Excimer Laser: A Module of the Alopecia Areata Common Protocol

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Alopecia areata (AA) is an autoimmune condition characterized by T cell–mediated attack of the hair follicle. The inciting antigenic stimulus is unknown. A dense perbulbar lymphocytic infiltrate and reproducible immunologic abnormalities are hallmark features of the condition. The cellular infiltrate primarily consists of activated T lymphocytes and antigen-presenting Langerhans cells. The xenon chloride excimer laser emits its total energy at the wavelength of 308 nm and therefore is regarded as a ''super-narrowband'' UVB light source. Excimer laser treatment is highly effective in psoriasis, another T cell–mediated disorder that shares many immunologic features with AA. The excimer laser is superior in inducing T cell apoptosis *in vitro* compared with narrowband UVB, with paralleled improved clinical efficacy. The excimer laser has been used successfully in patients with AA. In this context, evaluation of the potential benefit of 308-nm excimer laser therapy in the treatment of AA is clinically warranted. Herein, the use of a common treatment protocol with a specifically designed module to study the outcome of excimer laser treatment on moderate-to-severe scalp AA in adults is described.

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Introduction

Alopecia areata (AA) is an autoimmune condition characterized by T cell–mediated attack on the hair follicle (Madani and Shapiro, 2000). The inciting antigenic stimulus is unknown. A dense peribulbar lymphocytic infiltrate and reproducible immunologic abnormalities are hallmark features of the condition. T lymphocytes have a critical role in the pathogenesis of disease. Gilhar *et al.* (1998) have reported that AA can be reversed in human scalp skin specimens of AA when transplanted to severe-combined immunodeficiency mice. The observance of hair regrowth in those with AA, who are treated with cyclosporine, a known inhibitor of T cell function, further confirms the central role of T lymphocytes in the development of disease (Miller *et al.*, 1993; Wingren *et al.*, 1995; Shapiro *et al.*, 1997; Gilhar *et al.*, 2012).

Several AA treatments utilize topical immunomodulation to induce an intermittent allergic contact dermatitis in affected areas (Happle *et al.*, 1983; van der Steen *et al.*, 1992). UV radiation in the form of UVA or UVB has been used to induce an immune response in AA, with the suspected mechanism of clinical improvement surrounding UV-induced apoptosis of pathogenic T cells. (Gundogan *et al.*, 2004) Narrowband UVB is a more potent inducer of T cell apoptosis, and therefore demonstrates clinical efficacy over broadband UVB (Coven *et al.*, 1997; Ozawa *et al.*, 1999).

The xenon chloride excimer laser emits its total energy at a wavelength of 308 nm and therefore is regarded as a ''super-narrowband'' UVB light source. In contrast, narrowband UVB primarily emits polychromatic, non-coherent light in the 311–313 nm wavelength range. Excimer laser treatment is highly effective in psoriasis, another T cell–mediated disorder that shares many immunologic features with AA (Bónis *et al.*, 1997; Asawanonda *et al.*, 2000; Feldman *et al.*, 2002). Although the exact mechanism by which the excimer laser clears psoriasis is not known, it is postulated that an increased induction of T cell apoptosis leads to a decrease in T-lymphocyte proliferation (Passeron and Ortonne, 2006). With decreased T cell depletion and decreased antigen presentation, the excimer laser may stabilize diseases like psoriasis and AA (Park *et al.*, 2012). In vitiligo, there may be a more complicated process with stimulation of melanocyte migration and proliferation in the hair follicles along with the laser-induced immunosuppressive effect. It is known that the 308 nm wavelength is more efficient at inducing DNA lesions on lymphocytes than typical narrowband UVB (Novak *et al.*, 2002). The excimer laser has been used successfully in patients with AA (Gundogan *et al.*, 2004; Zakaria *et al.*, 2004; Raulin *et al.*, 2005). In one series of 11 children with recalcitrant AA of the scalp, regrowth was noted in 60% of patches treated with the excimer laser for 12 weeks versus no regrowth in untreated control patches (Al-Mutari, 2009). A larger study of 18 children and adults with 42 recalcitrant alopecic patches demonstrated regrowth in 17 (42%) of patches after 12 weeks, with 13 of 18 scalp lesions showing complete regrowth (Al-Mutari, 2007). In addition to the immune effects, the direct effect of excimer photons on the melanocytes may also have a role in the successful treatment of AA. The excimer laser technique has not yet been explored in large, multicenter trials.

All available treatments for AA have limited benefit, and none are curative or Food and Drug Administration-approved. As approximately 2% of the world population has a lifetime risk of developing AA (Safavi, 1992; Safavi *et al.*, 1995), and the effect of disease on the psychosocial well-being of those affected can be devastating, the need for more effective, safe treatments is of

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Abbreviations: AA, alopecia areata

utmost importance. In this context, evaluation of the potential therapeutic benefit of 308-nm excimer laser therapy in the treatment of AA is clinically warranted. This paper outlines the use of a component module of a common protocol to plan and execute a treatment study for AA.

Study description

This study protocol is a module of the newly designed common protocol for AA. The common protocol has been designed by a working group of the National Alopecia Areata Foundation to promote treatment studies for AA. It is a versatile protocol that can be shared with any investigator who is interested in initiating a treatment study for AA scalp disease. By simply following a common set of inclusion/exclusion criteria and study visits, investigators will have an opportunity to amend the protocol for their interests without having to design a new protocol from inception. Changes can be made to any component of the study, and for the module discussed, utilizing the excimer laser, statistics and study visits were altered for best clinical study practices.

The excimer module of the common study has been planned to investigate, in a prospective manner, the safety and efficacy of the 308-nm excimer laser in the treatment of subjects 18 years or older with moderate-to-severe AA of the scalp. Secondary objectives for this study include: (1) documenting the durability of the response of the excimer laser treatment on AA over a 6-week post-treatment observation period and (2) qualitatively assessing the subject's perception of their scalp disease with treatment.

This module is designed as a double-blind, randomized, controlled, multicenter, investigator-initiated study to examine the safety and efficacy of 308-nm excimer laser treatment in a voluntary population of subjects with chronic, moderate-to-severe scalp AA. A total of 78 eligible subjects will be enrolled in the study at five different sites in the United States. Study enrollees will be randomized to two treatment groups. Group 1 (excimer laser group) will undergo two times weekly treatments with the excimer laser to affected areas on the scalp, with at least one untreated patch ($6.1 \times 3.1\ cm^2$) serving as a control. Group 2 (control group) will receive non-active treatment with a sham device. All study team members and subjects will be blinded based on which transmission tip (sham vs. active) is used. Treatment or non-active treatment will occur for 24 weeks, during which the safety and efficacy will be assessed at visits 6, 12, 18, 24, 30, 36, 42, 48, 49, and 50.

The protocol of the study includes AA history, investigator, and patient assessment of disease activity, photographs, treatment, and adverse event monitoring. (Table 1) The active visits will be followed by a 6-week post-treatment period during which the durability of effect in treatment responders will be assessed.

Table 1. Protocol components for AA excimer laser study

Medical history
AA history
Vital signs
Brief physical exam
AA non-scalp assessments
AA scalp assessment (SALT) (Olsen *et al.*, 1999, 2004)
Scalp tattoo
Scalp photography
Subject assessment of hair loss
MED determination
Excimer laser active or sham treatment
Adverse event monitoring

Abbreviations: AA, alopecia areata; MED, minimal erythemal dose; SALT, severity of alopecia tool.

Discussion

The development of the common treatment protocol to streamline AA studies has been a valuable tool in the armamentarium for National Alopecia Areata Foundation and investigators interested in moving the science of AA forward. The working group for the development of both the common and excimer module of the protocol has attempted to address any permutation of a treatment study that can be constructed for AA. The specifics necessitated by a light therapy study have been included in this module with detailed and annotated instructions for each data point to be collected. Going forward, it will be imperative to standardize therapy for patients suffering with AA and this will be one of the first attempts at developing a set of scientific procedures that can address treating this devastating disease.

CONFLICT OF INTEREST

AJM has received consulting fees from Galderma, Procter & Gamble, Johnson & Johnson, Merz-Pharma Group, Allergan, and GuthyRenker.

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