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Ultraviolet phototherapy for treatment of various dermatoses

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ABSTRACT

Ultraviolet (UV) radiation has been applied to treat many chronic skin diseases. Based on the wavelength, UV radiation consists of three types, namely ultraviolet C (UVC), ultraviolet B (UVB), and ultraviolet A (UVA). The types of UV that are widely used in dermatology are narrowband ultraviolet B (NB-UVB), broadband ultraviolet B (BB-UVB), UVA1, and psoralen combined with UVA (PUVA). The interaction between UV and the skin determines the effectiveness of phototherapy. The biological effects of UV are used in the management of inflammatory skin diseases, malignancies, and various rare dermatoses. Apart from these benefits, UV increases the risk of photoaging and skin cancer. Therefore, further researches are necessary to enhance the effectiveness and safety of phototherapy. This literature review discusses the role of phototherapy in various dermatoses other than psoriasis and vitiligo.

ABSTRAK

Radiasi sinar ultraviolet (UV) telah digunakan untuk pengobatan penyakit kulit kronik. Berdasarkan panjang gelombangnya, radiasi UV dibedakan dalam tiga jenis yaitu ultraviolet C (UVC), ultraviolet B (UVB), dan ultraviolet A (UVA). Jenis UV yang digunanakan secara luas dalam dematologi adalah *narrowband* ultraviolet B (NB-UVB), *broadbrand* ultraviolet B (BB-UVB), UVA1, dan psoralen dikombinasikan dengan UVA (PUVA). Interaksi antara UV dan kulit menentukan efektivitas fototerapi. Efek biologi UV digunakan dalam pengelolaan penyakit kulit inflamasi, malignansi, dan berbagai penyakit kulit yang jarang. Terlepas dari manfaatnya, UV meningkatkan risiko fotoaging dan kanker kulit. Oleh karena itu, penelitian lanjut diperlukan untuk meningkatkan efektivitas dan keamanan fototerapi. Kajian pustaka ini membicarakan peran fototerapi dalam berbagai penyakit kulit selain psoriasis dan vitiligo.

Keywords:
phototherapy
ultraviolet B
UVA1
PUVA
dermatoses

INTRODUCTION

Ultraviolet (UV) radiation has been applied to treat many chronic skin diseases. The International Commission on Radiation (CIE) classifies UV into three subdivisions based on their wavelengths, namely UVA 400-315 nm, UVB 315-280 nm, and UVC 280-100 nm. In dermatology, phototherapy with narrowband ultraviolet B (NB-UVB), broadband ultraviolet B (BB-UVB), ultraviolet A-1 (UVA1), and ultraviolet A combined with psoralen (PUVA) has been used extensively. Phototherapy units produce radiation by converting electrical into electromagnetic energy.[1] Phototherapy is commonly used by dermatologists either as a single or in combination with topical and/or systemic therapy for the management of inflammatory, malignancies, and various rare dermatoses.[2] Phototherapy is proven effective and safe even for

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children and the elderly.[3,4] This literature review discusses the role of phototherapy in various dermatoses. The discussion is focused on dermatoses that are rarely managed, excluding psoriasis and vitiligo because the literature on the role of phototherapy in these dermatoses has been widely published.

A comprehensive database search was performed in MEDLINE, EMBASE, and the Cochrane library with the main keywords used were phototherapy, dermatoses, PUVA, ultraviolet, NBUVB, and each dermatosis discussed below. Selection was performed based on the article including randomized and nonrandomized clinical trials, open trials, and case reports or series published in the last 10 years (from 2010 to 2020). Other light base modalities such as excimer laser and photodynamic therapy were excluded from the discussion.

DISCUSSION

Biological Effects of Phototherapy

Effects of phototherapy on DNA

The direct damage of DNA is mediated by UVB radiation, while the indirect damage is caused by UVA exposure.[5] Nucleotides in DNA absorb UVB to form DNA photoproducts, such as cyclobutene pyrimidine dimers (CPDs) and 6-4 photoproducts or pyrimidine-pyramidone (6-4). Exposure to UVA causes DNA damage through the formation of unstable reactive oxygen species (ROS) and cyclobutene mono adducts, especially when it is combined with psoralen. DNA synthesis and repair mechanisms are also impaired due to UV exposure through the upregulation pathway of p53 gene expression.[6]

Effects of phototherapy on T cells

UV exposure activates regulatory T cells and increases the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α).[6] UV converts the trans- to cis- urocanic acid (UCA) isomer which upregulates the expression of genes contributing to apoptosis, cell cycle termination, and formation of oxidative stress.[5] cis-UCA also binds to serotonin-2A receptors, causing suppression of the immune system by converting the cytokines of T-helper (Th)1 to Th2 cells.[7] UV diminishes the interaction between APCs and T cells. One of the APCs, CD103-dendritic cells, produces retinoic acid and induces activation of regulatory T cells following UV exposure.[8]

Effects *of phototherapy on mast cells*

UV does not have much impact on the number of mast cells in the dermis, however, it suppresses their function. PUVA increases the stability of the mast cell membrane, reducing the release of histamine and other inflammatory mediators. In chronic UVA1 exposure mast cell apoptosis occurs, causing significant decrease in their number.[9]

Effects of phototherapy on keratinocytes

Keratinocytes release immunosuppressive cytokines, such as IL-6, -8, -10, -12, -15, granulocyte-macrophage colony-stimulating factor (GMCSF), and prostaglandins following UV exposure. These cytokines inhibit the expression of co-stimulatory molecules on APCs surface, decreasing their function and inhibiting T cells activation.[6] An acute inflammatory response manifested as sunburn occurs due to UV penetration, especially UVB in the epidermis and superficial dermis. Sunburn triggers the release of prostaglandins, leukotrienes, histamine, IL-1, and TNF-α, resulting in pain. Nitric oxide causes erythema on the skin that persists for 24 hours and fades within two to three days, followed by desquamation and pigmentation of the skin. Cells with frequent DNA synthesis phases are more susceptible to apoptosis by UV radiation. Therefore, keratinocytes are more susceptible than

melanocytes when radiated by UV.[10]

Effect of phototherapy on melanocytes

When melanocytes are exposed to UV, pituitary gland releases α-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH). These hormones stimulate melanocortin 1 receptors on the surface of melanocytes, leading to melanogenesis and redistribution of melanocytes, manifested as tanning.[10] NB-UVB induces proliferation and migration of melanocytes from their reservoir, the outer sheath of hair roots, to the epidermis. It also upregulates tyrosinase to increase melanin synthesis by melanocytes. This is the relevance of phototherapy in vitiligo.[11]

Effects of phototherapy on collagen

UV inhibits collagen synthesis and increases collagenase production. UVA plays a greater role because of its deeper penetration. PUVA suppresses collagen formation and triggers matrix metalloproteinase-I (MMP-1) synthesis from dermal fibroblasts via protein kinase pathway and induction of IL-1 and IL-6. MMP-1 is the main protease for degradation of type I and III collagen into small fragments. UVB decreases the amount of collagen indirectly by triggering keratinocytes to release IL-1, IL-6, and TNF-α, which eventually stimulating fibroblasts to produce MMP-1.[12]

Side Effects of Phototherapy

Photoaging

UV triggers skin photoaging which manifested as deep wrinkles, loss of elasticity, rough and dullness, uneven color, impaired wound healing, formation of purpura and telangiectasia, and growth of benign or malignant masses.[13] Histologically, photoaging is characterized by increasing elastin and collagen fragmentation at the dermo-epidermal junction with irregular thickness of epidermis and areas of atrophy and acanthosis. There is an increasing number of hyperplastic fibroblasts and inflammatory cells including mast cells, eosinophils, and mononuclear cells in the dermis. Melanocytes also increase to protect the skin against UV.[14]

Carcinogenesis

Chronic and excessive exposure to UV is the major risk factor for developing melanoma and non-melanoma skin cancer (NMSC).[15] Under normal circumstances, nucleotide excision repair (NER) and base excision repair (BER) protect DNA damage. If these systems failed, DNA mutation occurs.[16] Most DNA mutations do not have a major impact because the majority of genomes are not used in the transcription process. However, if mutations occurred in oncogenes and/or tumor suppressor genes, it results in malignancies .[10] UV-induced immunosuppression is another factor to prevent the eradication of immunogenic tumor cells.[16]

A retrospective study of 60.321 patients found that NB-UVB was not associated with skin cancer, even if the patient had more than 500 phototherapy sessions.[17] Another retrospective study also found similar results, the incidence of NMSC in patients receiving whole body NB-UVB was not significantly different compared to the general population.[18] However, The PUVA Follow-up Study observed 1,380 psoriasis patients prospectively with a mean follow-up time of 20.2 years. The incidence of melanoma increases 15 years after the first exposure to PUVA, especially in the patient with more than 200 sessions.[19] A 30-year prospective study found that patients with more than 350 PUVA sessions had a 30 times higher risk of developing squamous cell carcinoma (SCC) than the general population, while the risk of developing basal cell

carcinoma (BCC) was only five times higher.[20] Until now, there is no large-scale study related to the risk of skin cancer in UVA1. Two publications are reporting the incidence of skin cancer in patients receiving UVA1, however, the causality has not been proven .[21] NB-UVB is preferred over PUVA because of its good safety profile.[22]

Phototherapy in Various Dermatoses

Atopic dermatitis (level of evidence/LoE II)

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by recurring pruritus, usually beginning in infancy or childhood.[24,25] Phototherapy reduces the inflammatory response and improves skin barrier function, thereby preventing the penetration of allergens and irritants.[26] NB-UVB also has an antibacterial activity to prevent *Staphylococcus aureus* infection which is often found in AD.[27] In 2010, the American Academy of Dermatology (AAD) published guidelines for phototherapy in AD. The dose is adjusted based on skin type or the minimal erythema dose (MED) and must be monitored by expert physicians. P.[28]

TABLE 1. Guideline for narrowband ultraviolet B (NB-UVB) and psoralen ultraviolet A (PUVA) phototherapy in atopic dermatitis according to the American Academy of Dermatology in 2010*

Skin types	NB-UVB (mJ/cm^2) Dose			UVA (J/cm^2) Dose		
	Initial	Increasing dose every session	Maximum	Initial	Increasing dose every session	Maximum
I	130	15	2000	0.5	0.5	8
II	220	25	2000	1.0	0.5	8
III	260	40	3000	1.5	1.0	12
IV	330	45	3000	2.0	1.0	12
V	350	60	5000	2.5	1.5	20
VI	400	65	5000	3.0	1.5	20
The initial dose of UVB		50% minimal erythema dose				
Session 1 - 20		Increasing 10% from *minimal erythema dose*				
Session ≥21		Increasement based on physician's consideration				
If the patient does not undergo phototherapy for:						
4 - 7 days		Maintained dose				
1 - 2 weeks		Decreased 25%				
2 - 3 weeks		Decreased 50% or started from initial dose				
3 - 4 weeks		Started from the initial dose				

Phototherapy is given 3-5 times per week. A minimal erythema dose (MED) measurement is recommended because of the large MED range of NB-UVB based on skin type. The phototherapy unit should be calibrated once per week because the power of the UVB lamp decreases over time.
*Cited from original reference No. 28

NB-UVB is an effective, safe, and most widely used phototherapy modality for AD. A prospective study involving 30 children with moderate to severe AD showed a significant reduction in Scoring Atopic Dermatitis (SCORAD) after receiving twice-weekly NB-UVB for 12 weeks.[29] NB-UVB and medium-dose (MD-UVA1) have similar effectivity in reducing signs and symptoms of AD. PUVA and BB-UVB are not recommended for AD because of the risk of malignancy and low efficacy, respectively.[30] NB-UVB alone is as effective as the combination of NB-UVB and UVA.[31]

Chronic hand dermatitis (LoE II)

Chronic hand dermatitis is an inflammatory dermatosis characterized by erythema, desquamation, fissures, swelling, and vesicle formation with pain, itching, and burning in the hands.[32] Severe chronic hand dermatitis is often resistant to topical corticosteroid treatment. Data from UK large-scale survey found the majority of dermatologists use PUVA for the treatment of chronic hand dermatitis.[33]

An RCT of 60 subjects compared the effectiveness of topical PUVA with local NB-UVB for hand dermatitis unresponsive to ultra-potent corticosteroids. The control group received topical PUVA twice per week for 12 weeks with an initial UVA dose of 0.5 J/cm^2 which was increased to a maximum dose of 6 J/cm^2. The intervention group received localized NB-UVB twice weekly for 12 weeks with an initial UVB dose of 0.5 J/cm^2 which was increased to a maximum dose of 10 J/cm^2. The result showed both PUVA and NB-UVB are safe and effective for chronic hand dermatitis, although erythema was higher in the intervention group.[32] Another clinical trial indicated that there were no significant differences between the effectiveness of topical PUVA and localized NB-UVB in for chronic hand eczema.[34]

Polymorphic light eruption (LoE II)

Polymorphic light eruption (PMLE) is triggered by ultraviolet exposure or visible light. The clinical features of PMLE are vesico-papular, vesico-bulous, erythematous-edematous eruptions, resembling erythema multiforme or insect bites, and urticaria in areas of the body that are frequently exposed by sunlight, such as the neck, arms, and back of the hands.[35] Phototherapy is used as a second-line treatment for PMLE because of the "skin hardening" effect through the thickening of the stratum corneum, hyperpigmentation, epidermal hyperplasia, and immunosuppression. In PMLE, the initial dose of NB-UVB is determined based on skin type or MED. NB-UVB is given two to three times per week for a total of 15 sessions. If a photosensitivity reaction occurs, the patient is given prednisone 0.6 - 0.8mg/body weight for seven to 10 days. After completion, patients are advised to sunbathe for 20 to 30 minutes per week without sunscreen to maintain desensitization of the skin. PUVA is recommended if recurrence occurs after NB-UVB.[36] A case series demonstrated the effectiveness of NB-UVB in 91% of PMLE patients who received at least 15 sessions of therapy.[37] PUVA can be given at an initial dose of 1.5 J/cm^2 three times per week with 20% increase in subsequent sessions for four to eight weeks.[38] The results of a clinical trial in 25 patients showed the effectiveness of NB-UVB was similar to PUVA for PMLE.[39]

Chronic urticaria (LoE II)

Chronic urticaria may be accompanied by angioedema which lasting more than 6 weeks with individual lesions lasting less than 24 hours. Mast cells play a role in urticaria. Phototherapy increases the stability of the mast cell membrane, thus reducing the release of histamine and other inflammatory mediators.[40]

Clinical trial in 24 patients with chronic urticaria found either PUVA or NB-UVB three times per week for 20 sessions with the initial dose based on the patient's skin type showed a significant decrease in the total severity score (TSS) of urticaria after phototherapy ($p<0.05$) without significant differences between the two groups in terms of symptom improvement and urticaria TSS reduction ($p>0.05$). However, gastrointestinal complaints were higher in the PUVA group.[40] Another clinical trial assessed the effectiveness of NB-UVB and loratadine combination therapy versus loratadine monotherapy using an urticaria activity score (UAS). The mean UAS was lower after 8 and 16 sessions in the intervention group compared to control ($p<0.01$). It concluded that NB-UVB could be used as an adjunct therapy in chronic urticaria.[41]

Chronic pruritus (LoE II)

The etiology of chronic pruritus is unknown in more than 20% of patients, however, primary biliary cirrhosis and chronic kidney disease are associated with chronic pruritus.[43] Phototherapy is thought to reduce the production of IL-17, -23, -4, and -3 which inducing itch. UV also affects nerve signals through the endogenous opioid system and reduces the density of nerve fibers in the skin.[44] A clinical trial in 30 patients with uremic pruritus found that 15 sessions of NB-UVB significantly decreased the symptom compared to oral cetirizine and topical liquid paraffin ($p=0.001$).[45] However, recent guidelines from the European Association of the Study of Liver Disease and American Association for the Study of Liver Disease do not address the role of UVB for chronic pruritus due to limited evidence.[44]

Lichen planus (LoE II)

Lichen planus is a chronic mucocutaneous and nail inflammatory disease characterized by itchy, polygonal, purple flat papules with unknown etiology. It is suspected that the cellular immune system plays a role in the destruction of basal keratinocytes. The role of phototherapy on lichen planus is not fully understood, however, it is thought to affect T cell apoptosis, anti-inflammatory effects, and immunosuppression. Phototherapy can be used for both generalized and localized lichen planus.[46,47]

A clinical trial in 46 subjects found that NB-UVB given thrice weekly for six weeks was superior to prednisolone 0.3 mg/kg for the same period ($p=0.008$). Moreover, patient satisfaction was higher with phototherapy ($p=0.012$).[47] Case series in 10 patients with generalized lichen planus showed a complete response in 80% of patients who received NB-UVB thrice weekly. However, the recurrence rate in three to six months after completed phototherapy was high, ranging from 10-37.5%.[48] A case report in a pediatric patient with lichen planus pigmentosus-inversus refractory to topical corticosteroids exhibited a good response following localized NB-UVB twice weekly at an initial dose of 50 mJ/cm^2 for 30 sessions.[49]

Scleroderma (LoE II)

Scleroderma is a chronic autoimmune disease with involvement of the skin, joints, and internal organs. The clinical features of scleroderma include the thickening and elasticity of the skin. There are two types of scleroderma, namely systemic and localized. Localized scleroderma has

a better prognosis because there is no internal organ involvement. UVA and UVB are often used in the management of localized scleroderma.[12]

UVA increases the expression of the MMP-1 gene and decreases the levels of collagen I and III and TGF-β. In addition, the effect of UVA on increasing vascular endothelial growth factor (VEGF) and decreasing apoptosis of endothelial cells also results in a reduction of sclerosis in the dermis.[50] Although PUVA is effective with the mean cumulative dose of fewer than 400 J/cm^2, the use of psoralen is associated with increased side effects and discomfort for patients. Thus PUVA is not recommended for the management of scleroderma.[51] UVB increases the synthesis of α-MSH receptors on keratinocytes and melanocytes. α-MSH is an antifibrotic mediator that works by increasing the expression of MMP-1 mRNA.[52]

A systematic review of 62 pediatric and adult with active morphea showed that MD-UVA1 (50 J/cm^2), low dose-UVA1 (LD-UVA1) (20 J/cm^2), and NB-UVB five times a week for eight weeks has the same effectiveness.[53] Case reports of three patients with localized scleroderma who received UVA1 with a total dose of 540-1800 J/cm^2 showed improvement of collagen fibers texture with reducing of their size.[54] The Single Hub and Access Point for Pediatric Rheumatology in Europe (SHARE) recommends MD-UVA1 in children with localized scleroderma due to its effectiveness in improving tenderness and reducing skin thickness.[55]

Cutaneous T cell lymphoma (LoE II)

Cutaneous T cell lymphoma (CTCL) is a rare neoplasm of T cells in the skin. Mycosis fungoides (MF) is the most common type, occurring in more than 50% of all CTCL. The classic feature of MF is erythematous patches which eventually developing into plaques, tumors, and erythroderma.[56] Another type is Sezary syndrome (SS), manifested as erythroderma and the presence of circulating atypical T cells with or without lymphadenopathy.[57] MF is effectively treated using phototherapy.[58] NB-UVB and PUVA induce lymphocytes and keratinocytes apoptosis, decrease Langerhans cells proliferation, and suppress pro-inflammatory cytokine production. UVA, with its deeper penetration, induces faster lymphocytes apoptosis (12 hours after radiation), inhibits inflammation by modulating pro-inflammatory cytokines via phosphatidylinositol 3-kinase (PI3K) pathway.[58]

The results of the meta-analysis in 778 early-stage MF patients showed a superior response to PUVA (90.9%) compared to NB-UVB (87.6%), without the difference of side effects.[59] Median relapse of early-stage MF in patients receiving PUVA was longer than that in NB-UVB (p-value <0.0001).[60] A comparative study of 43 MF patients showed that patients receiving PUVA or NB-UVB had a longer median progression from patch and plaque stage to tumor stage as well as life expectancy compared to patients who did not receive phototherapy.[61] In 2015, the American Academy of Dermatology published phototherapy guidelines for MF. The dose of 8-methoxy psoralen (8-MOP) is 0.6 mg/kg with UVA exposure 2 hours thereafter. The frequency of PUVA is twice weekly with the initial dose is determined based on the patient's skin type.[62]

TABLE 2. Guideline for narrowband ultraviolet B (NB-UVB) and psoralen ultraviolet A (PUVA) phototherapy in mycosis fungoides according to the American Academy of Dermatology in 2015.*

Skin types	NB-UVB (mJ/cm^2) Dose		UVA (J/cm^2) Dose	
	Initial	Increasing dose every session	Initial	Increasing dose every session
I	130	15	0.5	0.5
II	220	25	1.0	0.5
III	260	40	1.5	1.0
IV	330	45	2.0	1.0
V	350	60	2.5	1.5
VI	400	65	3.0	1.5

If the patient does not undergo phototherapy for:	NB-UVB	PUVA
4 - 7 days	Maintained dose	Maintained dose
1 - 2 weeks	Decreased 25%	Decreased 25%
2 - 3 weeks	Decreased 50%	Decreased 50%
3 - 4 weeks	Started from the initial dose	Decreased 75%
>4 weeks	Started from the initial dose	Started from the initial dose

If no response occurs after 20 treatments, the dose of NB-UVB can be increased by 50 to 100 mJ/cm^2, in PUVA the dose can be increased by 0.5 to 1 j/cm^2.
*Cited from original reference No. 62

Pityriasis lichenoides (LoE III)

Pityriasis lichenoides (PL) is a papulosquamous dermatosis with unknown etiology. The clinical picture of acute PL is generalized papule with necrosis and scar formation, while the chronic condition is characterized by erythematous macula with scales that recur periodically. The PL spectrum consisted of pityriasis lichenoides et varioliformis acuta (PLEVA), febrile ulceronecrotic Mucha Habermann disease (FUMHD), and pityriasis lichenoides chronica (PLC). First-line therapy is topical corticosteroids; oral antibiotics (tetracycline, erythromycin, and azithromycin); and phototherapy.[63] Phototherapy modulates the immune response, thereby repairing PL lesions.[64]

A systematic review of 309 PL patients who received one of the BB-UVB, NB-UVB, or PUVA showed a complete response in 91%, 75%, and 69% of cases, respectively, whereas partial responses occurred in 0%, 20.6%, and 22% of cases, respectively. The recurrency after completing phototherapy was 25.7%.[65] A prospective study in Vietnam involving 29 PLC patients showed 82% complete response to NB-UVB (cumulative dose of 9,760.5 mJ/cm^2 over 4.6 weeks period) without recurrence after three months.[66] A systematic review demonstrated the effectiveness of phototherapy in 64 pediatric patients with a complete response was as followed: 89.6% in BB-UVB with recurrence of 23.1%, 73% in NB-UVB without recurrence, and 83% in PUVA with a high recurrence rate of 60%.[64]

Other Dermatoses

Phototherapy is also effective for other dermatoses, such as graft-versus-host disease (GVHD), granuloma annulare, systemic mastocytosis,

lymphomatoid papulosis, perforating dermatosis, and pityriasis rubra pilaris (PRP). However, the evidence are limited to retrospective studies or case reports (LoE IV), thus there are no phototherapy guidelines for these dermatoses.[67-72]

CONCLUSION

Besides psoriasis and vitiligo, phototherapy can be used for the management of various dermatoses either as a single or combination therapy. Strong scientific evidence shows that phototherapy is effective in the management of AD, CTCL, scleroderma, chronic hand dermatitis, chronic urticaria, lichen planus, chronic urticaria, photodermatosis, and chronic pruritus. However, phototherapy has side effects such as photoaging, risk of carcinogenesis, and photosensitivity reactions, thus the physicians have to take consideration while utilizing this modality. Until now, research in phototherapy is still being carried out to determine the therapeutic effect and the most appropriate dose for various dermatoses.

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