Laser Treatments for Vitiligo

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Vitiligo remains to be a major challenge in the field of dermatology. To this day, there is still no definitive cure. Although phototherapy has been the mainstay to manage vitiligo, it is associated with several adverse effects, such as tanning, burning, and skin aging, due to the unavoidable exposure of normal, uninvolved skin to intense ultraviolet radiation. Laser treatment has an advantage in treating vitiligo in a targeted way, and it appears to be a reasonable option for localized vitiligo. Moreover, a majority of patients have limited involvement of body surface area. An increasing number of reports have highlighted the value of lasers as a treatment option for vitiligo. The 308-nm xenon chloride excimer laser is already considered to be a treatment of choice for localized vitiligo. Additionally, there are emerging lasers that have been attempted as the treatment of vitiligo, including low-energy 632.8-nm helium-neon lasers, ablative fractional lasers, gain-switched 311-nm titanium:sapphire laser, and 355-nm monochromatic ultraviolet A1 laser. While evidences for these laser treatments of vitiligo are limited, some results seem to be promising. For example, studies have shown a responsiveness in otherwise refractory cases and via different mechanisms of action. However, most studies were uncontrolled and non-comparative, and have produced no conclusive results. Nonetheless, it is expected that we will witness greater development and advancement in laser treatments for vitiligo soon. In this article, we discuss the current state of laser treatments for vitiligo and proposed mechanisms of action.

Key words

Excimer; Laser treatment; Vitiligo

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INTRODUCTION

Vitiligo is a common acquired depigmentation disorder, resulting from the selective loss of melanocytes in the skin and mucosa.¹ It affects 0.5–2% of the population and remains a major challenge in dermatology because there is no definitive cure. Although it is generally asymptomatic, patients with vitiligo suffer from profound psychological distress, especially in ethnic populations.² Phototherapy, including psoralen plus ultraviolet A and narrow-band ultraviolet B (NBUVB) therapy, has been the mainstay for vitiligo.³ However, phototherapy is associated with several adverse effects, including tanning, burning, and skin aging, when administered over the long term, because normal, uninvolved skin is unavoidably exposed to intense ultraviolet radiation.⁴

An increasing number of reports have highlighted the value of lasers in the treatment of vitiligo (Table 1). The 308-nm xenon chloride excimer laser is the most widely used laser for vitiligo, and is currently considered the treatment of choice for localized vitiligo.⁵ Additionally, there are several other emerging lasers in the treatment of vitiligo, including low-energy 632.8-nm helium-neon (He-Ne) lasers, ablative fractional lasers, a gain-switched 311-nm titanium:sapphire (Ti:Sapphire) laser, and a 355-nm monochromatic ultraviolet A1 (UVA1) laser. However, most of them have demonstrated effectiveness only in small numbers of pilot studies.

Lasers have an advantage in treating vitiligo; they allow selective treatment of depigmented lesions, preventing unnecessary irradiation of uninvolved skin.⁵ Thus, laser treatment appears to be a reasonable option for localized

Table 1. Laser treatments for vitiligo

Laser modality	Clinical response	Mechanism of action
308-nm xenon chloride excimer laser	The 308-nm excimer laser is the most validated laser modality in vitiligo treatment. Treatment success (>75% repigmentation) was generally achieved in 15–61% of each vitiliginous patch. The most effective responses would be anticipated on the face and neck, while the hands and feet show minimal responses.	It can contribute to both immunomodulation and the migration and proliferation of melanocytes, like NBUVB. The excimer laser has been found to be a more potent inducer of T cell apoptosis than NBUVB. Both the excimer laser and NBUVB can increase the level of endothelin-1 mRNA at a dose close to the minimal erythema dose. The excimer laser induced immature pigment cell development that was not seen with NBUVB treatment
Low-energy 632.8-nm He-Ne laser	He-Ne laser treatment was effective in patients with segmental vitiligo on the head/neck in a pilot study. Marked responses (> 50% repigmentation) were achieved in 60% of patients after a median of 118 treatment sessions.	Medium from He-Ne laser-irradiated keratinocytes enhanced melanocyte migration, possibly by increasing basic fibroblast growth factor and nerve growth factor. It could normalize dysfunction in cutaneous blood flow and adrenoceptor responses in segmental vitiligo. It stimulated primitive pigment cell differentiation, an effect not seen with UVB treatment.
Ablative fractional laser	An additive effect of ablative fractional CO ₂ laser (100 mJ/spot) with NBUVB phototherapy for vitiligo has been shown. Combined treatment with a fractional CO ₂ laser plus high-potency topical corticosteroids and NBUVB showed an effective treatment response in refractory vitiligo. The addition of low-fluence fractional CO ₂ laser treatment (4 mJ/spot) showed minimal repigmentation in 21.7% of patients with refractory vitiligo.	Various cytokines and growth factors that are secreted during wound healing may act as mitogens for melanocytes. A significant increase in endothelin-1 mRNA expression was observed after low-fluence fractional CO ₂ laser treatment at 2 mJ/spot.
Gain-switched 311-nm Ti:Sapphire laser	A Ti:Sapphire laser was shown to be as effective as an excimer laser. The minimal erythema dose of a Ti:Sapphire laser is 1.7 times that of 308-nm excimer lasers.	Immunosuppressive effects of the Ti:Sapphire laser have been observed in atopic dermatitis animal models. Increased endothelin-1 mRNA, a melanogenic paracrine cytokine, was also observed.
355-nm monochromatic ultraviolet A1 laser	Clinical repigmentation was observed in 15/17 (88.2%) patients, and 52.9% (9/17) of patients showed good-to-excellent responses (> 50% repigmentation).	UVA1 wavelengths penetrate the skin more deeply than UVB, thus effectively better modulating the activities of immune and inflammatory cell populations in the dermis. UVA1 phototherapy modulated pro inflammatory cytokines, including tumor necrosis factor- α , interleukin-12, and interferon- γ . It also stimulated melanocyte activity.

vitiligo. Furthermore, children would be another indication for laser treatment because it does not require entering a phototherapy unit that could limit pediatric use. Although evidence for the use of lasers in the treatment of vitiligo is currently limited, some results are promising. In this article, we discuss the current state of laser treatments for vitiligo and proposed mechanisms of action.

THE 308-NM EXCIMER LASER

The 308-nm xenon chloride excimer laser was first described for the treatment of vitiligo in 2001,⁶ and the US Food and Drug Administration approved it for the treatment of vitiligo in 2007.⁷ It emits a monochromatic wavelength of 308 nm and induces photobiological effects similar to those of NBUVB that have maximum emission at 311 nm. It also delivers a higher fluence to depigmented lesions selectively, sparing uninvolved normal skin. There are only a few products available on the market, including XTRAC (PhotoMedex Inc., Horsham Township, PA, USA) and E1 (Pronexx Co. Ltd., Seoul, Korea).

Efficacy of the excimer laser

Several studies have assessed the efficacy of 308-nm excimer lasers in the treatment of vitiligo. There is a great diversity in treatment responses among studies, and treatment success (>75% repigmentation) is generally anticipated in between 15 and 61% of each vitiliginous patch.⁸⁻¹⁴ However, the treatment response is dependent largely on body site.^{9,11,12} In a recent retrospective study of 979 patients by Fa et al.,¹² the best response was noted on the face (>75% repigmentation: 40.86%) whereas the hands and feet showed the poorest response (>75% repigmentation: 9.17%).

Comparison of the excimer laser and NBUVB

There is currently little evidence to support the superior efficacy of excimer lasers compared with NBUVB. Hong et al.¹⁰ first compared the clinical efficacy of a 308-nm excimer laser with that of NBUVB in a pilot study of 23 vitiliginous patches in eight patients. They showed both better effectiveness and earlier appearance of repigmentation with 308-nm excimer laser treatment than with NBUVB treatment. However, Linthorst Homan et al.¹⁵ conducted a randomized comparison of an excimer laser versus NBUVB phototherapy after punch grafting in 14 patients with stable vitiligo, and showed no significant difference in the grade of repigmentation at 3 months. Regarding 308-nm monochromatic excimer light treatment, the superiority of excimer light over NBUVB is also

controversial with conflicting results among different studies.¹⁶⁻¹⁸

Meanwhile, the excimer laser has shown to be associated with a faster onset of repigmentation and fewer treatment sessions for a successful response compared with conventional phototherapy. Zhang et al.¹³ observed the onset of repigmentation after an average of 6.1 treatment sessions with an excimer laser, and Xiang et al.¹⁴ showed that 45.7% (92/201) of all patches treated with an excimer laser showed signs of repigmentation within the first 4 treatment sessions.

Treatment protocol

The treatment protocol for an excimer laser varies according to the clinical setting. Treatment is generally started at 100–300 mJ/cm², depending on the body site and Fitzpatrick skin type. The dose is increased by 50 mJ/cm² at each session until post-treatment erythema occurs, and the dose is then kept constant at the minimal erythema dose. A dose that will induce asymptomatic erythema, present for 24 to 48 hours after treatment, is considered ideal. Treatment sessions can be conducted one, two, or three times weekly. However, the ultimate rate of repigmentation seems to depend on the total number of treatment sessions, not their frequency, although repigmentation occurs more rapidly with more frequent treatment.¹⁹ Treatment is commonly performed on two non-consecutive days per week. We suggest a treatment protocol of the 308-nm excimer laser for vitiligo in Table 2, based on our experience and published ones.^{10,20}

Mechanism of action

Although the exact mechanism of action of an excimer laser in vitiligo is not fully understood, ultraviolet B (UVB) light seems to contribute to both modulating the immune response and the migration and proliferation of melanocytes.⁴ In early studies of psoriasis, a 308-nm excimer laser was shown to be more effective at inducing T cell apoptosis in lesional skin than NBUVB,^{21,22} and this immunomodulatory effect could also be responsible for the treatment response in vitiligo. During phototherapy, repigmentation begins at the hair follicle in many cases, and both NBUVB and excimer laser treatment have been shown to potentially induce melanocyte migration and proliferation from the niche located in hair follicles.²³⁻²⁵ Various cytokines, including stem cell factor, α -melanocyte-stimulating hormone, and endothelin-1, have been shown to be associated with mitogenesis and the migration of melanocytes during phototherapy,^{26,27} and an excimer laser dose close to the minimal erythema dose was

Table 2. Treatment protocol of the 308-nm excimer laser for vitiligo

Body site	Initial dose
Face and neck	150 mJ/cm ²
Trunk and extremities	200 mJ/cm ²
Hands and feet	300 mJ/cm ²
Post-treatment response	Dose modification
No erythema	Increase dose by 50 mJ/cm ²
Transient asymptomatic erythema within 48 hours	Maintain dose
Persistent asymptomatic erythema over 48 hours	Decrease dose by 50 mJ/cm ²
Persistent symptomatic erythema with pain or blister	Hold treatment until resolved, then reduce dose by 100 mJ/cm ²
General treatment principle	
A dose that induces asymptomatic erythema for 24–48 hours after treatment is ideal.	
Treatment should be performed on two non-consecutive days per week.	
Sunscreens should be removed from the treatment area because they absorb UVB light.	
For pediatric use, a dose reduction of 50 mJ/cm ² from the initial dose is recommended.	

demonstrated to potentially increase the level of endothelin-1 mRNA.²⁸ Recently, Lan et al.²⁹ demonstrated that irradiance (mW/cm²), rather than fluence (mJ/cm²), played an important role in UVB-induced immature pigment cell development; these results support the possible superiority of an excimer laser over NB-UVB in primitive melanoblasts.

Adverse effects

Post-treatment erythema is observed frequently, while burning, blisters, and itching are seen occasionally.⁷ Choi et al.⁹ reported that the most common adverse effects were long-lasting or symptomatic erythema (48.5%), while perilesional hyperpigmentation (14.3%) and blister formation (10.7%) were minimal, in their retrospective review of 69 patients. Most adverse effects were generally tolerable, and no serious adverse effect was reported.

LOW-ENERGY 632.8-NM HELIUM-NEON LASER

A low-energy 632.8-nm He-Ne laser (Omniprobe Laser Biostimulation System; Physio Technology, Topeka, KS, USA) has been addressed in the treatment of segmental vitiligo by a Taiwanese group.³⁰ Recently, a successful He-Ne laser (HLA-2000 Laser Therapy System; Hanil Meditech, Seoul, Korea) and topical tacrolimus combination therapy in one child with non-segmental vitiligo was reported in Korea.³¹

Clinical studies

Yu et al.³⁰ performed He-Ne laser treatment in 30 patients with segmental vitiligo on the head and neck. The laser was administered locally at a fixed fluence of 3.0 J/cm² once or twice weekly. Initial repigmentation was observed after an average of 16 treatment sessions, and marked repigmentation (>50%) was achieved in 60% of patients after a median of 118 treatment sessions (range, 16–148). In 3 of 30 (10%) patients, complete repigmentation occurred after 16, 20, and 24 treatment sessions, respectively. Only 16.7% (5/30) showed a poor response (<25%) after a median of 50 treatment sessions (range, 37–100).³⁰

Mechanism of action

An *in vitro* study showed that significant increases in basic fibroblast growth factor and nerve growth factor released from keratinocytes after He-Ne laser treatment, and the medium from He-Ne laser-irradiated keratinocytes could directly enhance melanocyte migration.³⁰ The same group also showed that He-Ne laser treatment could normalize cutaneous blood flow, which was significantly higher in segmental vitiligo compared with contralateral normal skin, and they concluded that He-Ne laser therapy could normalize dysfunction in cutaneous blood flow and adrenoceptor responses in patients with segmental vitiligo.³² They also showed that He-Ne laser irradiation promoted melanoblast differentiation via mitochondrial retrograde signaling, an effect not replicable with UVB treatment, even at high and damaging doses.³³

Limitations

Despite interesting results from laboratory and clinical studies of patients with segmental vitiligo, additional trials are needed to confirm the indications for the use of He-Ne lasers in vitiligo.

ABLATIVE FRACTIONAL LASER

The ablative fractional laser was first developed for the remodeling of scars; it has also been tried to induce repigmentation in vitiligo. There have been a series of reports of the clinical improvement in vitiligo after dermabrasion^{34,35} and ablative laser treatments.^{36,37} The ablative fractional laser does not ablate the entire epidermis, leaving normal intact skin between the coagulated necrotic columns. It decreases the risk of potential side effects, and re-epithelialization occurs within 24 hours via keratinocyte migration from the surrounding normal tissue.³⁸

Clinical studies

Shin et al.³⁹ first showed the additive effect of a 10,600-nm ablative fractional CO₂ laser (eCO₂; Lutronic Corp., Goyang, South Korea) to conventional NBUVB phototherapy for refractory vitiligo in their prospective, randomized, left-right comparative study of ten patients. All patients had symmetrical vitiligo lesions without improvement despite more than 1 year of conventional treatment. The laser was administrated with 2 passes of a pulse energy of 100 mJ/spot and a spot density of 150 spots/cm² at a 2-month interval. At 2 months after the 2 courses of ablative fractional treatment, 30% of patients showed more than a moderate response (>25% repigmentation) to combined treatment, while none reached more than a moderate response with NBUVB phototherapy alone. Thereafter, triple combination treatment with a fractional CO₂ laser, high potency topical corticosteroids, and NBUVB also produced an effective treatment response in refractory vitiligo in two recent prospective, randomized split-body, comparative studies.^{40,41}

Recently, we performed a retrospective study of the addition of low-fluence fractional CO₂ laser treatment for refractory vitiligo not responsive to 308-nm excimer laser treatment over 6 months. In total, 46 patients were enrolled, and the laser was used weekly with two passes at a pulse energy of 4 mJ/spot and a spot density of 300 spots/cm². Repigmentation was evaluated after five treatment sessions, and 21.7% (10/46) of the patients showed at least minimal repigmentation (in press).

Mechanism of action

It has been suggested that dermabrasion enhances the repigmentation rate by increasing penetration of the dermis by ultraviolet radiation, removing affected keratinocytes, and inducing various kinds of cytokines and growth factors that may act as mitogens for melanocytes.^{36,42} Theoretically, an ablative fractional laser would be expected to share the same mechanisms as dermabrasion and ablative lasers, but would minimize the side effects.³⁹ In our *in vivo* study, a significant increase in endothelin-1 mRNA expression was observed at 24 hours after low-fluence fractional CO₂ laser treatment at 2 and 4 mJ/spot (in press). In addition, microscopic ablative zones produced with a fractional CO₂ laser would be expected to promote the transepidermal penetration of topical agents, which may provide additional benefits for repigmentation in vitiligo.^{40,41}

Limitations

In most studies, fractional laser treatment was applied

as an adjuvant treatment to conventional phototherapy. Clinical trials to evaluate the genuine efficacy of fractional laser treatment alone are required to justify the use of the laser in the treatment of vitiligo.

GAIN-SWITCHED 311-NM TITANIUM:SAPPHIRE LASER

A gain-switched 311-nm Ti:Sapphire laser (Pallas; Laseroptek, Seongnam, Korea) has been developed following the peak spectrum of NBUVB (311 nm). It was approved by the Korean Food and Drug Administration for the treatment of psoriasis and vitiligo in 2015. The 311-nm Ti:Sapphire laser has some advantages compared with the 308-nm excimer laser, including deeper penetration by the 311 nm wavelength and the use of a solid medium with reduced maintenance costs.

Clinical studies

We performed a randomized, controlled, non-inferiority trial, based on a split-body protocol for the treatment of vitiligo.⁴³ The minimal erythema dose of the 311-nm Ti:Sapphire laser was 1.7 times that of the 308-nm excimer laser in a pretest of ten volunteers. A total of 52 paired lesions in 16 patients were assigned to either the excimer laser treatment group or the Ti:Sapphire laser treatment group so far. Twenty-two paired lesions completed the 12-week trial course, and an interim analysis showed that the Ti:Sapphire laser is as effective as the excimer laser in the treatment of vitiligo.⁴³ The profiles of adverse effects of the two lasers were similar; no serious adverse effect was observed in either group.

Mechanism of action

Ti:Sapphire laser treatment seems to be associated with immune modulation and melanocyte stimulation, like excimer laser treatment. The laser was demonstrated to effectively suppress the immune response and provide clinical improvement in an atopic dermatitis animal model.⁴⁴ Additionally, an increase in endothelin-1 mRNA, a melanogenic paracrine cytokine, was observed after Ti:Sapphire laser treatment in an *in vivo* animal study.⁴³

355-NM ULTRAVIOLET A1 LASER

A 355-nm monochromatic UVA1 laser was first introduced to treat psoriasis.⁴⁵ It has also been demonstrated to be effective in the treatment of vitiligo.⁴⁶

Clinical studies

Babino et al.⁴⁶ conducted an open-label, prospective study of 17 patients with vitiligo. The 355-nm UVA1 laser treatment was conducted twice weekly for 8 weeks at a fixed dose of 80–140 J/cm². Repigmentation was observed in 15 of 17 (88.2%) patients, and 9 (52.9%) showed good to excellent responses (>50% repigmentation). Adverse effects, including mild post-treatment erythema and itching, were observed rarely. The major limitations of the study were the absence of a comparison group and the small number of patients.

Mechanism of action

UVA1 wavelengths penetrate the skin more deeply than UVB, possibly better modulating the activities of immune and inflammatory cell populations in the dermis. It has been demonstrated that UVA1 phototherapy can modulate proinflammatory cytokines, including tumor necrosis factor- α , interleukin-12, and interferon- γ .⁴⁷ Furthermore, UVA1 stimulates melanocyte activity, increasing melanin density and elongation and branching of melanocyte dendrites, resulting clinically in increased pigmentation or tanning.

CONCLUSION

Although there are several therapeutic modalities available, the treatment of vitiligo remains difficult. NBUVB phototherapy, which is used most commonly for patients with vitiligo, shows limited responses in certain patients, and is associated with unnecessary ultraviolet radiation exposure to normal skin. Moreover, a majority of patients have limited involvement of body surface area. In a recent nationwide study by the Korean Society of Vitiligo, 75.3% of enrolled patients (n=1,272) showed involvement of <5% of the body surface area.⁴⁸ Thus, laser treatment is worthy of note, and various lasers have been tried in the treatment of vitiligo over the last decade. Some studies have shown promising results, with responsiveness in otherwise refractory cases, and with differing mechanisms of action, although most of them were uncontrolled and non-comparative. We expect the further development and advances in the laser treatment of vitiligo in near future.

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