

Targeted phototherapy for skin diseases

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ABSTRACT

Phototherapy is a therapeutic strategy in dermatology for treating several skin diseases. Conventional phototherapy has some disadvantages, hence a targeted phototherapy that emits selective laser or ultraviolet (UV) light and targets specific area of affected skin has been developed. Targeted phototherapy is considered to be more aggressive and has higher efficacy. Several targeted phototherapy devices emit one or several types of light. The use of targeted phototherapy has been studied in vitiligo, psoriasis, eczema, keloid, hypopigmented scar or striae alba, and oral lichen planus.

ABSTRAK

Fototerapi merupakan salah satu strategi pengobatan dalam bidang dermatologi untuk terapi beberapa penyakit kulit. Fototerapi konvensional memiliki beberapa kekurangan sehingga dikembangkan *targeted phototherapy* yang dapat mengeluarkan laser atau sinar ultraviolet dan ditujukan hanya pada area kulit yang terlibat. *Targeted phototherapy* dipertimbangkan lebih agresif dan memiliki efikasi yang tinggi. Beberapa sediaan alat *targeted phototherapy* dapat memancarkan satu atau lebih jenis sinar. Penggunaan *targeted phototherapy* telah diteliti pada kasus vitiligo, psoriasis, eksema, keloid, skar hipopigmentasi atau striae alba, dan lichen planus oral.

Keywords : targeted phototherapy - ultraviolet - skin diseases -indication - dosage

INTRODUCTION

Phototherapy is a therapeutic strategy in dermatology for treating several skin diseases.^{1,2} Conventional phototherapy uses a whole body cabinet or body part machine such as hand, foot or scalp machines, which results in exposure to unaffected body area. Not to mention, it is the slow irradiation system that causes a prolonged therapy session and the more frequent clinical visits. Other disadvantages in using conventional phototherapy are the inability to reach particular body such as genital area and

skin folds, the distress of providing therapy for children who are not comfortable with a vast machine and the larger space required for placing the machine.¹

Due to those disadvantages of conventional phototherapy, a new phototherapy technique was then developed to overcome this situation. This technique was called targeted phototherapy or also known as concentrated phototherapy, focused phototherapy, microphototherapy and localized phototherapy. Targeted phototherapy is defined as a therapeutic method using a device

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that delivers laser light or ultraviolet light spectrum of a specific wavelength focused on specific body areas or lesions.^{1,3} This definition includes different technologies used such as excimer laser, intense pulse light system (IPL) and ultraviolet (UV) light source with a sophisticated delivery system which is easy to be operated by hands.¹

This literature review discusses the targeted UV light phototherapy and the excimer laser, their advantages, type of devices, and also their usage in dermatology, in the aim to broaden our knowledge of therapeutic strategy so that a precise and appropriate therapeutical decision can be made.

DISCUSSION

Phototherapy Mechanism of Action

Ultraviolet light has a spectrum which is divided into 3 parts according to their wavelengths, namely UVC with the shortest wavelength (200-290 nm), UVB with the intermediate wavelength (290-320 nm) and UVA with the longest wavelength (320-400 nm). UVA is then divided into UVA1 (340-400 nm) and UVA2 (320-340 nm).^{4,5} The light sources include broadband UVB (BB-UVB) with a wavelength of 290-320 and a peak at 313 nm, narrowband UVB (NB-UVB) with a wavelength of 311-313 nm, UVA (320-400 nm, peaks at 355 nm), and UVA1 (340-400 nm, peaks at 365 nm).⁴ Excimer laser which emits monochromatic UV light, has various wavelength ranges depending on the molecules used, especially in the field of dermatology XeCl laser with a wavelength of 308 nm.¹

Various mechanisms were found and it was proposed that phototherapy can give either in systemic or local effect. Ultraviolet B rays have shorter wavelengths so that they do not penetrate as deeply as UVA rays do, but UVB rays have more energy. Ultraviolet B phototherapy primer

effect is on the function of keratinocytes and Langerhans cells. The effectiveness of UVB therapy in psoriasis especially lies on its antiproliferative effect.⁶ The decrease of pruritus after the treatment with both BB-UVB UVB and NB-UVB is caused by cell mast apoptosis.⁷ In the use of targeted BB UVB phototherapy,⁶ NB UVB⁸ and excimer laser,^{9,10} T cell apoptosis was found. The apoptosis mechanism may be caused by the damage of the epidermis and dermis cells which are susceptible to UV light exposure. Ultraviolet B rays cause DNA damage and formation of pyrimidine dimer.¹¹ In addition to T cell apoptosis, UVB radiation triggers changes in cytokine production, local immunosuppression, stimulation of melanocyte-stimulating hormone (MSH), increases migration, proliferation of melanocytes and melanogenesis.^{12,13}

Ultraviolet A has a longer wavelength, so it can reach the dermis and have an effect on fibroblasts, dermal dendritic cells, endothelial cells, T lymphocytes in the dermis and granulocytes.⁴ In atopic dermatitis, UVA is shown to cause apoptosis of T helper cells in the skin with eczema lesions through FAS/FAS-ligand system.¹⁴ In addition, UVA and UVA1-irradiation may also decrease histamine release by basophils and mast cells.¹⁵ The combination between UVA and psoralen (PUVA) has a more complex mechanism. Psoralen undergoes intercalation in the double-stranded DNA. Ultraviolet A exposure causes the formation of 3,4 or 4',5' cyclobutane monoadduct with pyrimidine bases on a single photon absorption. The double helix DNA then undergoes a cross-linking process when the absorbed second light photon by 2 monoadducts forming a bifunctional adduct. DNA replication is inhibited by the cross-linking results in cell cycle disruption and decreased epidermal proliferation. Once psoralen excited by the photons, it can react with oxygen molecules to form reactive oxygen

species (ROS), which can cause mitochondrial dysfunction and apoptosis of Langerhans cells, keratinocytes and lymphocytes.⁵

Both UVA and UVB cause decreased expression of ICAM-1⁴ and increased levels of immunosuppressive cis-urocanic acid that it can depress cellular immune response and inhibit Langerhans cells activities.¹⁶ The mechanism of action of targeted phototherapy is similar to the mechanism of action of conventional UVB/UVA phototherapy, but is thought to be more aggressive because the dose given can be higher than the erythemogenic dose, which results in a greater efficacy due to its ability to deliver the energy to the deeper dermis layer.¹

Targeted Phototherapy Device Availability

Targeted phototherapy device consists of 2 parts, a generator that generates the UV light, and a probe connected to the generator via an optical fiber cable that is easy to be operated by hands. Several other tools have probes with lamps connected to the adaptors via cables.

Some UV light-based targeted phototherapy preparations that emit one type of light and have been used on researches are BClear (Lumenis Inc., Santa Clara, CA, USA; emitting UVB light),^{17,18} Bioskin® (Centro Salute Montecani S.r.l., Montecatini Terme, Italia; emitting UVB light),^{19,20} Biopsorin (emitting NB-UVB light),²¹ The Resolve™ (Allux Medical Inc., Menlo Park, CA, USA; emitting UVB light),²² NEC lighting flat type NB-UVB (NEC lighting, Tokyo, Japan; emitting NB-UVB light),²³ Dermalight 80 Psoracomb (Dr R. Hönle, Munich, Germany; emitting UVB, NB-UVB or UVA light),²⁴ DermaPAL™ (Daavlin, Ohio, USA; there are 3 preparations provided, UVA, UVB and NB-UVB).

There are some targeted phototherapy preparations that are able to emit more than one type of light, they are DualLight™ (TheraLight, Inc., Carlsbad, CA, USA; emitting UVB (BB or

NB-UVB) and UVA light),²⁵ MultiClear (Curelight Ltd, Israel; emitting the combination of light between UVB (296-315 nm), UVA1 (360-370 nm) and intense blue light),²⁶ Psoria-Light™ Model PSI 1000: (emitting UVA and UVB light).

Excimer lasers which have been utilized on some researches and available in the market are Talos (Wavelight Laser Technologie, Jerman)⁹, Excilite-Deka (Florence, Italia)¹⁰, and Xtrac (Photomedex, Radnor, PA, USA).²⁷

The Benefits of Using Targeted Phototherapy

Some of the advantages of using targeted phototherapy for the patients are that the exposure is confined to the affected skin area, hence minimizing the acute side effect such as erythema as well as the chronic side effect such as skin cancer on the unaffected skin area,^{1,17-24,26-30} the quick energy delivery of targeted phototherapy surely shortens each therapy session.^{1,26,27} Unlike conventional phototherapy, it has the ability to reach difficult area of the body such as genital, scalp, ear and other area with skin folds^{1,17,19,20,24} and the dosage can be tailored depending on the affected area or lesion,^{9,17,19,31} so that therapeutic effect is achieved faster. All mentioned advantages result in less frequent clinical visits,¹ and increased comfort, especially for children patient.³⁰ The highlight of this device is that it can be used safely at home.²²

For the doctors or the operators, the advantages of targeted phototherapy are that the device is easy to operate,^{1,17} has the ability to do a good targeted PUVA,¹⁷ can be administered with different doses for different body parts,^{19,20,24} and does not need special electricity tools.¹ It also has a countertop design, does not need vast space to place the device, and is easy to perform minimal erythema dose (MED) or minimal phototoxic dose (MPD) with it.

Compared with the more bulkier conventional phototherapy, it is a lot more user-friendly and has a more economical device maintenance.¹⁷

Indication and Targeted Phototherapy

Dosages

The following are indications and studied targeted phototherapy dosage (TABLE 1):

Vitiligo

The use of UVB targeted phototherapy on localized vitiligo aged 5-62 years old skin phototype II-V, for as many as 30 therapy sessions; twice a week, the first dose for the thin skin was 50% MED and 75% MED for the other, increased dose of 10-20 mJ/cm² on each session, with a result of good to very good repigmentation on the face, medium repigmentation on the neck, trunk and genital, but no repigmentation on the upper nor lower extremities.¹⁷ Asawanonda *et al.* compared targeted BB UVB and targeted NB UVB in treating focal and generalized stable vitiligo aged 16 years old or more, given twice a week for 12 weeks with an initial dose of 50% MED which increased as much as 10%, repigmentation obtained was about 26-50% in 6 out of 10 patients and the response toward BB-UVB and NB-UVB was the same.²⁵ The use of a combination between oral corticosteroid and 0.1% tacrolimus ointment applied twice a day with UVB targeted phototherapy given twice a week for 5 months in 3-year old kids and adults with segmental vitiligo, resulting in a good repigmentation, and minimum side effect which was a transient erythema on the affected skin.³⁰

Al-Otaibi *et al.*³¹ reported the use of excimer laser on vitiligo with skin phototype III to V, given twice a week for 13 weeks. The treatment was started with 50 mJ/cm² for the eyes and genitalia, 100 mJ/cm² for body lesions, and increased by 50 mJ/cm² in every session

until erythema appeared, for 25 sessions or 100% repigmentation, whichever achieved first. The better result was seen on face, trunk and extremities, whereas hands and feet gave a bad response towards the therapy, side effects occurred were erythema, blistering and burning.

Psoriasis

Narrowband UVB targeted phototherapy has been studied on plaque psoriasis (skin phototype II-1V; average Psoriasis Area Severity Index (PASI) score 4,2), given once a week for approximately 12 therapy sessions with an initial dose of 90% MED and the dose was increased of as much as 25% on each session, a PASI score of 0,5 was obtained after the treatment had been finished showing an 88% improvement of the lesion without any side effects.²¹

The use of UVB targeted phototherapy compared to betamethasone valerate, with an initial dose of 200 mJ/cm², the dose increased daily, given for 5 days in 3 weeks, both of the groups experienced an improvement in PASI score, but after a 2 week-observation the group which used betamethasone valerate had more recurrence rate than the group treated with targeted UVB phototherapy.²⁴ Meanwhile another research conducted by Taneja *et al.*³² applied a BB-UVB with an initial dose of 1 MED and an increasing dose of 20% for 12 weeks, a significant PASI score was obtained compared to control group.

A study comparing a combination of topical psoralen (0,001% 8-methoxypsoralen) and UVA targeted phototherapy (PUVA) with psoralen and UVB by Asawanonda *et al.* reported that the use of a constant dose of UVA 5 J/cm² once a week for 12 weeks resulted in PASI score improvement with an average amount of therapy session of 4.75±3.5.³³

The use of excimer laser with an initial dose of 1/3 MED which was increased based on clinical response, given twice a week for 12 weeks. The results obtained were that 72% achieved improvement for as much as 75% on target plaque after the average of 6.2 times of therapy, 84% achieved improvement for as much as 75% on target plaque after the average of 10 times of therapy, 50% achieved improvement for as much as 90% on target plaque after the average of 10 times of therapy or less.²⁸

The use of NB-UVB targeted phototherapy on unresponsive to oral and topical treatment of acrodermatitis continua of Hallopeau, a form of acropustular psoriasis, with an initial dose of 80% MED, increased dose was of 20% on each session until reaching a maximum dose of 2000 mJ/cm², given twice a week, remission occurred with a minimal dystrophic nail plate after session 36th, no side effect was found and no recurrence on 12 month- follow-up.³⁴

Eczema

Irradiation of acute eczema of the volar and back of the hands using UVA1 for 15 times in 3 weeks showed that after the first week of irradiation all patients except one patient reported that they experienced a decreased itchiness, and after the 15th irradiation, 10 out of 12 patients showed a significant clinical improvement.³⁵ Those reports show that local UVA irradiation on the eczema lesion gives a good result.

A research done by Wollenschlager *et al.* on 57 patients with resistant localized mild atopic dermatitis using excimer laser showed complete remission in 84% patients (48/57) with a decreased in itchiness as the sign after 3-4 times therapy.³⁶

Keloid

A research done by Asawanonda *et al.* reported the use of UVA1 on 2/3 keloid lesion for 6 weeks, with 22 therapy sessions given 4 times per week, resulting in a flattened and softened lesion. In addition, histopathological examination found that collagen and elastic fibers returned back to normal.³⁷

Hypopigmented scar or striae alba

The use of excimer laser with an initial dose of MED minus 50 mJ/cm², the dose increased as much as 50 mJ/cm² on each session, given twice a week until 10 therapy sessions finished. The results obtained were that the average of visually assessed pigment correction percentage, relative to control group was 61% in patients with scar and 68% in patients with striae after 9 therapy sessions, whereas the average of pigmentation percentage using calorimetric measurement relative to control group was 101% in patients with scar and 102% in patients with striae after 9 therapy sessions.²⁶

Oral lichen planus

Köllner *et al.*³⁸ reported the use of excimer laser on 2 cases of oral lichen planus unresponsive towards the previous therapy, given 3 times a week in 4 weeks (12 therapy sessions) in case no.1 and 9 therapy sessions in case no.2 with an initial dose of 75 mJ/cm², with a cumulative dose of 1.550 mJ/cm² and 950 mJ/cm², follow-up was done in the first, second and fourth month after the therapy finished, improved lesions and no recurrence were the obtained results.³⁹ Paseron *et al.* reported the use of excimer laser on 4 cases of erosive oral lichen planus, given twice a week until 12 therapy sessions finished with an initial dose of 50 mJ/cm² the dose increased as much as 50 mJ/cm² on every 2 sessions until reaching

a maximum dose of 200 mJ/cm², one patient was healed, meanwhile for the other 2 patients, these therapies were only able to avoid disease progression. Trehan and Taylor⁴⁰ reported 9 cases oral lichen planus treated by excimer laser, with a dose of 100 mJ/cm² given once a

week, the results were that 5 patients improved after 7 times therapy, whereas the other patients gave intermediate or bad response towards the therapy. Side effects of laser usage in oral lichen planus were mild erythema³⁹ and erosion.³⁸

TABLE 1. Indications and dosages of targeted phototherapy

No.	Indications	Devices	Dosages
1.	Vitiligo	<ul style="list-style-type: none"> • UVB/NB UVB • Excimer laser 	<ul style="list-style-type: none"> • Twice a week, 1st dose : 50% MED (thin skin), 75% MED (other), increased 10-20 mJ/cm², 30 sessions. • Twice a week, 1st dose: 50 mJ/cm² (eyes and genitalia), 100 mJ/cm² (body), increased 50 mJ/cm²/ session, 25 sessions.
2.	Psoriasis	<ul style="list-style-type: none"> • NB UVB • UVB • 0.001% 8-methoxypsoralen and UVA (PUVA) • Excimer 	<ul style="list-style-type: none"> • 1st dose: 90% MED, once a week increased 25%/session, 12 sessions. 1st dose: 80% MED, increased : 20%/session, maximum dose: 2000 mJ/cm², twice/week, for 36 session (acrodermatitis continua of Hallopeau) • 1st dose :200 mJ/cm², increased daily, 5 days/3 weeks or 1st dose: 1 MED increasing dose : 20% for 12 weeks. • UVA 5 J/cm² once a week for 12 weeks. • 1st dose: 1/3 MED, increased based on clinical response, twice/week for 12 weeks.
3.	Hand eczema	UVA1	40 J/cm ² /day, 15 times in 3 weeks
4.	Keloid	UVA1	130 J/cm ² , 4 times/week for 6 weeks
5.	Hypopigmented Scar or striae alba	Excimer laser	1 st dose: MED minus 50 mJ/cm ² , increased 50 mJ/cm ² /session, twice a week until 10 therapy sessions finished.
6.	Oral lichen planus	Excimer laser	1 st dose: 50-100 mJ/cm ² . 1-3 times a week in 4 weeks , Increased: 50 mJ/cm ² /2 sessions until cumulative dose : 200-1.550 mJ/cm ² , follow-up: first, second and fourth month

CONCLUSION

Targeted phototherapy is a therapeutical modality that utilizes a device that can emit light/UV spectrum of a specific wavelength, and specifically targeted at the affected skin area in the aim to overcome the disadvantages of conventional phototherapy. Targeted phototherapy benefits the patients, the doctors and also the operators. It is provided in a various kind of device, and resulting in a satisfying outcome in dermatological conditions and diseases, some of which are vitiligo, psoriasis, eczema, hypopigmented scar or striae alba, oral lichen planus and many others.

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