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PHOTOTHERAPY (UVB) AND PHOTOCHEMOTHERAPY (PUVA) FOR PSORIASIS

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SUMMARY – The review covers the current practice of phototherapy with ultraviolet (UV) radiation without sensitizers and of psoralen photochemotherapy (PUVA) in the treatment of psoriasis. There are several types of UVB radiation in clinical use: traditional or broad band UVB (280 – 320 nm); selective UVB (305 – 325 nm); and narrow band UVB (311 nm). Forms of PUVA therapy are: systemic photochemotherapy (PUVA therapy with oral administration of psoralen); PUVA bath therapy; and PUVA therapy with topical psoralen application. PUVA therapy is more effective than UVB therapy in clearing psoriasis in most patients, but since UVB is easier to administer and does not involve an oral photosensitizing medication, it is often selected before PUVA. UVB and PUVA have been administered alone or in combination with topical corticosteroids, salicylic acid, anthralin, calcipotriol and tazarotene, and with systemic therapies such as retinoids. The most important potential long-term side effects of UVB and PUVA are accelerated skin aging and an increased risk of cutaneous cancer.

Key words: *Psoriasis, therapy; Ultraviolet therapy, methods; PUVA therapy methods, Ultraviolet therapy, adverse effects*

Introduction

Since ancient times, the beneficial influence of sunlight radiation on a broad variety of diseases has been recognized, and a variety of therapies based on these observations have been developed. The first artificial light source, in the form of a carbon arc, was used for the treatment of lupus vulgaris by Niels Finsen in 1903[1].

Early in the 20th century, so-called helio- or actinotherapy for psoriasis enjoyed great popularity, especially in Europe. In the beginning, phototherapy for psoriasis was performed primarily by using broad spectrum ultraviolet radiation. In 1923, Alderson started to use quartz-jacketed mercury vapor lamps at erythemogenic doses to improve psoriatic skin lesions; in 1925, Goeckerman added crude coal tar to enhance the effects of ultraviolet radiation. Since then, therapeutic regimens of psoriasis have been amply modified, including both variation of ultraviolet radiation spectra and combination of phototherapy with adjunctive agents[2].

Phototherapy (UVB)

Phototherapy (UVB) is indicated for patients with generalized plaque, guttate psoriasis, or palmoplantar psoriasis who have not responded adequately to conventional topical therapies[1]. Since UVB is easier to administer and does not involve an oral photosensitizing medication, this form of phototherapy is often selected before psoralen photochemotherapy (PUVA). In addition, factors that suggest use of UVB therapy in comparison to PUVA therapy are: brief history of psoriasis, as it is possible that

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maintenance treatment will be unnecessary (acute guttate psoriasis); less than 30% of the body surface involved by the disease before treatment; thin, macular psoriasis; young age; and skin type I or II[3].

There are several types of UVB radiation in clinical use: 1) traditional or broad band UVB lamps deliver radiation over 280 – 320 nm; 2) selective UVB phototherapy (SUP) has peaks at 305 and 325 nm; 3) narrow band UVB lamps (Philips TL_{01}) deliver almost exclusively 311 nm radiation[4].

Patients treated with narrow band UVB lamps (311 nm) showed faster clearing of psoriatic lesions, fewer episodes of excessive erythema, and longer period of remission when compared with broad band sources[5-10]. When TL-01 phototherapy and PUVA were compared, there was little overall difference in efficacy[11-13].

Before therapy is started, the minimal erythema dose (MED) should be determined. MED is the minimal amount of energy required to produce a uniform clearly demarcated erythema response, usually at 24 hours. MED is determined by exposing small areas of normal skin to increasing doses of ultraviolet radiation, preferably using a dose series with geometric increments (for example, successive doses increased by 40%)[14]. The initial dose may vary and is usually 0.75 – 0.9 MED[15].

Another approach is to plan the starting dose for phototherapy according to the patient's skin type. Fitzpatrick developed a concept of skin types to categorize more quickly an individual's response to sunlight[16]. The skin type is based on the person's reaction to 30 min mid-day sunlight for the first time in the summer (Table 1).

The choice of the starting dose for UVB phototherapy based on skin type assessment is more widely practised in the U.K. than MED testing[17]. At our Department of Dermatology and Venerology, we also use this method.

The minimal frequency of treatment is three times a week (usually on Monday, Wednesday and Friday), although four or five treatments *per* week (on each week day) are preferable and result in a higher rate of success. The twice weekly schedule is usually ineffective[15,18,19]. For total clearing, usually defined as less than 5% total body surface involvement for patients who begin with at least 30% body coverage, an average of 25-30 treatments are required in both three- and five-times weekly regimens, but patients with very thick plaques may need more treatments or a change in therapy[1,15]. When patients have reached a plateau in their response, a tapering maintenance schedule begins, enabling them to gradually decrease the frequency of treatments before discontinuing phototherapy. The remission induced by UVB phototherapy is temporary and its duration displays considerable individual variation. Stern *et al.* demonstrated that postclearing UVB phototherapy, even at a modest average frequency of six treatments *per* month, significantly and substantially increased the interval during which the disease remained under excellent control[20].

UVB and topical agents

Topical corticosteroids are frequently used in conjunction with UVB phototherapy, but there is no consensus as to whether they enhance the therapeutic response to UVB. Several studies failed to demonstrate any significant difference either in the number of treatments needed to obtain clearing, or in the duration of remission[21-23]. Although they may accelerate an early response, the continued use of steroids does not increase the efficacy of pho-

Table 1. Skin type classification and corresponding UVB minimal erythema dose

Skin type		Reaction to first sun exposure of 3 MED	MED (mJ/cm^3) for UVB
I	Always burn, never tan	20 – 30	
II	Usually burn, tan less than average	25 – 35	
III	Sometimes burn, tan about average	30 – 35	
IV	Rarely burn, tan more than average	45 – 60	
V	Brown-skinned persons	60 – 100	
VI	Dark-skinned persons	100 – 200	

MED = minimal erythema dose
(adapted from Fitzpatrick TB. The validity and practicability of sunreactive skin types I through VI. Arch Dermatol 1988;125:869-71)

totherapy and may result in a shorter duration of response[1,4].

Topical salicylic acid, which is often used in the treatment of psoriasis, can decrease the effectiveness of phototherapy by providing photoprotection[24].

Calcipotriol and other vitamin D analogues have a well documented effect in the treatment of psoriasis. Many studies have shown that the addition of topical calcipotriol can enhance the effect of UVB therapy[25-29]. It is important to instruct patients to apply calcipotriol after phototherapy. This precaution may keep the calcipotriol ointment from impeding the transmission of UV light, to prevent the destruction of calcipotriol by UVA radiation, and to possibly minimize any discomfort that could arise in a small number of patients if calcipotriol ointment is applied just before phototherapy[30]. The Ingram method uses UVB light (either broad band or narrow band) followed by topical anthralin. With either source, the healing is more rapid and the cumulative UVB dose lower than with monotherapy[7,31-33]. Well known side effects are skin irritation and considerable cosmetic inconveniences such as staining of the skin and clothes. The Goeckerman regimen (UVB + tar) is not clearly superior to UVB monotherapy and has lost acceptance in recent years[2,4].

Tazarotene, a third generation retinoid, can also enhance the effect of phototherapy. Several studies have shown that tazarotene plus UVB phototherapy are superior to UVB monotherapy in terms of both efficacy (greater reduction in plaque elevation, scaling and erythema) and rapidity of action[34-36]. Schiener *et al.* compared narrow band UVB with either topical calcipotriol or topical tazarotene. The comparison revealed no significant therapeutic difference between the two regimens[37].

UVB and systemic agents

The treatment of psoriasis with acitretin in concert with UVB is emerging as a viable clinical strategy. Compared with either acitretin (25 – 50 mg) or UV light monotherapy alone, the combination regimen enhances efficacy and limits treatment frequency, duration, and cumulative doses. Moreover, patients whose psoriasis does not clear with monotherapy will often achieve significant clearing with the combination of acitretin and phototherapy[6,38-40].

Combinations of phototherapy with methotrexate or cyclosporin A are to be avoided, since both agents enhance the probability of UV induced skin tumors[2].

Side effects

The main short-term problem is erythema (sunburn reaction). Slightly erythematogenic UVB doses are considered necessary to clear psoriasis effectively but severe sunburn reactions should be avoided. Well known ocular side effects of UVB include conjunctivitis and keratitis, and therefore eye protective glasses should always be worn by both the patient and the phototherapy technician[15,18].

The most important potential long-term toxicities of UVB phototherapy are accelerated skin aging and an increased risk of cutaneous cancer. Photoaging, in contrast to true chronologic aging, is defined as skin changes as the result of repeated ultraviolet exposure rather than due to passage of time alone. It is clinically characterized by coarseness, wrinkling, laxity, increased fragility, mottled pigmentation, telangiectases, and atrophic or fibrotic areas[41].

UVB phototherapy adds to the cumulative lifetime UVB exposure, which is an etiologic risk factor for skin cancer. However, there was no significant increase in the risk of squamous cell carcinoma or basal cell carcinoma following long-term exposure to UVB according to the patient data from the 16-center United States PUVA study[42]. Long-term studies in Europe of extensively UVB-treated patients with psoriasis, the majority with type II skin, also failed to show an increased incidence of skin cancer[43,44]. On the contrary, Stern *et al.* studied 59 skin cancer patients with severe psoriasis treated with tar and/or UVB, matching case controls to allow for a number of confounding factors. For high exposure UVB (more than 300 treatments) and/or high tar exposure (more than 90 months of at least weekly use), the rate of cutaneous carcinoma was 4.7 times that of the non-high exposure group[45].

Although there are isolated case reports of melanoma occurring in patients who received phototherapy, a clear correlation has not been established[15].

Photochemotherapy (PUVA)

Photochemotherapy (PUVA) is a therapeutic method that uses psoralen and exposure to longwave ultraviolet A radiation (320 – 400 nm). Psoralens are tricyclic furocoumarins naturally occurring in certain plants, most of them being also synthetically produced[46]. Psoralens can be used systemically or topically or as bath therapy. Currently, 8-MOP (methoxsalen) is most commonly prescribed, but 5-MOP (bergapten) is also used where avail-

able. The synthetic furocoumarin, 4,5,8-trimethylpsoralen (TMP) is used for bathwater-delivered PUVA mainly in Scandinavia. 8-MOP and 5-MOP are available as oral preparations, which contain either crystals, micronized crystals or solubilized psoralens in a gel matrix. The liquid preparation induces earlier, higher and more reproducible peak plasma levels than the crystalline preparations[47].

Psoralen molecules intercalate between strands of DNA, and when they are exposed to UVA, they form adducts with the DNA and thus interfere with cell proliferation[48,49]. Psoralens are metabolized in the liver and their metabolites are excreted in urine 12-24 hours after peroral administration[50].

The action spectrum of UVA ranges from 320 nm to 380 nm, however, shorter wavelengths of 320-340 nm have recently been shown to be efficient in PUVA therapy[51,52].

Practically all forms of psoriasis respond to PUVA, although the management of erythrodermic or generalized pustular psoriasis is more difficult[47,53]. The factors that suggest use of PUVA therapy in comparison with UVB therapy are: long history of psoriasis, so that maintenance therapy is an almost certain requirement; more than 30% of the body surface involved by the disease before the treatment; thick plaques; involvement of the palms and soles; nail disease; failure to respond to UVB phototherapy; very active, aggressive disease with marked inflammatory component; and skin types III and IV[3].

All patients should be evaluated for their suitability for PUVA prior to commencement of treatment (Table 2).

Table 2. PUVA contraindications

Absolute	
	Xeroderma pigmentosum
	Gorlin's syndrome
	Hereditary dysplastic nevus syndrome
	Systemic lupus erythematosus
	Dermatomyositis
	Trichothiodystrophy
	Bloom's syndrome
	Cockayne's syndrome
	Previous malignant melanoma
Relative	
Major	
	Age less than 10 years[1]
	Previous or current non-melanoma skin cancer
	Previous exposure to arsenic or ionizing radiation
	Current premalignant skin lesions
	Concomitant immunosuppressive therapy
	Pregnancy
	Porphyria
Minor	
	Age less than 16 years[1]
	Cataracts[2]
	Bullous pemphigoid
	Previous or concomitant treatment with methotrexate
	Significant hepatic dysfunction[2]
	Previous internal malignancy

[1]A lower age limit may be acceptable where topical psoralen is used; [2]Oral psoralen only.

(British Photodermatology Group. British Photodermatology Group guidelines for PUVA. Br J Dermatol 1994;130:246-55)

Forms of PUVA therapy

Systemic photochemotherapy (PUVA therapy with oral administration of psoralen)

All patients require complete eye examination when initiating oral PUVA therapy, because psoralens can form photoproducts with lens proteins and their accumulation results in cataracts[49]. Evaluation of liver function before PUVA is advised, particularly in patients at risk of hepatic disease.

The usual dose of psoralens is 0.6 – 0.8 mg/kg of 8-methoxypsoralen or 1.2 – 1.4 mg/kg of 5-methoxypsoralen given 2 h prior to the skin exposure to UVA radiation. The newer capsules allow for exposure 1 h after ingestion[4,47].

The choice of initial UVA dose is of paramount importance. There are very high interindividual differences in the phototoxic response. Individual phototoxic response is assessed by determining minimal phototoxic dose (MPD). MPD is a dose of UVA radiation which produces, upon administration of appropriate psoralen doses, a sharply demarcated erythema on the exposed area after 72 hours. In practice, MPD is determined by exposure of small areas of the thigh region to increasing UVA doses of 0.5 – 5 J/cm^2 for skin types I and II, and 1.5 – 9 J/cm^2 for skin types III and IV. The phototoxic erythema threshold value is determined by erythema readings 72 to 96 hours later[54].

Two therapeutic protocols of PUVA-treatment for psoriasis were developed simultaneously. The European PUVA Study (EPS) protocol includes MPD as initial dose, followed by four exposures *per* week. The weekly UVA dose increase is 0.5 to 2.0 J/cm^2, depending on the patient's phototoxic and pigment response[55]. Dermatologists from the USA mostly use the United States Cooperative Clinical Trial (USCCT) protocol. The initial UVA dose is determined according to the patient's skin type. PUVA therapy is performed 2-3 times *per* week, with a 0.5 – 1.5 J/cm^2 increase in the UVA radiation dose[56].

Success rates reported by the USCCT and EPS are essentially similar: 88% *vs* 88.8% treatment response better than marked improvement. However, in the former trial, the median number of exposures until clearing was higher (25 *vs* 20) and therefore the duration of the clearing phase was twice (12.7 *vs* 5.3 weeks) as long as in the latter[55,56].

Maintenance therapy is performed quite commonly when the European regimen is used. It consists of four weeks of twice-weekly treatments at the last UVA dose used for clearing, followed by four once-weekly exposures[47,49,57].

According to the recommendation of the British Photodermatology Group, maintenance therapy following routine clearance of psoriasis should be avoided in order to minimize cumulative UVA exposure. Maintenance PUVA should only be considered if there is a rapid relapse of psoriasis following clearance or as part of a rotational regimen of second-line treatments[58].

PUVA bath therapy

PUVA bath therapy has been popular in Scandinavia for many years, however, since recently it has attracted interest worlwide. Patients are bathing for 20 min in 150 l of water containing 0.5 – 1.0 ml/l of 8-methoxypsoralen or trimethylpsoralen at 37 °C[4]. UVA radiation is given immediately after the bath, as the desired phototoxic effect vanishes rapidly[59,61].

The advantages of PUVA bath therapy include the absence of gastrointestinal (nausea, vomiting), hepatic (elevation of liver transaminases) and ocular side effects because there is no systemic photosensitization[61-63].

In three European studies, PUVA bath therapy has shown greater efficacy than oral PUVA therapy[62-64]. The same therapeutic effect required smaller cumulative UVA doses and lower number of exposures.

PUVA therapy with topical psoralen application

The application of 8-MOP in creams, ointments or lotions followed by UVA irradiation is efficacious in clearing psoriasis but has several disadvantages. The non-uniform distribution on the skin surface induces unpredictable phototoxic erythema reactions and irregular patches of cosmetically unacceptable hyperpigmentation[65].

Combination treatments

Topical adjuvant therapies with corticosteroids, anthralin, and more recently with calcipotriol and tazarotene have been tried with some success. Topical application of corticosteroids reduces the time to remission, however, relapses occur sooner than without their use[66]. The efficacy of PUVA therapy is increased by topical application of cignolin[67]. Two studies have shown that phototherapy can be enhanced by the use of calcipotriol. The first and the largest study of this kind was performed in France and Belgium, and 103 patients were involved[68,69]. The second study, performed the UK, involved 13 patients only. In the PUVA bath study[70], the efficacy of tazarotene in combination with PUVA bath therapy was evaluated in 12 patients with extensive plaque psoriasis. The tazarotene plus PUVA bath therapy

was clinically and statistically superior to the vehicle plus PUVA bath therapy.

The combination of PUVA with systemic retinoids (today we employ acitretin only, 30-50 mg) is one of the most potent therapeutic regimens for psoriasis[42]. One tends to employ retinoids first for 2-3 weeks. This flattens lesions and reduces scale, facilitating PUVA therapy. This combination, called RePUVA, has been reported to reduce the number of exposures by one-third and the total cumulative UVA dose by more than one-half[71]. RePUVA is used for 'poor PUVA responders', generalized pustular psoriasis, and psoriatic erythroderma[47,48].

The combination of PUVA and methotrexate during the clearing phase reduces the duration of treatment, number of exposures and total UVA dose, and is also efficacious in clearing patients unresponsive to PUVA or UVB alone[72].

In view of the possible long-term side effects (immunosuppression, skin carcinogenesis), the combination of PUVA plus cyclosporin A cannot be recommended[73,74].

Side effects

Erythema is the most common acute side effect of PUVA therapy. It is well known that erythema from PUVA is delayed by 48 to 72 hours or longer in case of severe reaction compared to that from UVB, which usually peaks within 12 hours. In two large studies, the incidence of erythema accompanying PUVA therapy was 32.3% and 48%[55,59]. Mild pruritus is a very common complaint. The most common cause of pruritus is dryness of the skin and it responds to lubricants. PUVA therapy can cause another type of pruritus, commonly called 'PUVA itch', which is a deep, burning sensation[75]. It is a symptom of phototoxicity. For extensive erythema and pruritus, non-steroidal anti-inflammatory drugs and topical corticosteroids may be required. Photo-onycholysis and subungual hemorrhages are delayed signs of acute phototoxicity in the nail bed[47,76].

Oral administration of psoralens can induce systemic side effects in the absence of light. Therapy with 8-MOP is not infrequently disrupted by acute gastrointestinal adverse reactions, mostly nausea and vomiting. In contrast, 5-MOP appears to be almost as efficacious as 8-MOP, and is virtually free from these effects. However, 8% of subjects are reported to develop an apparently harmless, asymptomatic, maculopapular, intertriginous eruption early during the treatment, which subsides spontaneously despite continued treatment[77]. Hepatic adverse effects of psoralens are uncommon, except perhaps in conjunction with a pre-existing liver dysfunction[78-80].

Careful pretreatment, ophthalmologic evaluation, and eye protection during and after UVA exposure are necessary to avoid acute inflammation of the conjunctiva and cornea. Despite experimental data that indicated a risk of premature cataract formation, prospective studies did not find an increased frequency of cataracts in patients treated with PUVA therapy[81-84].

The major concern with prolonged and repeated phototherapeutic regimens is the induction or promotion of skin cancers. The risk factors for the development of skin carcinoma following PUVA therapy include cumulative dose of UVA radiation, skin type, previous treatment for psoriasis (arsenic, UVB, methotrexate), and previous skin alterations[85]. Almost all data were obtained from psoriatics as they are the largest group of patients receiving PUVA.

In the past 12 years (1990-2001), several studies have been published that support the earlier U.S. findings[86-88], that PUVA can act as a complete carcinogen in humans. In 1990, Stern *et al.* reviewed the incidence of male genital tumors in their ongoing study, with a 12.3-year follow-up in 892 men[89]. There was a strong dose-dependent increased risk of genital tumors associated with PUVA and UVB in separate. The risk of invasive squamous cell carcinoma (SCC) of the penis and scrotum was 95.7-fold that in the general population. These findings were supported by Perkins *et al.* who, in a retrospective survey of 130 men with an average exposure of 1142 J/cm^2 in 98 months, found that 4% had SCC (31-fold risk in the general population) and three patients had genital tumors (362-fold rate found in the general population)[90]. Another highly relevant study was that of Brynzeel *et al.*, who examined 260 patients after an average follow-up period of 8.6 years. Of these, 4.6% had SCC and the risk was 12-fold that in the general population, independently of other risk factors[91]. Lever and Farr examined 54 British patients who had received high doses of UVA radiation (>2000 J/cm^2), after a mean of 11.2 years. The diagnosis of SCC of the skin at the sites protected from natural ultraviolet radiation was made in 19% of the patients[92].

Stern *et al.* performed a prospective study in a cohort of 1380 patients with psoriasis who were first treated with PUVA in 1975 and 1976, and evaluated risk factors associated with the development of cutaneous SCC and basal cells cancers (BCC). From 1975 through 1996, 237 (17.17%) patients developed 1422 cutaneous SCC. From

1975 through 1997, 247 (23.70%) patients developed 1042 BCC.

Based on all studies, it can be concluded that high-dose exposure to PUVA is associated with a persistent, dose-related increase in the risk of SCC, even among patients without substantial exposure to other carcinogens. Exposure to PUVA has by far less effect on the risk of BCC[93].

Based on a recent study in 944 Swedish and Finnish patients, bath PUVA with trioxsalen seems to bear no relevant risk of carcinogenesis[94]. In addition, no association between cutaneous cancer and 8-MOP bath PUVA was found in 158 Finnish psoriatic patients[95]. These data on long-term safety of bath PUVA are encouraging, however, there are other opinions as well. Shepard and Panizzon conclude that all forms of PUVA therapy, irrespectively of the route of 8-MOP administration, contribute to a dose-dependent increase in the risk of non-melanoma skin cancer[96].

Except for anecdotal reports, malignant melanoma has not been observed in PUVA treated patients until recently, and no increase in melanoma was found in a large number of studies reported so far. However, in 2001, Stern reported on 26 invasive or *in situ* melanomas in 23 patients from a cohort of 1380 patients enrolled in the PUVA follow-up study (16-center study). Stern concluded that 15 years after the first exposure to PUVA, an increased risk of melanoma was observed in the cohort of PUVA treated patients, this risk being greater in patients exposed to high doses of PUVA (more than 250 treatments) and appearing to increase with time[97].

Although this report needs to be confirmed by other multicenter trials, it is alarming since the association between exposure to ultraviolet light and development of melanoma has been well established in both humans and experimental animals. Until this study is validated, it is recommended that the guidelines for PUVA therapy be rigorously followed and that the contraindications be extended to include history or family history of melanoma and patients who have already received >200 treatments[98].

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Sažetak

FOTOTERAPIJA (UVB) I FOTOKEMOTERAPIJA (PUVA) U LIJEČENJU PSORIJAZE

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Ovaj pregledni članak obuhvaća suvremenu primjenu fototerapije s UV zračenjem bez senzibilizatora i psoralensku fotokemoterapiju (PUVA) u liječenju psorijaze. U kliničkoj je primjeni nekoliko vrsta UVB zračenja: klasično ili UVB zračenje širokog spektra (280 – 320 nm); selektivno UVB zračenje (305 – 325 nm); UVB zračenje uskog spektra (311 nm). Oblici PUVA terapije su: sistemska fotokemoterapija (PUVA terapija s peroralnim uzimanjem psoralena); liječenje PUVA kupkama (PUVA *bath*); PUVA terapija s lokalnom primjenom psoralena. Iako je u većine bolesnika PUVA terapija učinkovitija od UVB terapije, UVB terapija se obično odabire prije PUVA terapije zbog lakše primjene, kao i stoga što ne uključuje uzimanje oralnog fotosenzibilizatora. UVB i PUVA rabe se samostalno ili u kombinaciji s lokalnom primjenom kortikosteroida, salicilnom kiselinom, antralinom, kalcipotriolom, te sa sistemskom primjenom lijekova kao što su retinoidi. Najznačajniji potencijalni dugoročno štetni učinci UVB i PUVA terapije su ubrzano starenje kože i povećani rizik od raka kože.

Ključne riječi: *Psorijaza, liječenje; Liječenje ultraljubičastim zračenjem, metode; Fotokemoterapija (PUVA) metoda, Liječenje ultraljubičastim zračenjem, štetni učinci*