiemetic drug may be taken half an hour before the psoralen dose [25].

Ocular complications such as grittiness, pain, photophobia, tearing and blepharospasm may be observed as a result of phototherapy. Patients receiving systemic PUVA treatment should be referred to an ophthalmologist before treatment and with periodic intervals during treatment. Protective glasses should be worn during phototherapy. After systemic PUVA, adults should wear protective glasses for at least 12 hours; children and adults with co-morbid cataract should wear the glasses for 24 hours. The use of artificial tears may decrease the discomfort and provide the patients symptomatic relief. Patients should protect themselves from sunlight for 4 hours after bath PUVA methods and 2 hours of local PUVA methods [26].

In order to prevent photoallergic reactions patients should avoid drugs that are susceptible for photosensitization and cosmetic products with fragrances. These drugs are [27].

- Antibiotics such as tetracyclins, quinolones and sulphonamides
- Nonstreoidal Anti-inflammatory Drugs
- Diuretics such as furosemide, bumetanide and hydrochlorothiazide
- Sulphonylureas
- Statins
- Phenothiazines

- Epidermal growth factor inhibitors
- Antifungals such as terbinafine, itraconazole, voriconazole and griseofulvin

Polymorphous light eruption represents with an erythemopapular rash in skin areas not exposed to sun. If polymorphous light eruption is observed after phototherapy, the treatment is continued. Topical corticosteroids and emollients may be applied in mild cases. Systemic steroids may be necessary in severe cases. Herpes simplex may become reactivated during phototherapy cycles. The herpetic lesions should be covered and constrained from phototherapy. In very severe cases, phototherapy sessions can be skipped and antiviral treatment may be initiated [25].

The dermatoses may flare due to phototherapy as well, this especially occurs with PUVA treatment. In this situation, other possible causes of the flare should be investigated and if possible eliminated. If the flare is absolutely due to photoaggravation, phototherapy is terminated and alternative treatment methods should be searched [25].

Patients who have received phototherapy are at increased risk for precancerous skin lesions and skin cancers. The patients should routinely be screened for actinic keratosis, squamous cell cancers, basal cell cancers and melanoma. In patients with Fitzpatrick skin types 1 and 2, the risk of squamous cell cancer increases with 200 sessions of PUVA or UVA1 and with 300 sessions of nbUVB. The genital skin should always be covered during treatments since the risk of genital skin cancer is even higher. The patients should always wear sun protection. The cumulative UV dose and treatment durations may be diminished by the use of combined treatment methods [25].

Treatment Combinations

Methotrexate (MTX)

MTX acts synergistically with nbUVB and PUVA treatments; however, its combination with PUVA is not commonly favored due to the increased risk of phototoxicity. MTX and nbUVB combination is more commonly used. It has a lower risk of phototoxicity. MTX is started 3 weeks prior to the initiation of phototherapy with a dose of 15 mg/week. When the psoriatic plaques subside, MTX is stopped

and treatment continues only with phototherapy [28].

Acitretin

Acitretin may be combined with nbUVB (re-nbUVB) or PUVA (re-PUVA). Due the increased risk of squamous cell cancer with PUVA, re-nbUVB is more commonly preferred. Retinoid treatment is initiated 2 weeks prior to phototherapy. 25mg/day dose is used in patients weighing greater than 70 kg and 10mg/day dose is used in patients weighing less than 70 kg. By combining phototherapy and retinoids, the cumulative phototherapy dose, the total number of treatment sessions and treatment duration decreases. The efficacy of phototherapy increases when it is combined with acitretin. Retinoid treatment is continued long after phototherapy is stopped until long term control of the disease is achieved [29,30].

Cyclosporine

Cyclosporine should not be combined with phototherapy due the increased risk of non-melanoma skin cancers, especially squamous cell cancer. Patients who have received phototherapy beforehand, should be screened for non-melanoma skin cancers before initiating cyclosporine treatment and during cyclosporine treatment [31].

Contraindications of Phototherapy Modalities

Contraindications of UVB Therapy

The absolute contraindications of UVB therapy are [3,4,11,32].

- Photosensitive Autoimmune Dermatoses (Systemic Lupus Erythematosus, Dermatomyositis, anti-Ro antibody positivity)
- Photodermatoses or genodermatoses with increased cancer risk
- Xeroderma Pigmentosum
- Bloom Syndrome
- Rothmund Thomson Syndrome
- Cocayne Syndrome
- Trikothiodystrophy
- Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome)
- Albinism

Contraindications of PUVA Therapy

All of the absolute contraindications of UVB therapy also apply for PUVA therapy. Furthermore, PUVA is contraindicated in pregnancy, lactation and idiosyncratic reactions to psoralene [3,4,11,32].

Contraindications of UVA1 Therapy

UVA1 phototherapy is contraindicated in [16,18].

- Severe photosensitive diseases such as Xeroderma Pigmentosum and Porphyria
- UVA sensitive photodermatoses or photosensitive atopic dermatitis
- Use of photosensitizing drugs
- History of melanoma or non melanoma skin cancers
- Long-term immunosuppression (eg. Organ transplantation)
- Pediatric patients (<18 years of age)
- Previous radiotherapy exposure

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