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Lasers in the Treatment of Vitiligo

Isil Kamberoglu Turan

Abstract

Vitiligo is an acquired cutaneous hypopigmentary disorder characterized by multiple depigmented macules and patches. There are numerous therapy modalities consist of topical corticosteroids and calcineurin inhibitors, phototherapy, surgical interventions and laser treatments are evaluated. Last 10 years, firstly excimer laser treatment has showed good results in repigmentation rates. “Excited dimers” produces a 308-nm ultraviolet (UV) monochromatic coherent wavelength, which lies within the UVB spectrum that absorb DNA as a chromophore to breakage DNA chain that causes a decrease in T-lymphocyte proliferation. Some articles have shown different responses depends on the type of vitiligo, number of sessions, interval periods and localisation. Researchers have also compared efficacy and also side effects of excimer laser between other methods. Combination therapies with excimer laser will be also treatment of choice via topical steroids or topical calcineurin inhibitors. Some of the patients developed delayed-onset permanent hypopigmentation need resurfacing methods such as CO₂ or Er:YAG laser which mainly aims to ablate the epidermis in specific coagulation columns to promote the penetration of externally applied agent. As an alternative treatment modality in vitiligo, lasers may help to raise patient compliance and reduce potential risk for skin cancer. Its convenience is limited by high cost and accessibility.

Keywords: vitiligo, treatment, excimer, laser, refractory, CO₂

1. Introduction

Vitiligo is an autoimmune skin disorder with a 0.5–2.0% incidence worldwide without sex or age. It is characterized by hypopigmented macules and patches due to dysfunction of melanocytes. Etiology of the disease could not elucidated yet. The significant association between vitiligo and other autoimmune diseases, including alopecia areata, diabetes mellitus, Addison’s disease, pernicious anemia, Graves’ disease, Hashimoto’s thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis and inflammatory bowel disease. Vitiliginous patches are often psychologically distressing and also have risk to loss of social status so that they cause negative impact of quality of life index. Two major forms are generally recognized that are *segmental* and *nonsegmental* types. Treatment of vitiligo is challenging and consensus of treatment modalities have changed beyond the types and places where the lesions mainstay. There are various phototherapy treatments which consist of PUVA, narrow-band UVB (NUVB), excimer laser and lamp commonly based on stimulation of melanocytes in the outer root sheath of hair follicles and on the margins of lesions besides that residual intralesional melanocytes migrate and repopulate the vitiliginous areas. Topical corticosteroid, calcineurin inhibitors, vitamine E and pseudocatalase could combine with these modalities to increase

treatment response. Furthermore in stable vitiligo patients, surgical methods such as full-thickness tissue graft (punch graft), split thickness graft, and suction blister graft, cellular grafts contains cultured melanocytes/keratinocytes have shown promising results [1, 2].

2. Laser treatments approach in vitiligo patients

2.1 Excimer laser for immunomodulation in adult vitiligo patients

Monochromatic excimer light was first described for the treatment of psoriasis in 1997 and 4 years later Baltás et al. reported the first case of successful use of the excimer laser for the treatment of vitiligo in 2001 [3]. In vitiligo patients, the widely use narrowband UVB (NUVB) that contains 310–313 nm wavelength has safety profile. At that wavelength arrival we can also conduct monochromatic excimer laser (MEL) with an obligation of limited skin areas to protect nonlesional apart. Mostly clinicians uses 308 nm wavelength according to obtain skin epidermal barrier to induce immunotargeted therapy. New concept of era called targeted phototherapy is usually recommended for localized forms of vitiligo affecting less than 10% of the body surface area. Although these localized modality could prevent hyperpigmentation of uninvolved skin, it could not achieve to deprive new lesion output. In the literature we do not have so much scientific verifications. In Egypt, Eldin et al. *analyzed* 30 patients with nonsegmental vitiligo with at least two symmetrical vitiliginous patches. They treated twice a week for 6 weeks with 308-nm MEL and NUVB for 6 weeks these contralateral lesions. Three punch biopsies were taken from baseline and 6 weeks later. At the MEL group statistically significant rise in the number of basal pigmented cells in the earlier period [4]. According to that, MEL would be treatment of choice rather than NUVB because of rapid onset, lower cumulative doses and lesser treatment sessions. This study is the only proof of histopathological verification for comparison of these proven treatment modalities. Narrowband UVB, excimer laser and lamp has spreaded out similar wavelength even though they have different radiation properties. Mostly articles have shown that excimer laser and lamp have similar repigmentation rate and also minimal side effects so that clinicians should decide how to treat due to cost benefit analysis.

Lopes et al. published a metanalysis, they conducted there is no difference between repigmentation rate for all three treatment options. 308 nm excimer laser has much more safety profile than narrowband UVB because it works lesser time without affecting uninvolved skin and also affect deeper skin via changeable impulse frequency and intensity. However, excimer laser is characterized by monochromatic, coherent, and high-energy light, whereas NB-UVB consists of polychromatic, incoherent light with lower intensity [5]. Yan et al. declared that lesions located on the face and neck had better repigmentation rate with excimer lamp controversially extremities have better response with NB-UVB. Le Duff et al. observed that the excimer lamp is less expensive than the laser, allowing cost/effectiveness prolificacy however treatment period has been longer [6]. Sun et al. presented a scientifically supportive study such as seven randomized controlled trials. They declined that excimer laser has as similar as therapeutic effects with lamp and also combination of 308-nm excimer laser with 0.1% tacrolimus or with tacalcitol ointment can improve the repigmentation rate [7]. Different responses could be based on different angle of UVB-light emission to epidermis via fiber optic devices of excimer laser. Mostly, narrowband UVB treatment is used the most effective for nonsegmental vitiligo, while excimer laser treatment is commonly chosen for localized vitiligo by clinicians.

Efficacy of the excimer laser depends the number of session in a week or total cumulative doses. Fitzpatrick skin types of III and above typically respond better than lower skin types. As usual, facial, neck and axillary regions have quick response opposed to acral parts of body. Clinicians should refer minimal erythema dose (MED) and increment arrival differs between 10 and 25%. Frequency of the laser did not play a role in pigmentation although rapid onset of treatment depends on suitable action plan. Shen et al. determined that time of repigmentation begins earlier as same as in 2.0 and 3.0 frequency period than 1.0 but also all of them have same pigmentation areas [8]. According to small spot size, these modality is not suitable for patients with vitiligo involving large body surface areas (>15%). Repigmentation differs site by site consist of perifollicular, diffuse, marginal, and combined. The perifollicular pattern was the most common seen.

There is a negative correlation between the duration of the disease and the percentage of repigmentation which could be named as unresponsiveness. Topical corticosteroids have been a mainstay in vitiligo treatment for decades. However refractory vitiligo patients should need combination modalities. As known, topical corticosteroids have significant adverse effects such as skin atrophy, striae, erythema, acne, increased glucose level, glaucoma. According to that, topical pimecrolimus or tacrolimus ointments have been promising for the treatment of choice. Shin et al. would like to analyze combination of NUVB and excimer laser to unresponsive patients, they also determined that acral lesions are difficult part to treat but combination could be greater choice due to less adverse effect to difficult cases mainly in facial vitiligo group [9]. Latif et al. investigated two randomly selected vitiliginous patches, first group of lesions had taken combination of excimer laser and betamethasone dipropionate and calcipotriol ointment twice daily and second group had taken only excimer laser two unconsecutive days in a week for 12 weeks. They concluded that in nonsegmental vitiligo lesions treated with topical combination of vitamin D3 analogue and steroid with 308 nm MEL gave significant results rather than excimer laser alone and it could be promising option for the treatment of vitiligo [10]. All 10 patients who have bilateral symmetric vitiliginous patches received xenon chloride excimer laser three times weekly and calcipotriol ointment was applied twice Daily one side of the body. While conversely, during the 15th month follow up Goldinger et al. compared a combination of excimer laser and calcipotriol with excimer laser alone, and found no significant difference between them [11]. Passeron et al. analyzed the efficacy of combined tacrolimus (twice daily) and 380 nm excimer laser (twice a week) or difference of monotherapy. Twenty three lesions had taken excimer laser and tacrolimus combination but also 20 lesions had taken laser monotherapy and all lesions have similar repigmentation rates such as 100 versus 85%. They determined that UV-sensitive areas do not have different response rate but in UV-resistant areas combination treatment is clearly superior to laser monotherapy via synergistic effects [12]. Park et al. have shown that increment at the molecular level of tyrosinase and melanin in human melanocytes with combination of excimer laser and tacrolimus rather than each monotherapy in the first 6 month. However, this superiority was not observed in the patients who treated more than 6 months [13]. Wang et al. published an article, all patients received laser therapy twice weekly combined with tacrolimus cream twice daily for 12 weeks. Dermoscopy is a useful tool for asses the outcome of the laser. They found statistically significant induction of residual perifollicular pigmentation and perilesional hyperpigmentation in active disease rather than stable disease [14]. Topical antioxidant cream which includes superoxide dismutase and catalase activity could combine with excimer laser. Soliman et al. published an article the comparison of excimer laser alone and antioxidant cream combination via 30 patients have similar vitiliginous patches has followed up maximum 24 sessions, they found excellent cosmetic results regard minimal side effects [15] Bapur et al.

also has propagated topical tacrolimus or topical clobetasol-17 propionate ointment enhance the efficacy of excimer laser [16]. As a summary, there is big gap for to discuss which topical choice has better results.

In segmental vitiligo patients, excimer laser has claimed as a treatment of choice. As a proof, Bae et al. made a treatment schedule that received 20 mg of prednisolone daily for the first 3 weeks, twice a week excimer laser and twice a day tacrolimus ointment. They found more than half of the patients with segmental vitiligo showed 75% or more repigmentation with combination therapy for mean period is 1 year [17]. Jag et al. also investigate small sample size, firstly gave low-dose oral prednisolone (0.3 mg/kg/day) for 4–8 weeks, 0.1% topical tacrolimus twice daily, and excimer laser twice a week for 12 weeks. They found higher response rate rather than current therapies [18].

Bae et al. evaluated 311 Titanium-Sapphire Laser (TSL) Treatment in vitiligo that based on 14 patients with non-segmental vitiligo are treated with TSL twice a week. They determined working principle as similar as NUVB an EL by immunomodulation and melanocyte stimulation. Main advantage is not necessary to check gas charging and also penetrate deeper than 308 nm wavelength of excimer laser [19].

BinSheikan et al. suggested a surgical needling technique means 30 Gauge inserted almost parallel to the skin surface towards the dermoepidermal junction moving towards the pigmented site to depigmented skin could increase the efficacy of excimer laser [20]. Mutairi et al. reported that combination of split-skin grafting from normal skin to vitiligo part with excimer laser twice a week have long-lasting good results in stable vitiligo patients. All of them satisfied to treatment and respond excellent as well [21].

Leukotrichia also called poliosis mainstays white hair involving the scalp, eyebrows, and pubis has frequently seen together with segmental vitiligo. Kim et al. evaluated the effect of the presence of leukotrichia on the response to excimer laser therapy at the first time and they suggested that leukotrichia has poor response due to lack of melanocyte reservoir. They also did not find any difference between vitiligo types [22]. All in all, disease duration longer than 12 months, presence of leukotrichia and plurisegmental subtype were identified to be independent poor prognostic factors for excimer laser treatment.

Adverse effects of treatments are mild and acceptable which are pruritus, burning sensation, and dryness. MEL has a favorable risk-to-benefit ratio which has only minimal side effects are mainly acute and self-limited phototoxicity especially erythema does not persist longer than 24 hours. Furthermore another local site effects are tolerable that consist of blisters, itching or perilesional pigmentation but do not seen frequently.

If the patient does not improve meanly after 30 sessions twice or three times weekly, it is suggested that further treatment could provide any significant response [23].

Dermatology quality of life index (DLQI) scale could provide us convenient and important data for benefits of the treatment. It occasionally contained validated questionnaires such as symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. In some analysis reports has concluded that long duration of disease, hand and face lesions and female patient have greater impairment of life index but also Shobaili et al. has shown that excimer laser has better improvement in quality of life index [25]. Alghamdi et al. made a survey in Saudi Arabia to prove dermatologists' clinical assessment for vitiligo treatment. They found excimer laser was the most common modality used to treat focal and segmental vitiligo and occasionally used in private clinics [26].

Excimer laser treatments respond faster recovery period and induce repigmentation rate so that clinicians use fewer treatments with less cumulative dose in order to achieve repigmentation compared with traditional phototherapy. The best result

is noticed on UV-sensitive areas and also does not affect unlesional part of the body regard as the face and neck; whose has shorter history of vitiligo. Combination with topical steroid or topical calcineurin inhibitor (tacrolimus and pimecrolimus) increases the efficacy. The excimer laser has proven to be a useful tool in the treatment of vitiligo.

2.2 Excimer laser in child vitiligo patients

NBUVB is a safe and effective, well-tolerated treatment option for childhood vitiligo as well as for vitiligo in adults declared as a treatment of choice. Besides the adult population, children who has vitiligo also treated with excimer laser that based on xenon chloride lasers has been delivering radiation of 308–310 nm, with a variable spot size. Acral regions, resistant areas, hidden places are favorable for excimer laser. Gianfaldoni et al. determined treatment schedule should consist of twice weekly among 13 weeks to achieve good response [27]. Clinicians should estimate minimal erythema dose (MED) and begin with 10% lesser than it. Occasionally, face and neck has responded well but acral lesions has repigmented slowly. Cho et al. suggested that treatment response rate has correlated with anatomic site of the vitiligo lesion especially in localized type [28].

2.3 UVA1 target laser in children

Another optional treatment modality could regard as UVA1 target laser consists of an active medium and a Neodymium-doped yttrium orthovanadate (Nd:YVO₄) crystal that is “energetically pumped” by another laser with 808 nm wavelength divided sequentially second (532 nm) and third (355 nm) harmonic wavelength delivery. Laser Alba allows the treatment of limited boarded lesional skin areas so that clinician can use a more appropriate dose of energy, leading to shorter duration and less frequent treatment sessions. The treatment with Laser Alba 355 is well—tolerated and already known acute side effects, such as erythema or pruritus have rarely been described.

Furthermore, innovative modalities consist of excimer laser, focused microphototherapy and also Laser ALBA should investigate to create new options [27, 29].

2.4 Fractional CO₂ laser for ablation modalities

As you know, vitiligo therapy is challenging though there is no definitive cure regime. Ablation therapy has recently been coalesced into combination therapy for vitiligo. These ablation modalities contains dermabrasion, erbium-YAG resurfacing, and ablative CO₂ laser treatment. Ablation modalities are not curative but they are useful to induce Koebner phenomenon to increase curative topical regimes. Fractional ablative laser has worked as a principle of photothermolysis to moderate skin resurfacing. Firstly, beneficial effect of fractional CO₂ laser on vitiligo is postulated to detachment of epidermis will release of cytokines and growth factors for immune response that plays a role as mitogens for melanogenesis. Additionally, fractional CO₂ laser via photothermolysis could decrease to skin surface so that absorb topical treatments and also increase efficacy of narrowband UVB treatment. Koebner’s phenomenon defined as the development of isomorphic lesions at traumatized uninvolved skin due to that fractional modalities to be concluded follicular hyperpigmentation as a different addition for pathogenesis. King et al. published a metanalysis, they determined ablation modalities (ER-YAG or fractional CO₂ laser) manage faster and effective repigmentation than the traditional methods that have explained via four different such as more penetration, skin remodeling, melanocyte migration and cytokine secretion [30]. Despite of that Koebner phenomenon

has not seen in stable lesions so that individual remedy should be chosen. In a recent article Yuan et al. aim to investigate three different fractional laser types. Ablative fractional laser consist of CO₂ lasers have much more satisfied results than non-ablative lasers [31]. On the contrary, Mofty et al. evaluated that TCA peeling depends on Koebner phenomenon redounded repigmentation is much more cheap, easier and effective than ablative CO₂ laser [32]. Lu Li et al. has tried different model with CO₂ laser. They applied sequentially CO₂ laser during half month interval and used twice daily betamethasone then took NUVB. They checked the response rate at the baseline, 3th and 6th month and also found repigmentation more than half of the patients to compare without betamethasone ointment. They suggested patient got tolerable pain and gain more satisfied repigmentation rate than ER YAG laser is expected [33]. Helou et al. concerned a different modality contains CO₂ laser three times 1 month apart following that sunlight tanning at least 2 hours has also significant results. These different opinions will be future play as an easy to apply due to cost-benefit analysis [34]. Nevertheless, there is no defined protocol for ablation to stimulate melanocyte transmission.

More advanced ablation modalities could combine with other topical remedies to optimize results. Feily et al. comprised two group stable refractory vitiligo patients got autologous transplantation and phototherapy alone or with fractional CO₂ laser. They found perifollicular repigmentation was statistically significant detectable in CO₂ laser group before the transplantation [35]. Vachiremon et al. suggested that fractional ablative CO₂ laser could combine with NUVB to shorten duration time of recovery and increase the penetration of light immunomodulation and also topical clobetasol propionate ointment [36]. Additionally that, acral part could not reach the treatments so that alternatives should try. By using CO₂ laser, clinicians have seen lesser hypertrophic scars than ERYAG laser also so that treatment of choice in ablative lasers could manifested. Mohamed et al. searched the combination of 5-Fluorouracil cream and CO₂ laser due to ablation of dermis to penetrate cream to migrate melanocytes in acral vitiligo patients. They declined that combination treatment is safe and tolerable technique for these resistant types [37]. Chen et al. investigated the topical tacrolimus combination with CO₂ laser, they suggested tacrolimus would be good option with ablation therapies, also [38]. Using with CO₂ laser, hypertrophic scarring was not reported because of the superficial ablation that means removing only the epidermis, avoiding the dermis.

As a summary, ablation-based combination therapy is safe and might be more effective than treatments without ablation therapy for increment of repigmentation.

2.5 Erbium laser for ablation modalities

The Er:YAG laser emits light at 2940 nm, with the water affinity being nearly 15 times greater than that of the CO₂ laser. Use of the Er:YAG laser requires more skill than does use of the CO₂ laser as the clinical endpoints allowing the laser surgeon require to intervene further penetration into the reticular dermis, are not seen with Er:YAG laser ablation. Furthermore, the plateau response of diminishing ablation characteristic of the CO₂ laser is not seen with the Er:YAG laser [1, 24]. Lotti et al. used a different innovation in a ablative model with Fraxel Erbium Laser (fractional erbium laser) make epidermal erosion 1 day after apply topical latanoprost solution and finally use UVA laser. The patients have nine sessions so on 90% of them obtained a repigmentation rate higher than 75% [39]. Bayoumi et al. tried to use erbium laser firstly for aiming dermabrasion after that 48 hours hydrocortisone 17-butyrate cream applied three times a day daily for 3 weeks followed by a 1-week steroid-free interval and narrowband UVB treatment was performed on both sides

twice weekly for 12 weeks. They succeed in refractory lesions due to Koebner's phenomenon almost half of the lesions treated at least 50% repigmentation rate and more than 16% achieved a complete or almost complete repigmentation [40]. As a point of view, that difference from non-treated part, dermabrasion has induced penetration of UVB and topical steroid so it cause enhancement of melanocyte stimulation. For example Yan et al. have a different perspective they insisted on energy should be set at the level of at least 1200 mJ. They divided four parts such as one of them is control group given NUUVB and other three of them took different frequency of energy to calibrate most effective and least painful method of these modality. They found better response at the medium or high energy protocols [41]. Mohtari et al. tried to find a unresponsiveness vitiligo part a new modality that is firstly used ER:YAG laser than applied clobetasol or 5-FU dressing and found better cosmetic results via ablation [42]. As expected, periungual vitiligo hard places to treat responded well. Two-thirds of the patients (66.7%) showed moderate to marked repigmentation via ER:YAG after dressing 5-FU [43].

On the whole, the acral regions were considered the most resistant to traditional treatment modalities. According to that, ER:YAG laser with topical corticoid, tacrolimus or 5-FU application could be promising treatment modality for unresponsiveness patients.

2.6 Q-switch laser for depigmentation modalities

Depigmentation is the unique treatment choice who develop vitiligo more than 90% body surface area, for the term "universal vitiligo" is commonly used. Topical agent such as MBEH (monobenzyl ether of hydroquinone) has main role to epidermal ablation and resurfacing. Laser therapies depend on therapies via difference to intact areas such as epidermal and dermal types. Specifically, Q switch laser could achieve faster depigmentation compared with chemical agents and the decrease the risk of scar formation. Q-switched Nd:YAG (QS ND:Yag) laser can deliver energy at two different wavelengths of 1064 and 532 nm in nanosecond pulses to cause both a photothermolytic and photoacoustic damage to melanocytes [1, 24].

Majid et al. followed up 15 patients covered more than 80% depigmentation areas whole body who have not respond MBEH least 3 months, They focused on Q-switch laser at 532 nm for epidermal component for need any session took 6th week arrival while continuing MBEH topical agents use has rapid onset improvement and minimal adverse effect [44]. Komen et al. has published a questionnaire about the result of Q switch (QS) Ruby laser that concluded 48% of the treated patients showed >75% depigmentation after a mean of 13 months' follow-up. This is the first study that comparison between active vitiligo during QS Ruby laser treatment have properly better results than stable vitiligo [45]. As a choice of MBEH, sometimes, the depigmentation site has gave up to fight immune system and looked more darker so that clinicians has to improve concentration. Modi et al. rather to use 532-nm Q-switched neodymium-doped yttrium aluminum garnet (QS Nd:Yag) laser via 2 sessions with 15 weeks intervals have good results. They offer to give 3 or 4 months apart to allow for maximal treatment response [46]. Majid et al. has followed up 25 patients with universal vitiligo from 2 to 5 years and determined QS-Nd:Yag laser leads to a long-term therapeutic effect in a majority of cases when used at 532-nm wavelength. Less than one third of cases during the follow-up period could preserve the therapeutic benefit achieved with laser treatment [47]. Boukari et al. has followed patients for 36 months depigmented 20 lesions via Q Switch laser and determined that risk of depigmentation parts mainstays in sun exposed areas have need maintenance therapies [48].

In conclusion, QS Nd:YAG laser at 532-nm wavelength seems to be a safe and effective treatment in depigmenting approach to universal vitiligo. The safety and long-term benefit achieved should qualify QS laser treatment as first-line treatment who did not respond topical bleaching creams. Moreover, QS laser combine with topical bleaching creams and sunscreen use, can achieve rapid satisfactory therapeutic outcome in universal vitiligo.

3. Conclusion

Vitiligo is a difficult disease to treat because of that new modalities should be investigated. As you known, traditional remedies such as NUVB and topical corticosteroids or tacrolimus did not respond well than new era has developed a concept called targeted phototherapy. Regarded as a targeted phototherapy excimer laser has same wavelength as same as NUVB to focused on apoptosis of T lymphocytes. However, excimer laser is characterized by monochromatic, coherent, and high-energy light, whereas NB-UVB consists of polychromatic, incoherent light with lower intensity. Excimer laser has significant safety profile and got better results than NUVB so that clinicians should decide the option to evaluate cost benefit analysis. Other traditional topical remedies could also apply with excimer laser to induce effectiveness. In segmental vitiligo patients or child population, excimer laser could be treatment of choice also due to localized areas. Another point of view of the laser treatment is ablation. Using the Koebner phenomenon, CO₂ laser and ER:YAG have worked as a principle of photothermolysis to moderate skin resurfacing. Traditional remedies could also combine with ablative laser types to increase the absorption of the treatments. Clinicians further to analyze depigmentation need. If patient has more than 80% depigmented areas, Q switch laser combine with topical bleaching creams and sunscreen use, can achieve rapid satisfactory therapeutic outcome in universal vitiligo. Vitiligo does not have a steady all known treatment protocols even though clinicians should further to investigate new combinations.

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