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REVIEW ARTICLE

Effectiveness of a 308-nm excimer laser in treatment of vitiligo: a review

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Abstract Vitiligo is a relatively common acquired disorder, characterized by progressive loss of melanocytes from the epidermis and the epidermal appendages. The disease is associated with considerable morbidity because of a major impact on the quality of life. The treatment for vitiligo is generally unsatisfactory and challenging. There are a variety of therapeutic possibilities including topical corticosteroids, topical calcineurin inhibitors, as well as phototherapy with Psoralen plus UVA (PUVA), narrow-band UVB, and a 308-nm excimer laser and/or lamps. Furthermore, surgical methods encompass grafting and transplantation while depigmentation treatments and psychological support may also be considered. The objective is to assess the effect of the 380-nm excimer laser in the treatment of vitiligo based on the available studies and case series. We searched the relevant literature about vitiligo and excimer laser published between 1990 and 2012 using the MEDLINE database. We reviewed all relevant articles about 308-nm excimer laser and light sources assessing their efficacy in the management of vitiligo as well as their side effects. The value of combination treatment methods was also analyzed. The available studies provide strong evidence that the excimer laser represents the most effective approach to treat vitiligo compared to ordinary phototherapy. Excimer laser is relatively safe and effective for localized disease. UV-sensitive areas respond best as well as a short duration of the disease. More frequent treatments achieve better results. Compared to other treatment modalities, the excimer laser most likely constitutes the treatment of choice for localized vitiligo. Its efficacy can be further improved in combination with other therapies such as corticosteroids, pimecrolimus, or tacrolimus.

Keywords 308-nm excimer laser · Vitiligo · Randomized controlled trials · Combination treatments · Phototherapy · Pimecrolimus · Tacrolimus

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Vitiligo is a common disorder affecting about 0.1–4 % of the population. Symptoms usually start before the age of 20 years. The exact pathogenesis remains unknown although several contributing mechanisms have been implicated, including genetic, autoimmune, and biochemical factors; oxidative stress; and neural or viral causes [1]. There are two main clinical variants of vitiligo: *generalized*

vitiligo, characterized by symmetrical patchy white areas that may spread to any part of the body, and *segmental vitiligo*, defined by unilateral depigmented macules. Shock, sunburn, pregnancy, physical illness, and trauma have been reported as trigger factors. The disease has a great impact on the quality of life [2, 3].

Therapy for vitiligo is challenging. A variety of approaches have been proposed, including topical and systemic steroids, topical calcineurin inhibitors, phototherapy, and surgical intervention including graft and melanocyte transplant. Total depigmentation is indicated as an alternative way, when vitiligo involves more than 60–70 % of the body surface.

Phototherapy can be delivered as broad-band ultraviolet B (UVB), narrow-band (NB) UVB, Psoralen plus UVA (PUVA), and targeted phototherapy using light sources or excimer lasers and lamps. Phototherapy enhances the migration and proliferation of melanocytes resulting in repigmentation and has a further impact on the immune response [4, 5].

In the past decade, an increasing number of reports have highlighted the value of the excimer (excited dimer) in the management of vitiligo. Excimer lasers (308 nm) and excimer lamps allow targeted phototherapy at high doses of 308-nm wavelength, which is close to 311 nm, that was proven to be most effective. It has the advantage of enabling also the treatment of small, nonaccessible or resistant areas when compared to ordinary phototherapies [6–8].

NB UVB units irradiate both diseased and normal skin, whereas targeted sources deliver high-intensity lights to depigmented areas. Rapid therapeutic responses have been reported after targeted phototherapy that may contribute to the reduction of the cumulative UV dose [5].

Goldberg et al. used excimer laser and UVB light sources to analyze the histologic and ultrastuctural changes in *hypopigmented stria distensea* cases. Six months after the final treatment, the biopsies were evaluated for both standard and electron microscopic changes in melanocytes. Both laser and UVB sources showed increases in melanin content [9].

Based on increasing numbers of reports and studies indicating the value of excimer laser in the management of vitiligo, we here critically review the published literature and provide recommendations based on the available evidence (Table 1).

Technology and practical use

Excimer (308 nm) is based on a self-contained gas system of xenon chloride (XeCl). The light is delivered by an optical fiber with spot sizes ranging from 10 to 30 mm and light impulse energy from 3 to 6.5 mJ/cm^2 according to the model used. There are few different products of excimer lasers and light sources available in the market. Photomedex^{TM} produces Xtract^{TM} as a first laser of this kind, which achieved FDA approval in 2000. The currently available light source by Photomedex is VTRAC ^{TM}. Quanta-derma^{TM} used to manufacture a 308-nm excimer laser, which now is built on demand only. Now, a small, mobile handheld 308-nm excimer lamp is marketed instead with 50–6,000 mJ/cm^2 power density and a spot size up to 16 mm. Excilte-U ^{TM} is another excimer system developed and launched to the market by DEKA.^{TM}

The output is initiated by a foot switch and consists of a train of short pulses with a pulse width of 30 ns delivered through a fiber optic handpiece, and it is operated 3 mJ per pulse with pulse repetition of up to 200 Hz. The laser allows fixed fluencies to be delivered starting from 100- and 50-mJ/cm^2 increments to a maximum dose of 2,100 mJ/cm^2 [9, 10].

Sessions are performed two to three times a week. Initial doses are determined either by minimal erythema dose or constant at 100–200 mJ/cm^2 depending on area and indication. The maximum dose usually reaches 2,000–3,000 mJ/cm^2. The initial dose for the treatment of vitiligo varies and depends on the body site, for example, for perioral, 100 mJ/cm^2; face, 150 mJ/cm^2; trunk and arms, 200 mJ/cm^2; wrist, 250 mJ/cm^2; elbow, 300 mJ/cm^2; knee, 350 mJ/cm^2; hand and foot, 400 mJ/cm^2; and toe and finger, 600 mJ/cm^2. The subsequent dose should be based on the duration of erythema. An increase by 50 mJ/cm^2 is given in case of no erythema.

Mild erythema is regarded as the optimum treatment fluence, and the same fluence should be kept. When erythema persists for more than 48 h, a decrease by 50 mJ/cm^2 is needed. If blisters appear or a burning sensation is felt, the treatment should be discontinued until resolution, and the treatment is resumed with a decrease of fluence by 50 mJ/cm^2 [8–10]. Patients and physicians wear protective glasses during the procedure.

Results of vitiligo treatment with 308-nm excimer laser and light

Evaluation

Most studies graded score repigmentation in four groups, according to percentage of repigmentation. Improvement in repigmentation is measured on a visual scale and graded as follows [10]: grade I (1–25 %), grade II (26–50 %), grade III (51–75 %), and grade IV (76–100 %).

Start of repigmentation

First repigmentation can start after four treatments and 2 weeks in Asian skin (type 4) on the face and approximately after eight treatments on the extremities [11].In most studies, topical medication was stopped at least 1 month

Table 1 Studies reporting the efficacy of the 308-nm excimer laser

Authors	Study design	No of patients	No of sessions/ duration in weeks	Remarks
Baltas et al. [6]	Case study	6	2/24 weeks	Repigmentation after 8 weeks
Spencer et al. [8]	Pilot study	18	3/12 treatments	Repigmentation after 2 weeks, 57 %
Esposito et al. [16]	Uncontrolled pilot study	24	2/36 weeks	Stable 12 months; various initial doses depending on localisation
Choi et al. [20]	Case study	50	2/15 weeks	Face and neck repigmentation, 75 %
Ostovari et al. [21]	Blind controlled	35	2/12 weeks	Effective on stable localized lesions
Kawalek et al. [25]	Double blind/placebo controlled	6	3/24 weeks	Combined excimer and topical tacrolimus (20 % laser alone, 50% laser plus tacrolimus)
Passeron et al. [33]	Randomized comparative	14	2/12 weeks	Combined tacrolimus (20 % laser plus placebo;70 % laser plus tacrolimus)
Hadi et al. [17]	Retrospective	32	2/15 weeks	Skin type III better
Hadi et al. [18]	Retrospective	97	2/15 weeks	50 % vitiligo patches showed 75 % pigmentation and more. Face responded better
Taneja et al. [10]	Uncontrolled	15	2/3 weeks	Face better, good results without leukotrichia
Hofer et al. [12]	Controlled, prospective	24	3/6–10 weeks	Repigmentation started after 13 treatments
Casacci et al. [27]	Randomized, investigator blinded half side comparison	21	2/24 weeks	Comparison, 308-nm excimer light and narrow-band UVB; 308-nm excimer light is more effective
Sassi et al. [35]	Randomized controlled	84	2/12 weeks	Combined with topical hydrocortisone 17 butyrate cream excimer laser plus hydrocortisone 75 % clearance
Zhang et al. [11]	Therapeutic evaluation	38	2/16 weeks	After 30 treatments in 61 %; more than 75 % repigmentation
Yang et al. [14]	Controlled comparative	51	2/12 weeks	Comparison, narrow-band UVB and excimer laser. Perifollicular pattern repigmentation in NB UVB 29%, in excimer 37.5 %
Al-Otaibi et al. [15]	Controlled prospective	34	3/13 weeks	Face responded better; in higher skin types, better response
Yang et al. [22]	Randomized, single-blinded comparative	49	2/30 weeks	Combination with topical pimecrolimus and excimer in children, 308-nm excimer safe in childhood, combination better
Le Duff et al. [28]	Randomized blinded	17	2/24 weeks	Comparison, 308-nm excimer lamp and 308-nm excimer laser/similar effect. Lamp induced more erythema
Cho et al. [23]	Retrospective	30	2/variable	Safe in childhood; best response on face
Greve et al. [7]	Retrospective	9	2–3/variable	Poor response on hands, related to low density of hair follicles
Hong et al. [29]	Comparative	23	2/20 weeks	Excimer versus NBUVB; excimer more effective
Oh et al. [31]	Randomized, single-blinded comparative	16	2/16 weeks	Combination topical tacalcitol with excimer, limited effect
Nistico et al. [34]	Randomized controlled	53	2/12 weeks	Group I, excimer/oral vit E; group II, excimer/topical tacrolimus/oral vit E; Group III, oral vit E topical immunomodulators enhance clinical response, especially in more resistant anatomic sites

before treatment by excimer and phototherapy stopped 3–6 months before excimer treatment [6–11]

Repigmentation results

Hofer et al. reported an onset of repigmentation after an average of 13 treatments in lesions located on the face, trunk, arm, and/or leg, locations that are known as high responder areas and after 22 treatments in lesions located on the elbow, wrist, dorsum of the hand, knee, and dorsum of the foot, known as low responder locations [12, 13].

To determine the optimal frequency of treatment with the 308-nm excimer laser, there are different results. Although repigmentation may be fastest with the three times a week

regimen, repigmentation initiation seemed to depend on the total number of treatments rather than frequency of treatment [13].

The poor response on the hands and feet could be due to the low density of hair follicules there, since repigmentation usually originates from outer root sheet melanocytes in hair follicles [7]. Most lesions with grade IV repigmentation are progressive, and 80 % of totally improving lesions are located on the face. The best and final result can be seen after an average treatment duration of 6 months for head and neck and 8 months for extremities. This improvement was noted clearly on Korean vitiligo patients who have skin type 4 [14].

The percentage of lesions that achieve >75 % repigmentation differs and depends on more parameters than skin type. So, it was reported >75 % in 20.7 % by Al-Otaibi et al. [15] and in 29 % by Esposito et al. [16]. Complete repigmentation was seen in only 7 % by Yang et al. [14] and 25 % by Hadi et al. [17, 18].

Session numbers

The number of sessions per week plays an important role in both total efficacy and onset of response. Zhu et al. [19] found grade IV repigmentation (>75 % repigmentation) in patients treated every 14 days, 26 % treated two times/week and 32 % treated three times/week. More frequent treatments show better results. However, more side effects were noticed with excimer laser therapy given three times a week [12].

Treatment site and effectiveness

The face is the most favorable followed by the neck, trunk, and extremities. Hand and feet respond least, especially periungual areas, probably because no hair follicles are found in these areas. Hadi et al. reported that 77.6 % of treated facial lesions achieved 75 % repigmentation or more [18]. Studies showed better results if excimer laser therapy was started early at a duration below 2 years. After a duration of 2 years, effectivity is reduced to almost half [19, 20]. Ostovari et al. found that among UV-resistant areas, knees, elbows, and wrists responded significantly better [21]. This observation was confirmed statistically by Hofer et al. [12]. Children respond better than adults [22, 23]. Plaque size also matters: small reacts better than large (Table 2) [20–24].

Repigmentation pattern

Darker skin was reported to respond better; however, this is not statistically confirmed [25, 26]. Although the hair follicle is major source of melanization which is thought to be responsible for the perifollicular pattern of repigmentation, a vitiligo lesion can get melanization from melanocytes that stay in the surrounding normal skin, and this explains the marginal pattern [20]. Other theories suggest alternative sources of melanocytes, such as melanocyte precursors or stem cells which remain in vitiligo lesions of glabrous skin other than the hair follicle. This may explain the diffuse pattern of repigmentation [27]. Repigmentation following excimer laser seems to be higher than with NB UVB [24].

Table 2 Evaluation of repigmentation responses with excimer laser in vitiligo

Localization	The face has the best response; hands and feet, the worst
Skin type	Dark skin reacts better than light skin
Plaque size	A small lesion reacts better than a large one
Patient history	New spots respond better than old ones
Age	Children respond better than adults

Side effects

In most studies, the side effects are mild, transient, and localized without systemic problems as seen in PUVA. Local side effects represent as erythema, blisters, or perilesional pigmentation but do not appear frequently. Any phototoxic or photoallergic reactions were not observed. Some patients may report heat sensation and/or pruritus during treatment, which was not related to the treatment itself. However, all side effects are well tolerated in general. In most of the studies, patients' satisfactions were high with the visual analog scale.

Patients showed no relapse in most of the selected and reviewed studies, even after 1–2 years. The achieved repigmentation was stable in most of the treated vitiligo lesions during the 12-month follow-up period [12]. Faster onset of repigmentation may play an important role in supporting patient motivation and compliance [27].

308-nm excimer lamp versus 308-nm excimer laser

There was no significant difference in efficacy between 308-nm excimer laser and 308-nm excimer lamp in vitiligo. Side effects were seen more frequently with the 308-nm excimer lamp in treating vitiligo, because the lamp induces more erythema at the same doses. These two devices could have different photobiological effects at the cellular level [28].

308-nm excimer light versus narrow-band UVB (311–313 nm)

In vitiligo patients with symmetrical hypopigmented areas, one body side was treated twice weekly with 308-nm

excimer light while narrow-band UVB was used on the opposite side. Of the patients, 37.5 % achieved an excellent repigmentation score with excimer, but only 6 % were treated with narrow band. The cumulative UV dose for lesions treated with 308-nm excimer was lower than that required with narrow-band UVB. Fewer treatment sessions were needed to achieve repigmentation compared to traditional phototherapy [7, 24, 27]. The 308-nm excimer laser-targeted phototherapy delivers higher fluences in less time without affecting uninvolved skin [14]. There is no direct comparative study between excimer laser and PUVA. Hong et al. compared the narrow-band UVB phototherapy with short-term effects of 308-nm xenon chloride excimer laser. The 308-nm excimer lasers were found to be more effective than phototherapy, as they produce more rapid and profound repigmentation [29].

Combination therapies with excimer laser

Combination therapy can increase the efficacy of excimer laser or lamp treatments, especially with topical steroids and topical calcineurin inhibitors (Table 3). Topical calcipotriol did not increase the effect compared to the laser treatment alone [26].

Mouzakis et al. combined excimer laser (twice weekly) with 0.005 % calcipotriene (twice daily). Patients achieved 75 % repigmentation on the face after 10–20 weeks. The faster response may be related to the numerous facial hair follicles [30].

Oh et al. discussed the results of combination treatment of vitiligo with 308-nm excimer and topical tacalcitol (HT) in high concentration. This 16-week open, prospective, randomized, single-blinded comparative study had a limited effect neither as mono nor as combination in vitiligo [31].

Table 3 Combination treatments with excimer laser in vitiligo

Topical combinations with excimer laser	Result
Tacrolimus 0.1 % [25, 33, 34]	Synergistic effect, enhances the clinical response in resistant anatomical site
Hydrocortisone 17 butyrate cream [35]	Beneficial effect
High-concentration tacalcitol ointment [31]	Limited effect
Pimecrolimus 1 % [22]	Statistically superior to single laser treatment
Topical khellin 4 % [32]	Enhance the response in resistant areas
Calcipotriol [26]	Did not enhance the efficacy
Calcipotriene 0.005 % [30]	Rapid response on face (10–20 weeks)
Punch grafting [36]	Comparison of excimer versus NB UVB after punch grafting; both treatments induced repigmentation, with excimer 71.4 %, lower cumulative dose

In only one study (Sareceno et al.) is a combination of excimer with topical khellin 4 % discussed to enhance the pigmentation with best response on face and hands and side effects such as erythema, burning, and perilesional hyperpigmentation. The cost of this treatment, however, is higher than other conventional phototherapies [32].

Yang et al. combined 308-nm excimer laser with using a combination of topical pimecrolimus in children; lower cumulative dosages were needed with 308-nm excimer laser, and common side effects were observed like burning sensations and erythema. Lesions on fingers and trunk did not show statistical difference, but the combination was superior on the face [22].

The combination therapy with twice daily topical application of 0.1 % tacrolimus ointment was clearly superior, especially in UV-resistant areas [33].In UV-sensitive areas, the effects were slightly increased when tacrolimus was combined. In UV-resistant areas, when combined with tacrolimus, repigmentation rate was 75 % or more. The author discussed that localization of the lesion has a predominant role. The high percentage of UV-resistant areas decreases the efficacy. Adverse effects have been limited and tolerance was excellent [33].

Another double-blind, placebo-controlled study in 24 symmetric vitiliginous patches also showed an enhanced response time and repigmentation rates in vitiligo especially in Fitzpatrick skin types III–IV [25].

In a very recent randomized controlled study performed by Nistico et al., excimer light was combined with tacrolimus and oral vitamin E in 53 vitiligo patients for 12 weeks. Group I was treated with excimer light 308 nm twice weekly plus oral vitamin E; group II was treated with excimer light 308 nm twice weekly plus 0.1 % tacrolimus once a day and oral vitamin E, and group III was treated with oral vitamin E alone. Only group II presented good repigmentation in 40 % and excellent repigmentation in 30 %. Combinations with topical immunomodulators with excimer are considered to enhance the clinical response in resistant areas [34].

Combined with topical hydrocortisone 17 butyrate cream, 75 % reduction of vitiligo lesions was achieved at 12 weeks (308-nm excimer laser plus twice daily for three periods of week with topical hydrocortisone 17 butyrate cream followed by a 1-week steroid-free interval) compared to 48.2 % excimer monotherapy in a randomized controlled trial. Recalcitrant vitiligo on the face and neck may have benefitted most from this combination [35].

After punch grafting in vitiligo patients, 308-nm excimer laser as well as NB UVB induced repigmentation, but no statistically significant difference was found, besides the fact that with excimer laser, the effect was achieved with a 71.4 % lower cumulative dose [36].

Conclusion

In the past 10 years, several new methods are available for vitiligo treatment. The question when managing patients with vitiligo is not whether to treat or not to treat but to decide which treatment is most appropriate for the patient [13].

Excimer laser treatments show faster onset of repigmentation and need fewer treatments with less cumulative dose in order to achieve repigmentation compared with traditional phototherapy. Both 308-nm excimer and 311-nm narrowband UVB are photobiologically very close, but the laser light is monochromatic, penetrates deeper, and is applied in a targeted way that allows the delivery of higher fluences to the lesion and spares the uninvolved skin resulting in more and faster effectivity with less side effects. So, 308-nm excimer laser therapy is a safe and effective method of phototherapy for vitiligo [31, 34–37]. As first-line therapy, it should be applied when vitiligo is localized. The best response is noticed on UV-sensitive areas such as the face and neck; in others, a combination with steroids, tacrolimus, or pimecrolimus may be considered.

If the history of vitiligo is short, better results are achieved, and frequent sessions are more successful than less frequent ones. Side effects are transient, mainly as minimal erythema, rarely as blister or burns. Combination with topical steroid or topical calcineurin inhibitor (tacrolimus and pimecrolimus) increases the efficacy.

In children, excimer laser therapy is also indicated and successful, achieves faster results with lower cumulative dose and sessions, and spares uninvolved skin as well. The excimer laser has proven to be a useful tool in the treatment of vitiligo. Patients treated with excimer laser achieve excellent results in a short period rather than many months.

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