Chapter

Overview of the Role of 308 Monochromatic Excimer Phototherapy for the Treatment of Alopecia Areata

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Abstract

Treatment of alopecia areata (AA) remains challenging despite the advancement in all these years. Excimer phototherapy has been claimed to offer a practical alternative therapeutic option without significant risks. It is considered a "super-narrowband" UVB light source that emits energy at 308 nm. Excimer laser treatment achieves a remarkable effect in T cell-mediated disorders; thus, it has been used successfully in patients with AA. Compared with narrowband UVB, the excimer laser can induce apoptosis *in vitro*, paralleled by improved clinical efficacy. Both excimer laser and lamp have a similar effect, but they differ in technology. In this chapter, an evaluation of the effectiveness of 308 nm monochromatic excimer phototherapy in AA treatment is clinically warranted. The evidence-based studies that adopted this option using both laser and light are discussed. In addition, the formulation of therapeutic protocol to study the outcome of excimer treatment on moderate-to-severe AA in adults and children is described.

Keywords: alopecia areata, update treatment, 308 monochromatic excimer, targeted phototherapy, evidence-based studies

1. Introduction

Alopecia areata (AA) may cause significant cosmetic and psychological distress in affected persons due to the unpredictable course of the disease. The management of patients with AA is challenging, with no definite cure established. Corticosteroids have been the mainstay treatment used *via* topical, systemic, or intralesional routes. Other various treatment options have been tried, including systemic immunosuppressants such as methotrexate, azathioprine, and sulfasalazine and contact sensitizers such as dinitrochlorobenzene (DNCP), diphencyprone (DPCB), and squaric acid dibutyl ester (SADBE) [1, 2].

Phototherapies including psoralen plus ultraviolet (PUVA), UVA-1, and narrowband UVB (NB-UVB) were used to treat AA with some success rates. However, the disadvantage of these modalities is the exposure of a large area of normal skin to

irradiation along with the alopecia area, making the increment of irradiation dose limited. Despite that, this method could be an effective alternative for patients who are resistant to systemic and topical therapy. Topical PUVA or phototoxic PUVA consists of a solution containing 8-methoxypsoralen that was administered to the affected areas of the scalp around 20 minutes before exposure to ultraviolet radiation. The dose was based on the patient's skin phototype [3]. UVA-1 (340–400 nm) was superior to narrowband-UVB (NB-UVB; 311 nm), as it can penetrate the deep layer of the skin where the hair follicle is situated.

Recently, 308 excimer laser/light therapy has been used for treating AA with the significant results and fewer adverse reactions. This technology has the ability to induce apoptosis of affected T-cells. The advantages of excimer therapy include a lower cumulative UV dose involved, a shorter time of treatment, and the option of targeting individual lesions without affecting the surrounding healthy skin [4]. It is now considered a good option in treating different immune-mediated skin diseases. Moreover, excimer can be emitted as coherent (laser) or non-coherent light, both seem compelling, with the cost-effectiveness ratio more favorable to light.

2. What is excimer?

Excimer, also known as "excited dimer," is a class of diatomic molecules composed of atoms that are electronically excited and associated with the second atom in its ground (thermally unstable) state. The molecular ground state is unbound or weakly bound (by van der Waals forces). This means that a population inversion can be established automatically when the excited state occurs. Excimer lasers are capable of producing powerful and efficient broadband emissions at various spectral regions throughout the ultraviolet region. The most common types of excimer laser are the rare gas halides, which exhibit high power, average power, and single pulse energy. These include ArF, KrF, XeC1, and XeF. The last two types of excimers with weak ground states exhibit the most structured spectrums of overlapping remission transitions [5].

Formerly, excited dimers were represented only by homonuclear diatomic molecules with a steady excited state but repulsive ground states. Subsequently, excimer was extended to include any polyatomic molecule with a repulsive or weakly bound ground state—excimer molecule with heteronuclear dimer known as "exciplex" or exciting complex. For instance, Xe2* is an excimer molecule, while XeCl* and KrCl* are exciplex molecules.

The new ultraviolet B ray source, exciplex "xenon chloride lamp," emits monochromatic 308 nm light representing the natural evolution of the excimer laser (**Table 1**). The monochromatic excimer light (MEL) produces 50 mW/cm^2 power density at a distance of 15 cm from the source and has a maximum irradiating area of 504 cm^2 [6].

2.1 Historical aspect

The excimer laser was proposed in 1960 by Fritz Houtermans. Incidentally, in 1967, Mester et al. noted that using low-level laser therapy (LLLT) to treat cancer in mice with shaved backs could induce hair regrowth [7]. Later, the use of noble gas halides (originally Xe Br and then Xe Cl) was developed by many groups in 1975. These groups include the Avco Everett Research Laboratory and Sandia Laboratories [8, 9].

Variables	Excimer laser	Excimer lamp
Wavelength	308 monochromatic	304–308 monochromatic
Coherence	yes	non-coherent
Spot size	small	Large
Erythema	Less pronounce	More pronounce
Treatment cost	More expensive	Favorable cost

Table 1.
Comparison between excimer light and excimer lamp.

It was used for the first time in medical applications in 1997 when Bónis *et al*. tested its effect on psoriasis [10]. The study reported that excimer lasers might allow targeted, rapid phototherapy superior to conventional UV phototherapy with incoherent light. In 2001, Baltas et al. reported using the excimer laser to treat vitiligo [11]. Several studies have investigated the efficacy of 308 excimer on various dermatological disorders such as atopic eczema, mycoses fungoides, and AA [12–17]. All AA (single, multiple, and totalis) were identified and treated in those studies. Various protocols regarding the initial dose, increment dose, number of sessions per week, and complete course of treatment were applied.

2.2 Mechanism of action of 308 excimer in alopecia areata

AA is a T-cell-mediated autoimmune disease. It was believed that the immune system attacks the hair in the anagen phase, which leads to a rapid transition to catagen and telogen, resulting in hair loss. This process is triggered by the activation of the JAK/STAT cytokines, including IL-15 and interferon-gamma pathways [18].

The significant character of the hair follicle lies in its relative immune privilege, established by the suppression of surface molecules needed for presenting autoantigens to CD+ T lymphocytes and by the generation of an inhibitory local signaling environment. AA has been thought to develop due to cell death of protein 1 ligand (PD-L1), which leads to the collapse of immune privilege in the hair follicle [19].

Several triggers have been suggested to induce AA, including infection, drugs, trauma, and stress. Others such as autoimmune thyroid disease, atopy, and vitiligo are commonly associated. Psychological and physical insults may trigger the episodes of AA, but there is no evidence that they influence prognosis.

The high-dose monochromatic UV radiation of 308 excimer phototherapy can induce immunological suppression by altering cytokine production such as IL-4, IL-10, prostaglandin E2, platelet-activating factor, cis-urocanic acid, and trigger apoptosis. A study that used an excimer laser to treat AA in mice evaluated the number of perifollicular CD4+ and CD8+ in the treated patches before and after 12 weeks [20]. Results showed a significant decrease in the perifollicular infiltration of CD4+ and CD8+ with gross hair regrowth in the treated area.

It was suggested that the laser's effect on the activity and maintenance of T-cells could be mediated by the exertion of soluble mediators. The short wavelength of the excimer laser cannot penetrate human hair follicles, which means that the soluble mediators could potentially be utilized in inhibiting the activation of autoimmune reactions [20].

3. Evidence-based studies

Analysis of the biomedical literature database, PubMed, using the terms "excimer" and "alopecia areata" revealed that 16 of 38 studies analyzed were clinical trials, and five of these were control trials. Some of these studied protocols are given in **Table 2**. Of the control trials, one included 16 participants with 99 patches of AA [21]. The author of this study concluded that the excimer laser was safe and effective in AA. However, its effect on hair regrowth might be delayed compared with intralesional corticosteroids.

In 2004, Gundogan C et al. successfully treated two patients whose AA had progressively worsened for 3 and 14 weeks. They had used a 308 nm xenon chloride excimer laser (dosage: 300–2300 mJ/cm^2 per session). The entire affected area showed homogenous and thick hair regrowth after 11 and 12 sessions within a 9-week and 11-week period. Relapse was not reported during the 5 and 18 months [22].

Christian Raulin et al. reported that hair regrowth was achieved with the 308 nm xenon chloride excimer laser for AA of the scalp in a prospective side-by-side trial. One representative lesion was chosen; one-half of it was treated, and the other half remained untreated. Only the treated area showed hair growth; after 27 sessions over 3 months (200–4000 mJ/cm^2, a cumulative dose of 52.6 J/cm^2), this was probably not a spontaneous remission [23].

A study published by Zakaria et al. tested nine patients with AA using a 308 nm excimer laser, started with 50 mJ/cm^2 less than the minimal erythema dose. Then, doses were increased from 50 mJ/cm^2 every two sessions. The treated lesion was irradiated twice a week for 24 sessions. Each lesion had an opposite side untreated target lesion serving as a control. The results of the study revealed that the 308 nm excimer laser can stimulate hair growth in all patients with partial AA. This proves the effectiveness of laser treatment and excludes the possibility of spontaneous hair

Author	Patient No.	Type of AA	Successful rate	Treatment protocol
Zakaria *et al*., [14]	*n* = 9	Single, AT, AU	55.6	Twice/ week/24 session
Chao-Chun Yang et al., [15]	*n* = 17	AA, AT, AU	29.4	2–3 times/ week/14–118 sessions
Alhamzawi [17]	*n* = 18	MAA	55.5	Twice/week/24 sessions
Al-Mutairi, [24]	*n* = 18	MAA, one AT	41.5	Twice/ week/24 session
Ohtsuki *et al*., [25]	*n* = 16	Single, multiple	62.5	Once/2 weeks/8–40 sessions
Byun JW *et al*., [26]	*n* = 10	Multiple AA	75	12 weeks/Twice/ week
Arakawa Y. *et al*., [27]	*n* = 11	AU	36.3	2-week interval/16 weeks

AA—Alopecia areata, AU—Alopecia universalis, AT—Alopecia totalis.

Table 2.
Various studies have used 308 excimer laser/light in the treatment of alopecia areata.

regrowth. No relapse was noted in those patients who lost their hair over a follow-up period of 3 months. Moreover, no hair regrowth was observed in patients with either AA universalis (AAU) or AA totalis (AAT) [14].

In 2007, Al-Mutairi investigated the effect of the 308 nm excimer laser in the treatment of patchy AA. Eighteen patients, seven males and eleven females, with 42 recalcitrant patches (including one adult with AAT) were enrolled. The lesions were irradiated with the 308 nm excimer laser twice a week for 12 weeks. On each patient, one lesion was left as a control for comparison. New hair regrowth was observed in 17 (41.5%) patches, with 13 of the 18 lesions on the scalp showing a complete regrowth of hair. Lesions on the extremities failed to show a response. Atopic diathesis had an unfavorable effect on the outcome of treated patients. The author concluded that the 308 nm excimer laser is an effective therapeutic option for patchy AA of the scalp and some cases of patchy AA of the beard area. In contrast, it does not work for patchy AA of the extremities [24].

Ohtsuki et al. conducted a study to evaluate the effects of the 308 nm excimer lamp on three patients with single AA resistant to conventional therapy. They gave each of the three subjects the laser at two-weekly sessions. After 10 sessions, the hair growth rate in all three patients had returned to normal [25].

In a study conducted by Byun JW et al., 10 patients with AA were investigated, and the alopecic patch was divided into control and treated sides. The excimer laser was administered twice a week for 12 weeks. A therapeutic effect on AA was achieved, proven by photographs and phototrichogram [26].

In a clinical study of 11 patients with AAU conducted by Arakawa Y. et al., participants were treated with a 308 nm excimer light at 2-week intervals for more than 16 sessions. Four patients achieved good responses, and two patients exhibited poor responses. The authors concluded that the 308 nm excimer light therapy significantly affects some AAU patients resistant to other treatments and may be an alternative therapeutic option for AAU. The study suggested that the administration of a high radiation dose is required to achieve a strong inflammatory skin reaction [27].

In a prospective study, Alhamzawi evaluated the efficacy and safety of a 308 nm monochromatic excimer lamp in treating 18 patients with multiple AA. The treatment protocol consisted of two sessions per week for 12 weeks. The excimer safety was evaluated by objectively recording adverse reactions and patient satisfaction. Follow-up continued for 6 months after treatment to assess the level of recurrence. The results significantly affected resistant cases of multiple AA with considerable safety and tolerability (**Figure 1**) [17].

Fenniche S. et al. evaluated the efficacy and safety of combining topical khellin (a furanochromone photosensitizer whose chemical structure is close to that os psoralens) and 308 nm excimer light in the treatment of a refractory ophiasis, of 1-year evolution, in a 5-year-old boy. The trial showed complete hair regrowth with no recurrence one year later [28].

A controlled study by Li A., Meng X., et al. used a 308 nm excimer lamp with minoxidil in 38 patients with AA. Each alopecia lesion was divided into the control and treated sides. Topical minoxidil (2% solution) was used on both sides, with a 308 nm excimer lamp only added on the treated side. The primary objective of the study was to compare the number of hair growth on the treated and control sides. The results indicated that the number of hair growth on the treated side was significantly greater than that on the control side [29].

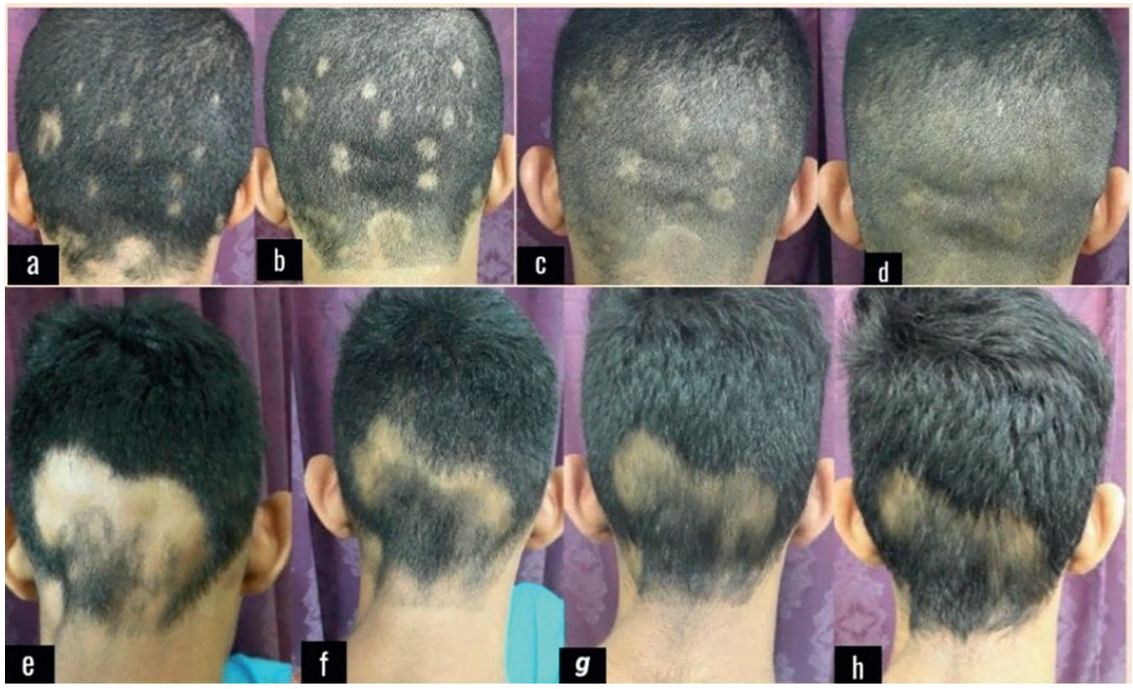

Figure 1.
Two patients with alopecia areata successively treated by 308 excimer lamp, a & e baseline, b & f 4 weeks after treatment, d & h 12 weeks after treatment.

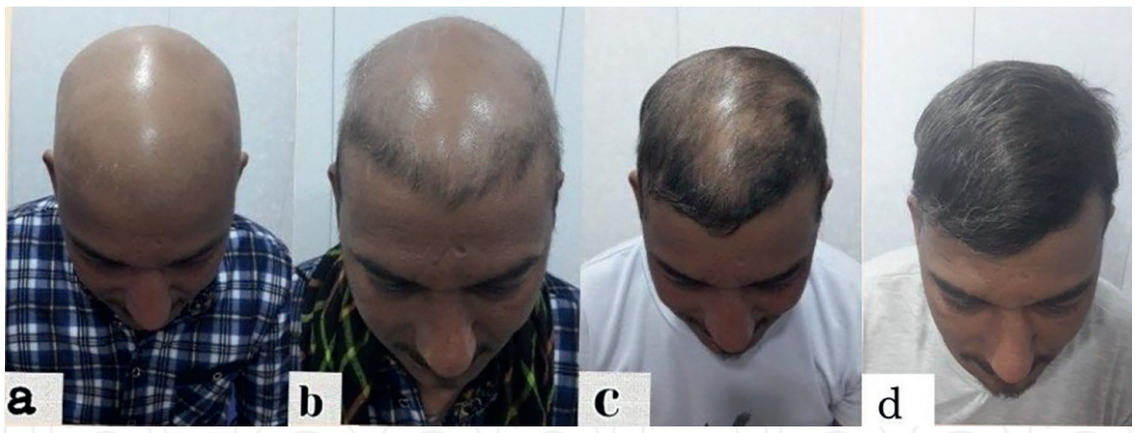

Figure 2.
Alopecia totalis treated by combined therapy of twice weekly 308 excimer light with monthly intramuscular triamcinolone acetonide.

Alhamzawi Nabeel K. tested the effect of combining 308 excimer phototherapy with IM triamcinolone acetonide on 10 patients with alopecia totalis. All patients received monthly IM triamcinolone acetonide (TAC) for six pulses and twice-weekly excimer phototherapy for 24 sessions. Four patients (40%) achieved complete regrowth of hair (100% regrowth), and three patients exhibited a satisfactory response (>70% regrowth). Two patients reported an unsatisfactory response (>10 to <70% regrowth). The study showed that younger patients responded better, as did those with a shorter history of the disease (**Figure 2**) [30].

Notably, the combination treatment of 308 excimer with systemic therapy is superior to excimer monotherapy, especially for resistant AA cases [30].

4. Targeted phototherapy

Also called focused phototherapy, it involves the emission of ultraviolet radiation directly at skin lesions through special delivery mechanisms. Targeted phototherapy includes laser and nonlaser technologies.

Excimer lamp is a targeted phototherapy that delivers a specific wavelength of 308 nm of UVB radiation to localized areas of skin lesions. Compared to NB-UVB, targeted phototherapy is more effective and safe. Unlike other laser devices, its templates are compatible with the contours of the target area, which means that they do not expose the normal skin to radiation. The effects of the laser can be delivered with a low cumulative dose and a shorter treatment duration, which are ideal for patients looking for a quick and effective solution. The spot size of the excimer lamp is wider than that of the excimer laser, which helps speed up the treatment of large areas of hair loss within a short time [31, 32].

4.1 Advantages of targeted phototherapy

1. Delivers high doses of energy within a short treatment session

2. Easy to handle and allows efficient treatment of difficult areas such as the scalp, nose, genitals, oral mucosa, and ears

3. Treats only the involved areas, sparing uninvolved regions, thus minimizing unwanted side effects of phototherapy such as erythema and long-term risk of skin cancer

4. Easily administered to children who are intimidated by large phototherapy machines

5. Occupies less space than conventional phototherapy machines

6. Short treatment sessions

4.2 Disadvantages of targeted phototherapy

1. Not recommended for lesions over 10% of the body area.

2. Time consuming for treatment of extensive areas.

4.3 Indications of targeted phototherapy

Localized psoriasis
Localized vitiligo
Mycosis fungoides
Atopic dermatitis
Alopecia areata
Localized morphea
Urticaria pigmentosa

4.4 Contraindications

Photosensitive disorders
Xeroderma pigmentosa
SLE
History of malignant melanoma

4.5 Side effects of excimer light treatment

The treatment aims to induce visible erythema in the treated lesion (supra-erythematous dose) but not cause a blister or second-degree burn. Too high a dose can lead to blister formation. Side effects may include painful erythema, desquamation, erosion, and reactivation of herpes infection.

Although long-term exposure to ultraviolet radiation ultimately causes skin aging and skin cancer, the risk of excimer light therapy is suggested to be less than that of narrowband UVB.

4.6 FDA devices of targeted phototherapy

Excimer laser machines, which are approved by the FDA, have been introduced by companies such as Alcon (Wave Light®, USA) and PhotoMedex. (XTRAC®; USA). The disadvantages of these equipment include their heavy weight, high cost, and difficult maintenance.

The FDA-approved nonlaser-targeted phototherapy includes Excilite® (DEKA, Florence Italy; 304 nm), Pxlite (308 nm), and Exciplex (Excimer Therapies; 308 nm). These machines are less bulky and cheaper and have a comparatively larger treatment surface than that of the excimer laser.

The nonlaser machines are considerably smaller than the laser machines, with fewer maintenance problems, and are cheaper. They have multiple delivery programs and automatic calibration for quick delivery of dosages so that the treatment time is short. Some of these machines have UVA (330–380 nm) and UVB (narrowband; 290–330 nm) spectra [32–34].

5. Treatment protocol

Despite the absence of a universally proven protocol that sustains prolonged remission, many therapeutic regimens for using excimer are available, which can benefit both children and adults with AA. Although the two types (laser and lamp) have similar effects, the difference between them is their technology. An excimer lamp is less expensive than an excimer laser, and it has a more prominent spot size that delivers a high dose of UV radiation to the selected treatment area. Wide spot size helps in treating a larger area in a short time. Any treatment options are frequently based on several parameters, including:

1. Age of the patient

2. Disease duration

3. Disease activity

4. Extension

5. Location

6. Analysis of dermoscopy features and scalp biopsy focused on the hair cycle and degree of inflammation

7. Patient expectations

8. Risk/benefit factors

9. Cost of therapy in terms of time and financial resources

10. Presence of other comorbidities such as low iron stores, thyroid abnormalities, low vitamin D, or other autoimmune diseases

11. Whether the patient has previously received treatment?

Before starting the treatment with monochromatic excimer light, you must calculate the minimal erythematous dose on healthy, unexposed skin. The volar aspect of the forearm is commonly used to determine the starting dose (usually 0.5–0.7 MED).

1. To identify MED, the tested areas irradiated with multiple doses (usually 50 mJ/cm^2, 100 mJ/cm^2, and 150 mJ/cm^2 etc, up to 300 mJ/cm^2, using different templates and wait for the result after 24 hours.

2. Carry out the treatments with one or two sessions per week until clinical response occurs. Calculate the delivered amount of UV taking into account the skin type, site, age, and response to treatment. In most cases, clinical improvements will be evident after a few treatment sessions. Mild side effects such as fair erythema may be observed (in at least 50% of patients) after the first and second applications. Other adverse reactions such as mild swelling, pruritic sensation, and hyperpigmentation may be noted in the treated areas but can be resolved spontaneously at two weeks post-treatment.

3. The starting dose is 50 mJ/cm^2 less than the identified MED, then increments are scheduled with 50 mJ/cm^2 every week. The dose is increased until the appearance of fine or asymptomatic erythema. If the erythema fades in less than 48 h, the treatment will remain fixed, and if it persists longer than 48 h, the dose will be reduced by 50 mJ. If the condition worsens, the treatment should be postponed until the next visit.

4. Irradiate the treat patches of AA twice weekly.

5. Continue the treatment for 12 weeks (24 sessions). If no response is noted after eight sessions, stop the treatment.

6. Avoid repeating the irradiation on the same treated area.

7. Use a template proportional to the size of the alopecia patch to avoid affecting the healthy skin.

8. Evaluate the therapeutic effect.

In evaluating AA treatments, clinicians require valid, clinically meaningful outcome measures.

In 2004, the SALT (Severity of Alopecia Tool) score emerged as a key milestone in the AA field, providing a standardized method to derive 0–100% of the scalp-hair loss. Building on this achievement, the AA-IGA (Alopecia Areata Investigator Global Assessment) provides an ordinal, static measure with five distinct clinical gradations of SALT score ("None" = 0, "Limited" = 1, "Moderate" = 2, "Severe" = 3, and "Complete" = 4). AA-IGA is a meaningful clinician-reported measure of scalp-hair loss, reflecting patients' and expert clinicians' perspectives and treatment expectations [35]. Assessment of hair regrowth is based on the change in the SALT score or AA-IGA.

The percentage of hair that grew back after laser treatment was assessed using a six-grade scale. The first grade was A0, where no change was detected in the number of hair (poor). The second grade was A1, with 1–25% regrowth (mild), and the third grade was A2, which was equal to 25–49% (moderate). The fourth grade was A3, with 50–74% regrowth (good), and the fifth was grade A4, with 75–99% regrowth (very good). The sixth grade was A5, with 100% regrowth (excellent).

Absolute change in SALT score = SALT score at baseline − SALT score after treatment. Percent scalp hair regrowth is based on SALT score = (100 × [baseline SALT score − SALT score after treatment])/baseline SALT score.

The results indicated that hair growth in more than 50% of the area was regarded as a successful response, while that with less than 50% range was considered to be an inadequate response. The poor response was evaluated when the SALT equaled zero. The overall response rate was the percentage of patients who responded positively to the treatment [17].

Evaluation is carried out at four points (baseline, 4 weeks, 8 weeks, and 12 weeks). The SALT score was recorded from the baseline to the last visit and digital photographs were taken at the same points.

The efficacy of the equipment was evaluated by the objective recording of adverse reactions and patient satisfaction. Follow-up continued for 6 months to 1 year after treatment to assess the level of recurrence. Excimer can be used as a monotherapy or combined with another treatment. The additive treatment can be topical, such as corticosteroid or calcineurin inhibitors, and it can be in the form of systemic therapy, such as methylprednisolone or triamcinolone acetonide.

6. Who can benefit from excimer therapy?

Studies have shown that excimer is safe and can be used for everyone. Here are the necessary specifications for candidates.

- Excimer can be used for patients with contraindications to systemic or topical therapy.
- For those with resistance or those who are not suitable for other procedures
- Disease duration: compared to those with long-term lesions, patients with a disease duration of >1 up to 4 years respond better to this procedure.

- Extension of the disease: patchy alopecia (single or multiple) responds faster than AU and AT.

- For patients with no associated comorbidities or other autoimmune diseases [3, 4, 14–17].

7. Conclusion

308 excimer phototherapy is an existing technology in treating AA. It is safe, effective, and easily administered even in difficult areas. The duration of treatment is shorter than that of whole-body phototherapy. A complete response may take 20–30 sessions, with some responses noted as early as 6–8 sessions.

Calculating the UV dose should be monitored considering the skin type, age, lesion site, and treatment response.

Learning points

- 308 nm excimer light is a targeted phototherapy that delivers a specific wavelength (308 nm) of UVB radiation.

- It is available in the form of a coherent excimer laser and non-coherent excimer lamp.

- It requires a short treatment course than conventional UVB phototherapy.

- It is well tolerated by children.

- Different templates are used to protect the surrounding unaffected skin.

- It can deliver a high dose of radiation with a reduced cumulative amount.

- It can use equipment in areas that are difficult to reach with UVB phototherapies, such as genitals and ears

Conflict of interest

None.

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