

## Phototherapy of Psoriasis in the Era of Biologics: Still In

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**SUMMARY** This article reviews recent literature on phototherapy for psoriasis, particularly narrowband UVB. The efficacy, safety, tolerability and acceptance of phototherapy are discussed. It focuses in detail on how to improve the efficacy and safety in practice by trying to optimize the protocols, using combination therapy, monitoring the cumulative dose and providing skin cancer surveillance. Careful patient selection, individualized treatment, long-term therapy plan and complex approach to patients are the prerequisites for this. Narrowband UVB as the most widely used modality of phototherapy for psoriasis has a relatively good efficacy, cost, availability and minimal side effects. It represents a valuable treatment, which deserves more utilization and research. Although not so dynamic as in systemic drugs, research into phototherapy is ongoing. Even in the era of biologics, phototherapy remains an important therapeutic modality for psoriasis and other dermatoses and represents an essential part of modern dermatological therapy.

**KEY WORDS:** phototherapy, psoriasis, narrowband UVB, optimizing protocols, combination therapy

### INTRODUCTION

Biologics have temporarily pushed conventional systemic antipsoriatic therapy including phototherapy aside. However, their longer use in clinical practice has revealed that monotherapy is not sufficient in all cases. This renewed the interest and research in traditional systemic therapy not only as potential agents to be used in combination with biologics. In order to improve the efficacy, tolerance and safety of treatment with conventional drugs, it is necessary to additionally investigate and incorporate evidence based data into guidelines. This also applies to phototherapy.

Treatment and management of psoriasis requires long-term planning. Careful patient selection, individualized treatment and complex approach to patients are very important. Due to its relatively good efficacy, costs, availability and minimal side effects, phototherapy represents a valuable, but sometimes

underestimated method, which deserves more utilization and research (1-8).

The history of phototherapy started at the beginning of the last century, when lupus vulgaris was treated with UV light by Finsen, consequently honored with Nobel prize. Nowadays, there are many kinds of phototherapeutic modalities and methods (Table 1) available, with narrowband UVB (NBUVB) and photochemotherapy PUVA being most often used for psoriasis (1-8).

For reaching an optimal effect, phototherapy has to be individualized to the phase of disease and to the particular patient. This means that the responsible physician must be aware of the mechanism of action of various methods and dosage regimens, e.g., choice of an optimal method and protocol for the given disease and its pathophysiology. However, there is

**Table 1.** Modalities and methods of phototherapy

Method of phototherapy	Abbreviation	Spectrum (nm)
Natural (solar) phototherapy	Heliotherapy	UV, visible light, IR
Broadband UVB	BB UVB	290-320
Narrowband UVB	NB UVB	311-313
Selective UV phototherapy	SUP	300-330
Monochromatic excimer light	MEL	308
Broadband UVA	BB UVA	320-400
Photochemotherapy PUVA	PUVA	320-400
Extracorporeal photopheresis	ECP	320-400
UVA 1 phototherapy	UVA 1	340-400
High energy visible	HEV	400-500
Intensive pulse light	IPL	515 (-1250)
Photodynamic therapy	PDT	600-750
Light emitting device	LED	630 and 830

a relative lack of literature in comparison to systemic drugs. The manufacturers of irradiators do not have as much investigative potential as pharmaceutical companies, while the methodology and feasibility of such studies are considerably difficult.

### MECHANISMS OF ACTION

Phototherapy is defined as the therapeutic use of light, primarily ultraviolet light. The mechanisms of action on the skin are described as photobiological ones. At its most basic level, phototherapy represents the application of energy to the skin, which means delivery of photons to chromophores, absorption of photons in chromophores and biologic reaction of the photon absorbed energy, generating heat and biochemical effects in the skin. The most important chromophore for photobiological response after UVB is DNA (4,7,9,11).

The antiproliferative (antimitotic, cytotoxic) role of UV light was previously thought to be most prominent in phototherapy because of direct DNA damage followed by reduction in DNA, RNA, proteosynthesis and cellular proliferation. Current concepts on the mode of action underline the anti-inflammatory (immunomodulatory/immunosuppressive) mechanisms, i.e. direct effects on the induction of apoptosis (mainly Langerhans cells, T cells) and indirect effects *via* influencing numerous soluble mediators (cytokines, prostanoids, neuropeptides, signal transduction molecules, etc.) and cell-surface-associated molecules (adhesion molecules, surface receptors, etc.) (3,4,8,10). These all contribute to the anti-inflammatory effect of UV light (4,9,11,13). In psoriasis, UV light inhibits the hyperproliferation of keratinocytes and neoangiogenesis (3) and these antiproliferative effects are caused both by direct DNA damage and

indirectly by immune pathways. The mechanism of action differs with UVA and UVB, depending on their biophysical properties. So, as UVA as long-wave, low-energy radiation penetrates into the dermis and acts on fibroblasts, mastocytes, endothelial cells, dendritic cells and dermal T cells. Short-wave, high-energy UVB radiation penetrates the epidermis and only partially to the upper dermis and acts on keratinocytes, melanocytes, Langerhans cells, mastocytes and epidermal T cells. The UVB spectrum has been widely studied. It produces a direct and stronger immunosuppressive effect *via* production of photoproducts and DNA damage with consequent cell cycle arrest and late apoptosis, effects on soluble and surface structures and generally on signal transduction. UVA has an indirect and temporary effect *via* generation of reactive oxygen species with early apoptosis (4,6-8,10-14,21). The mechanism of immunomodulatory action of PUVA has been less well studied (4).

Both UVA (PUVA) and UVB reduce the expression of adhesion molecules, especially ICAM-1 (4,6-8,10,11,13,14), on keratinocytes and Langerhans cells. Both spectra cause isomerization of urocanic acid from trans to cis form that binds to 5-OH tryptamine receptors on mastocytes, dendritic cells and Langerhans cells, leading to their functional immunosuppression, blocking deliberation of histamine and causing trafficking of mastocytes to lymph nodes (13,14). Both UVB and PUVA cause apoptosis of keratinocytes, Langerhans cells, dendritic cells, macrophages and T cells (4,6-8,11,13). NBUBV especially reduces Th1 cells and their pro-inflammatory cytokines (IL-2, INF gamma and TNF alfa), and down-regulates the Th17 population *via* IL-23 axis (15); all these play a role in the pathogenesis of psoriasis (16).

NBUVB stimulates differentiation of regulatory T cells *via* RANK/RANL signaling pathway (receptor activator of NFκB ligand) on keratinocytes and Langerhans cells (17). It is an important mechanism for maintaining self-tolerance and suppressing excessive immune responses (18). Consequently, there is an increase in anti-inflammatory cytokines, mainly IL-10 (produced by keratinocytes, regulatory T cells and macrophages with phagocytosed apoptotic cells), alpha-MSH (produced by keratinocytes) and PGE2 (produced by keratinocytes and Langerhans cells) and others such as TGF beta, IL-4 and CGRP (calcitonin gene related peptide). These are the main mechanisms by which the immune reaction in psoriasis is shifted after NBUVB from Th1 towards Th2 immune response (4,11-14).

This broad action of UV light, mainly NBUVB, on various molecular targets explains the high efficacy of phototherapy. To further investigate the mechanism of action of UV light and immunity of the skin is a task for basic research.

### **INDICATIONS AND MEASURES BEFORE STARTING PHOTOTHERAPY**

In clinical practice, the rules and usage of phototherapy at individual dermatologic departments and offices differ and there is the need to coordinate or standardize protocols and generally to manage patients on phototherapy in order to reach an optimal risk/benefit ratio (protocols, dosimetry, patient information, informed consent, combination therapy, cancer surveillance, nurse education and training, etc.).

The most commonly used method of phototherapy for psoriasis is NBUVB, for example, in Scotland it accounts for 85% (Professor Fergusson's lecture at EADV Congress in Gothenburg, 2010) and in Czech Republic 81% (19). The main reason is the simplicity of performance over PUVA both for patients and for medical staff. A significant decrease in the use of PUVA is caused not only by the introduction of NBUVB, but also by the availability of biologics (3). Nevertheless, before starting phototherapy it is advisable, for quality and safety reasons, to undertake the following steps:

- indication and proper patient selection – motivated, compliant patient
- exclusion of contraindications – history, clinical examination of whole body surface
- assessment of skin and disease reactivity to sun, tanning beds or previous phototherapy
- verbal and written education and/or informed consent
- assessment of severity – PASI or BSA as needed
- determination of skin type or minimal erythema dose (MED), choice of phototherapy protocol and treatment plan

- appropriate phototherapy record forms and documentation (2,3,5,8,14).

Indications for NBUVB are all types of moderate to severe psoriasis (severity in area, intensity, course, therapeutic response, quality of life), e.g., in cases where topical therapy is not sufficient to control the disease. On the other hand, it is also indicated in cases where systemic drugs are contraindicated, poorly tolerated or not sufficiently effective. NBUVB is considered to be the first choice of phototherapy methods in moderate to severe plaque psoriasis because of safety reason in comparison to PUVA (2,3,8,20). The most suitable indication is psoriasis with thin scales and then in children and pregnant women (1,6,8,14,20,21). Photochemotherapy PUVA is indicated in thick scale psoriasis, in cases of low clinical response or short remission after NBUVB. In chronic plaque psoriasis, broadband UVB and SUP are slightly less effective than NBUVB and more erythemogenic (1-8,20), but they have good effects in eruptive and seborrheic forms (38). Further contraindications must be ruled out and patient adherence must be confirmed. NBUVB is contraindicated in photodermatoses and in patients with cutaneous malignancies. Relative contraindications are skin type I, multiple atypical nevi, immunosuppression in organ transplant patient, epilepsy and physical or psychical obstacles like claustrophobia, cardiac insufficiency or inability to stand in the UV cabin (1-8,10,14). After assessing the indications and contraindications, the physician should inform the patient about the benefits as well as the side effects and possible risks of phototherapy and also provide practical information about the process of phototherapy course.

This basic education should include the use of protective goggles, shielding genitalia in males, and also face and dorsa of hands if not affected, and protection of parts with herpes simplex in history and avoiding of sunlight exposure during phototherapy course (4-8,10,14). It is advisable to provide the patient with a written information form or even informed consent form, where needed. The purpose of this counseling and instruction is not only to protect the physician in medico-legal aspects, but first of all to reach better compliance of patients. They will find here answers to frequently asked questions and also advice how to avoid the most often errors during phototherapy.

### **IMPROVING CLINICAL PARAMETERS OF PHOTOTHERAPY**

Every drug and treatment is evaluated for parameters like efficacy, tolerability, safety, and particularly in dermatology also acceptance and convenience.



Are there any possibilities to improve these parameters in phototherapy?

Acceptance of phototherapy is traditionally very good. Although relatively time consuming, patients consider phototherapy to be a comfortable and effective therapeutic method, which is reflected in quite good adherence. If not regulated, many patients would even like to attend phototherapy for a long time. As to the convenience, phototherapy is bound to phototherapy departments or centers, so the availability, geographical accessibility and compliance can be sometimes a problem. These factors represent the major limitations of UV-based therapy (14). From the physician's point of view, phototherapy needs adequate technical, space and staff equipment with higher costs and intensive agenda according to compensation records and reimbursement from health insurance companies than in ordinary dermatologic offices. Our survey in the Czech Republic showed good situation concerning availability and accessibility (57 hospital or office based phototherapy centers), with the exception of border regions (19). In our country, phototherapy is covered by health insurance companies. In case of poor accessibility, home phototherapy can be useful in motivated and equipped patients under the physician's monitoring (regular visits, clinical follow up). United States experience shows a high level of compliance, improved quality of life, and lower direct and indirect cost (time and salary lost, transport costs, etc.) in comparison to other treatments for severe psoriasis, including methotrexate, PUVA, acitretin, and biologics (23,24). Generally, both UVB and PUVA therapies have been shown to be 4-6 times more cost-effective as compared with biologics (22). Of course, home phototherapy is not a solution for all patients, both for financial (purchasing the device) and medical reasons (overuse, underuse, inappropriate use) (23,24). The tolerability of NBUVB is good with occasional erythema (UV dermatitis) and xerosis as the almost single side effects that can be well managed (1-11). However, the main issues are efficacy and safety.

## SAFETY

Safety of phototherapy is an ongoing topic. There are more than fifty years of clinical experience with phototherapy depending on the modality used (2,4,6). Although UV light generally has a carcinogenic potential, till now there are no clinically relevant human data on skin cancer with NBUVB in psoriasis, e.g., data available on human use are inconclusive for a significant risk (2,3,6,10,25,26). Another situation is in photochemotherapy PUVA because in high doses there is a substantially increased risk of squamous cell

carcinoma and melanoma and a small increase in the risk of basal cell carcinoma (2,3,5,14,25,26). However, with higher cumulative doses the potential risks must be taken into account also in NBUVB (20). In PUVA, there is a recommendation for the whole life maximal cumulative dose of 1000 J/cm<sup>2</sup> (or 200-300 sessions) (2,3,5,20). For NBUVB, the limit is not given as a cumulative dose, but according to current consensus, the cumulative number of 450-500 sessions should not be exceeded (20). For improving safety it is necessary to encourage all physicians to calculate it and not to regulate phototherapy by limiting it to "two courses a year", etc. This ceiling must be taken as relative and individual (27), also according to the fact that in severe psoriasis only stronger immunosuppressive drugs (methotrexate, cyclosporine A) are alternatives to phototherapy (6,20,27). It is advisable to identify patients whose cumulative dose has exceeded the ceiling as the risk-takers and to follow them more carefully. Some authors recommend to record cumulative doses of single courses not only in medical forms, but in a kind of patient UV passport (5,6). Nevertheless, patients with repeated phototherapy (>200-250 sessions) should undergo dermato-oncologic screening at least once a year (10,14).

On assessing the risks of phototherapy, it is necessary not to mix them up with the risks of tanning beds and sun-tanning. There are fundamental differences between them. The latter exposure to UV light is medically uncontrolled, most people are the risk phototype I or II, do not use any sunscreens, and their behavior is often of addictive type (28), so the number of visits/exposures is not limited. On the other hand, phototherapy is justified by its benefits for the patient, resulting in reduction or clearance of the disease and its stabilization. In comparison with systemic antipsoriatic drugs, the risk/benefit profile of phototherapy is very good because it generally lacks the properties of systemic immunosuppressive drugs.

Besides shielding unaffected areas, regular patient monitoring during phototherapy by the physician, monitoring of cumulative doses and skin cancer monitoring, there is also a technical possibility how to improve the safety, i.e. with focused, targeted phototherapy. Refinements of the delivery systems for UVB are beneficial in reducing the unnecessary exposure of uninvolved skin (29). However, current devices are only suitable for localized psoriasis or for a low number of lesions because of small irradiation area, thus requiring unacceptably long time in disseminated psoriasis. Computerized, robotized whole body device with high output that would, after scanning the affected area, selectively irradiate only the involved skin in short pulses, is the perspective. Yet, there is the question of cost-effectiveness of such a sophisticated device.

## EFFICACY

The efficacy of phototherapy can reach clearance in 63%-80% of patients with a course of NBUVB (20) and generally phototherapy can achieve PASI 75 on average in 75% of patients after 4-6 weeks (2,4,6). This is very good efficacy in comparison with systemic drugs and even with biologics. Recent analysis (30) showed superior effects of PUVA even over certain biologics (adalimumab, alefacept, efalizumab, etanercept, ustekinumab). An optimal phototherapy protocol should lead to complete clearance or marked improvement (PASI >75) with a minimum number of sessions, a low cumulative dose, and with the least possible acute and chronic side effects (6,10,20). This is a difficult task because phototherapy and its dosages, although working with exact physical variables, does not have a direct dose-effect relationship, and tolerance is the deciding and limiting factor. So, a higher dose does not always mean a higher effect. Photobiological effects are more similar to those of biologics or topical immunomodulators. Clinical response is here also very individual depending on genetic heterogeneity, i.e. immune, metabolic and pharmacogenomics properties. Because of different (heterogenic) immune background of the disease, people with the same appearance of psoriasis (phenotype) may have different therapeutic responses to the same treatment. Metabolic and pharmacogenomic heterogeneity plays a role mainly in systemic drugs for psoriasis (31), but also in phototherapy there are genetic dispositions for tolerance and positive reactions to UV (biomarkers, e.g., polymorphism of vitamin D receptor) that could in the future be used for prediction of therapeutic response in individual patients (32).

Thus, in order to enhance the effect of treatment, physicians do not just need to actualize the knowledge by studying professional literature, but also from self-learning based on their own experience. However, experience with a relatively small number of patients is usually not enough to draw general conclusions. To get statistically significant data, large numbers of patients treated and assessed by comparable methodology are needed. There is an initiative from phototherapy centers in Scotland in this sense, called Photonet (Scottish Managed Clinical Network for Phototherapy), which could enable analysis for detecting optimal protocols from the efficacy and safety point of view (20,33). Professor Fergusson and co-workers in Dundee created this registry in 2002 in a bid to standardize phototherapy treatment throughout Scotland. All centers send their data in structured forms (patient demography, protocol, efficacy and tolerance data) to this registry. So they obtain data from large patient samples and due to the

same methodology, their stratified analysis is powered enough to draw conclusions concerning optimal regimens and protocols. It also provides information forum for both healthcare professionals and patients. They can "discuss clinical issues, collaborate and share skills and information" ([www.photonet.scot.nhs.uk](http://www.photonet.scot.nhs.uk)). Nevertheless, as mentioned further, there are differences between study populations and results cannot be simply extrapolated to another population (33). Therefore, it would be optimal to create regional or national registries to obtain relevant data.

There are two possible ways to improve efficacy; first, to optimize protocols and/or to combine phototherapy with topical or systemic treatments. Nevertheless, to ensure the success of every treatment, the prerequisites are knowledge and skills, as well as the approach by physicians.

## OPTIMIZING THE PROTOCOLS

The protocol represents a treatment scheme, a schedule including the following parameters: starting dose, increments, frequency of increments, maximal single dose, frequency of sessions *per week*, total duration of phototherapy course and/or total number of sessions (6,20,34). Are there any reserves to improve or optimize the protocols? According to textbooks, the initial dose of NBUVB phototherapy is calculated on the basis of MED or skin type (phototype). The starting dose is recommended as 70% of MED (2-7,10,14,34), in US protocols only 50% of MED (5,8,20,29). In skin type regimen the initial dose is given according to the recommended dose ladder; e.g., in Europe, for phototype I=200, II=300, III=500, IV=600 mJ/cm<sup>2</sup> (2,5,7), or even on the basis of individual experience. In US protocols, the dose is by about one half lower (14,34). In many centers, according to data from the literature and from our Czech survey (10,14), MED is not determined. There is a concern of underestimating the initial dose with consequences like prolongation of the effect onset and therapy (10). According to a Scottish study in phototypes I-III, there were no significant differences in the efficacy of NBUVB therapy (increments by 20%) between three starting doses: group A, fixed dose; group B, 70% MED; and group C, 50% MED (35). So, what is the conclusion? These authors wisely state in the end of their article: "in populations with a broader range of erythema sensitivity" (than in Scotland), "the MED based starting dose could have an important impact on treatment effectiveness" (35).

Another key issue of debate is dose escalation, which depends on erythema response. The dose may be increased with each successive session in case



of 3 times *per week* frequency, and every other session when given 5 times a week (7). In MED based protocol, the percentage increments are on average by 30% of the last dose, an in case of minimal erythema by 20% (2,5,6). There are differences in protocol increments between departments probably due to the spectrum of patient population; Europe with 20%-40% increase *versus* United States with a lower increase by 10%-15% (3,8,14,34). This may be also influenced by local experience, tradition, more patients with lower phototypes in their population and maybe by the fear from potential complaints in patients with burning reaction. Fixed increments are used in skin type based protocols, mainly in the US, in the range of 0.03-0.15 J/cm<sup>2</sup> (3,8,34) that evolved from a low increment protocol for NBUBV. There is a presumption that the efficacy can be enhanced by larger increments because the erythemogenicity of NBUBV is lower, about one-fourth that of BBUBV (36). To the best of my knowledge, there are no concrete references about fixed increment protocols for NBUBV in European literature. In my opinion, adherent patients of skin type III-IV tolerate 0.1-0.2 J/cm<sup>2</sup> increments on an average and the onset of effect is faster (19,37). This increment represents approximately 20% of fixed starting dose for phototype III and 30% of fixed starting dose for phototype IV. This correlates with the percentage increments based on MED in European protocols mentioned above. Also, other data on this topic are of anecdotal or local character (for example, the internet website [www.psoriasis-international.org](http://www.psoriasis-international.org), supervised by professor Louis Dubertret, offers schemes with fixed increments of 0.1-0.3 J/cm<sup>2</sup>) and need to be confirmed by further clinical investigation. Proper dosimetry, calibration and sufficient number of patients are necessary to avoid bias and incorrect conclusions.

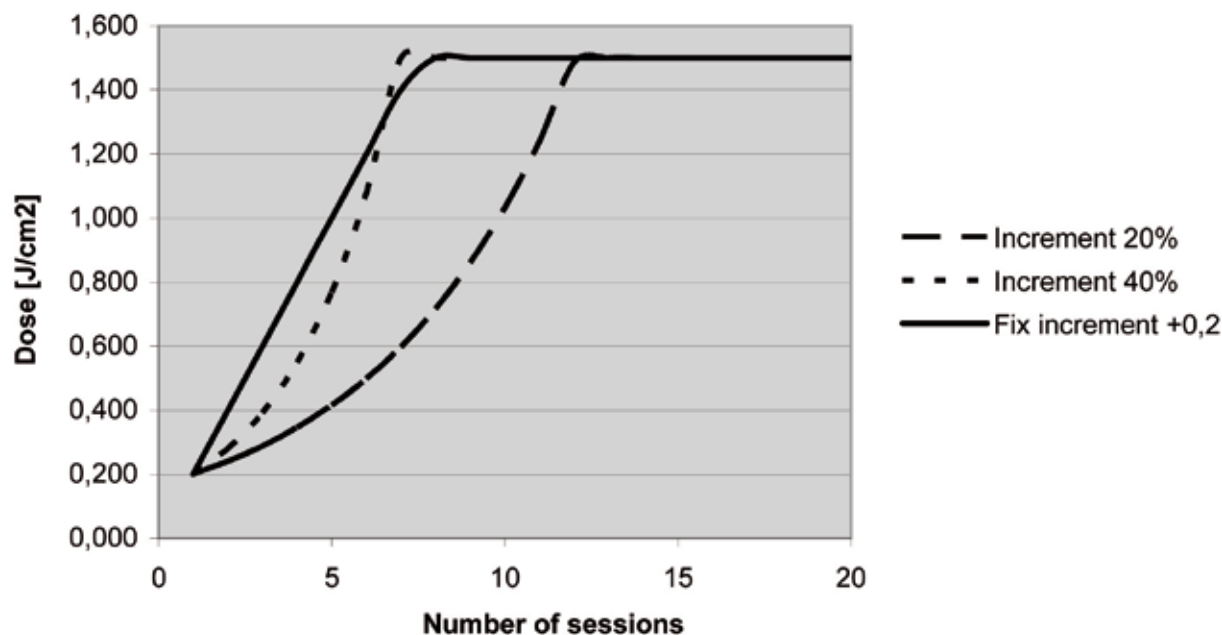
In daily practice, it is a challenge for physicians to choose the proper regimen (36,38,39) because the percentage increments regimen (exponential curve, Fig. 1), although recommended in the literature, means that it is not easy for a physician or nurse to calculate the individual dose before every session if a change is needed due to actual tolerance, efficacy and patient compliance (e.g., irregular attendance). This regimen has worse flexibility and lucidity. Fixed increments regimens (linear curve) are easy to follow by a nurse, and there is good flexibility. When working with a maximum single dose 1.5 J/cm<sup>2</sup>, under good patient tolerance, there is only a small or no difference in time to reach it and also in the cumulative dose between fixed increments by 0.2 J/cm<sup>2</sup> and percentage increments by 40% (Fig. 1). However, if working with small increments, e.g., by 20%, the maximum

single dose 1.5 J/cm<sup>2</sup> is reached about one or two weeks later and a slower onset of effect, prolongation of therapy and possible increase of cumulative dose to clearing can occur. The high-dose regimen (40%) results in fewer sessions with better long-term efficacy, but requires flexible dose adjustment in the second week, e.g., at the beginning, to prevent erythema (38). In Scotland, there is a preference of low-dose regimen, where less frequent sunburn-like erythema episodes occur (39). The optimal NBUBV phototherapy regimens for psoriasis may vary according to the population and settings; therefore, they call for future randomized studies for a given population with sufficient methodological records on safety and efficacy to justify the high-dose regimen (33).

So, which regimen to choose? In the literature, there is no universal answer. If there is well-trained staff, an educated and adherent patient, and also if the physician can regularly monitor the patient at least once a week and can flexibly change the dose according to reactivity and tolerance, the high dose regimen should not induce more burning reactions than the low dose one. Should the fixed or percentage increments be used? The fixed increments regimen seems to be more suitable and convenient for an "average" patient of skin type III-IV (and also for home phototherapy). Yet, individualization is needed in every patient. Thus, for example in patients with disposition to erythematous reaction at the beginning of phototherapy, the percentage increments regimen would be more suitable because the increments are slightly slower than in fixed increments regimen.

The maximum single dose should not exceed 3 J/cm<sup>2</sup> (8,14), but it is advisable, if efficacy allows it, to work for safety reasons with 1.5 J/cm<sup>2</sup> and 2 J/cm<sup>2</sup>. The often discussed frequency of sessions (2-5/week) is in fact a matter of dose, e.g., it indirectly correlates with the so-called reciprocity rule (relation of intensity and exposure time to the dose). So, in devices with low intensity, e.g., low dose regimen, the frequency should be higher, while in cabins with usual output (10 mW/cm<sup>2</sup>) attendance three times a week is usually sufficient. The frequency of five times a week in devices with usual output is time consuming for the patient, does not shorten total duration to clearance and increases total cumulative dose (10,40). Lower frequency, e.g., two times a week, requires longer duration of treatment (1.5 times longer) and needs more sessions in comparison to three times a week (41). Therefore, current recommendations work with the frequency of three times a week, as it is optimal from the aspect of patient time (2,4,5,7).

In this context, there is an interesting field for further investigation. It is known that in devices with



**Figure 1.** Narrowband UVB dose increments to 1.5 J/cm<sup>2</sup>.

very low or very high intensity, the reciprocity rule does not hold true. In psoriasis, devices with very high intensity, e.g., 308 nm UVB excimer lasers or non-laser monochromatic excimer light (MEL) devices working with supra-erythemogenic doses, can reach better clinical response by the same cumulative dose in comparison with usual NBUBV (Philips TL 01), or in other words, the same effect can be achieved with a fewer number of treatments and a lower cumulative dose (2,29,42).

Another field for clinical research is to further investigate topical photochemotherapy with NBUBV in the form of cream or solution (no references about bath delivery available, rare about peroral). This PN-BUBV is less well-established than PUVA (20), most references coming from India (10,43). What are the advantages of this combination? Psoralens in topical form are safer and more comfortable than the systemic route. Photosensitization is not as strong as with UVA, but still there is an increase by about 3.5 in NBUBV. So, it enables lower doses of UVB, thus improving the safety and topical PUVB is generally considered to be safer than PUVA at long term. There are fewer references comparing the efficacy, some of them documenting higher efficacy and lower cumulative dose than NBUBV alone, without an increase in side effects (10,43). Interestingly, psoralens alone without UV light bind to the receptors for epidermal growth factor, followed by a decrease in epidermal prolifera-

tion (14). They also have marked prooxidative properties (enhancing the generation of reactive oxygen species and free radicals) on cell surface membranes, so they can act independently of UV (44). In practice, PNBUVB is suitable especially for recalcitrant localized forms, e.g., palmoplantar psoriasis (10,44).

Cessation of phototherapy depends on clinical response. It is usually continued until complete clearance is achieved or no further improvement can be expected. This takes 2-3 months or 25-35 sessions on an average. Maintenance phototherapy with NBUBV in psoriasis is a matter of debate, there are no sufficient data to support it (2-6,20). Safety concerns are speaking against maintenance therapy for common use (2,4,20). Also practical aspects play a role, as it is time consuming and expensive (1,4). Thus, nowadays NBUBV and generally phototherapy is considered a treatment as induction therapy for psoriasis, but not recommended as maintenance therapy (2).

### COMBINATION THERAPY

Another way to increase clinical response (additive or synergistic effect) and also partially the safety of phototherapy is to combine it, first of all with topical therapy (2-4,6,10,20,29). However, before thinking about adding a combination to phototherapy, it is advisable to search for ways to improve phototherapy itself (besides looking for adherence, triggering factors, etc.) because it is simpler for both the patient

and the physician/phototherapy center (10). Combination with topical therapy requires more space, technical and staff equipment, it is laborious, takes more time, and generally the costs are higher. On the other hand, combination therapy may reduce the cumulative NBUVB dose and the potential carcinogenic risk and should not be dismissed without further studies (1,20).

### COMBINATIONS WITH TOPICAL DRUGS

Historically, Goeckermann introduced a combination of BBUVB with coal tar in 1925 and later on Ingram with anthralin (dithranol). NBUVB can be combined with both, including all current topicals (1,4,6,29). The most positive references are about dithranol for inpatient and calcipotriol for outpatient settings (4,10,29). Combination with calcipotriol is the most evidence based one, even in the recent German and American guidelines from 2011 (2,3).

A modified Goeckerman method with NBUVB is based on photosensitive and antimetabolic properties of coal tar, however, tar smells, stains and has irritative and carcinogenic properties. Dithranol with NBUVB has no photosensitivity potential and has a higher efficacy than tar. However, it bears a risk of irritation, so that not all patients tolerate it. There is another possible combination of NBUVB, namely with ichthyol. It is a sulfonated shale oil (ammonium bitumonosulfonate) with anti-inflammatory, antiseptic and antipruritic properties. It was originally used for treating wounds and later for treating some dermatoses, especially eczema and rosacea. Ichthyol has been proved not only by historical experience, but also by growing evidence based studies (45). The advantage of ichthyol over tar, dithranol and even calcipotriol is almost no irritative potential and no phototoxic or carcinogenic potential. Ichthyol also has antiproliferative and UVB erythema reducing effects that might play a role in psoriasis treatment (46). Furthermore, it can be easily washed off with water and has an advantageous price. Ichthyol still represents a valuable topical (good benefit/risk/cost profile) because, except for corticosteroids and topical immunomodulators, there are no other anti-inflammatory topicals in dermatology available. In the Czech Republic, some centers also use it for treating psoriasis. I have been using ichthyol in combination with NBUVB for many years and conducted a study in severe psoriasis patients, where 100% short contact ichthyol and NBUVB were used. The results confirmed very good efficacy (after 20 sessions: mean reduction in PASI = 72%, mean improvement in DLQI=53%), tolerability, safety and acceptance. It is suitable especially for psoriasis patients with irritable or potentially irritable terrain,

e.g., guttate, seborrheic or unstable psoriasis, in children and in all cases where dithranol or tar are not tolerated or cannot be used (37).

Treatment with topical corticosteroids during phototherapy is not a true combination therapy, but a concomitant therapy in the beginning of phototherapy. There is a trend not to use them during phototherapy ("corticosteroid holidays"), but it does not mean they are prohibited (2,3). In practice, they should be slowly tapered and ceased according to the onset of clinical response to phototherapy (29).

There are considerable differences in using emollients during phototherapy. According to variations in UV transmission and UV blocking potential in some of them, it is advisable to use them after rather than before phototherapy session (47). For better transmission, a short warm water shower (48) or the application of mineral oil can be used before treatment (8,10).

### COMBINATIONS WITH BATHS

In Germany, balneophototherapy is quite popular, mainly with salt baths (2,4,20) in asynchronous or synchronous way (49) with NBUVB, SUP or BBUVB. Some studies documented higher efficacy than phototherapy alone (49,50), but the cumulative dose was not reduced, there is no standardization in salt concentration and mineral content, and particularly the cost-effectiveness has not been advantageous so far (48,50).

### COMBINATIONS WITH SYSTEMIC DRUGS

Combination of NBUVB with systemic drugs is represented mainly by retinoids, e.g., acitretin (reNBUVB, rePUVA), because it has no immunosuppressive properties (2,3,4,6,8,29,51). This combination accelerates the onset of clinical response, enables reduction of acitretin dose (25-10 mg/day) and moderately also the number of sessions or cumulative dose, by 20% on an average. It is advisable to start acitretin one or two weeks before phototherapy, the dose should be increased cautiously because of epidermal thinning caused by acitretin, usually by 20%-30% (3,14). Combination with retinoids is safe, effective and may even help reduce cancer risk (4). Other antipsoriatic drugs such as methotrexate, biologics, e.g., etanercept, do not represent a true combination to increase the efficacy of phototherapy. Phototherapy is here a temporary adjunctive method for increasing the efficacy of these systemic drugs in case of clinical response loss or flare. Of course, in such combinations the cumulative dose of UVB is significantly lower. They are used anecdotally, and there is a long-term safety concern



(3,6,10,52,53), especially in smokers and obese patients, who are already at a higher risk (52). There are increasing references about the use of methotrexate in a sequential way, e.g., starting three weeks before phototherapy in a dosage of 15 mg/week and leading to significantly shorter time to clearance (3,29,54). Concomitant combination with cyclosporin A is strictly contraindicated in PUVA (2-7), in NBUVB it is not recommended and can only be used exceptionally and very cautiously as short-term course on resistant plaques (5,29).

### CONCLUSIONS

Even in the 21<sup>st</sup> century, phototherapy represents an important therapeutic modality for psoriasis and other dermatoses due to its good efficacy, safety, patient compliance profile and cost/benefit ratio. Even in the era of biologics, phototherapy remains an important therapeutic tool that cannot be replaced by any other current systemic therapy. Although not as dynamic as in systemic drugs, research to improve the efficacy and safety of phototherapy is going on.

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