Alefacept for Alopecia Areata

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

Patient 1 is a 42-year-old white man who has had alopecia areata (AA) for 17 years. His father also has extensice AA. Early in the course of the disease, the patient intermittently received prednisone, 15 to 30 mg/d for 2 years, with 1 year being the longest duration of continuous treatment followed by an additional 7-month taper. The patient also received topical fluocinolone acetonide 0.1% (Synalar; Medicis, Scottsdale, Ariz) solution and intral- sional triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, New York, NY) injections for most of the duration of the disease. He typically receives intralional triamcinolone, 10 mg/mL to his scalp and 3 to 5 mg/mL to his eyebrows, every 4 to 10 weeks. Intralional triamcinolone was helpful, with remissions lasting 2 months. Sulfasalazine administered failed secondary to drug eruption. He has never received contact sensitizers.

Patient 2 is a 37-year-old white woman who has had alopecia universalis for 14 years. For the first 2 years, he received intermittent courses of prednisone, starting at 40 mg/d and tapering off for 1 to 2 weeks, together with topical corticosteroids and intralesional triamcinolone, 5 mg/mL. The prednisone led to transient hair regrowth with rapid relapse after he finished the course of steroids. The patient subsequently received squaric acid dibutyl ester 0.01% applied twice per week to his scalp in conjunction with tretinoin 0.01% gel (Retin-A; Ortho Ne- utrogena, Skillman, NJ). He continued to receive intralional injections of triamcinolone, 5 mg/mL to his eye- brows and scalp, every 4 to 8 weeks. The patient began to respond after 3 months of treatment with squaric acid and had nearly total regrowth of hair on his scalp after 6 months. However, the squaric acid treatments became less effective during the next year and were discontinued. For the next 9 years, the patient received intralional triamcinolone 5 mg/mL to his eyebrows every 4 to 8 weeks, which resulted in transient hair regrowth. His scalp went untreated and remained completely devoid of hair. A 3-month trial with tacrolimus 0.1% ointment applied twice daily to his scalp had no effect.

Patient 3 is a 22-year-old Asian woman who has had alopecia universalis for 3 years. Her prior treatments include prednisone for 5 months with a maximal dose of 40 mg daily to which she had a transient response. She did not respond to diphenylcyclopropenone 2% applied weekly for 3 months. She had no response to sulfasala- zine, 2 g twice daily for 1 year. She also received intralional triamcinolone, 5 mg/mL, to her eyebrows for 1½ years, which resulted in transient hair regrowth.

Patient 4 is a 14-year-old white girl who has had AA for 3 years. She also has hypothyroidism, which was diagnosed 1 year ago, but has had symptoms of hypothyroidism for 5 years. Her prior treatments included class I topical corticosteroids twice daily for 3 years with no improvement and intralional triamcinolone, 10 mg/mL, for 1½ years with transient hair regrowth. A course of pred- nisone, 60 mg daily, tapered off for 4 weeks resulted in minimal sparse regrowth of pigmented terminal hair and improvement of her eyebrows. Treatment with diphenyl- cyclopropenone 0.1% to 0.5% for 9 weeks resulted in contact dermatitis but minimal sparse regrowth of pigmented terminal hair. She was unable to tolerate further treatments because of the contact dermatitis.

THERAPEUTIC CHALLENGE

Treatment of AA is often frustrating because of the lack of safe and effective therapies. Topical corticosteroids and topical macrolide immunomodulators are not effective, likely because of insufficient penetration of the skin surface to the hair bulb. Intralional corticosteroids often lead to transient responses; however, the pain associated with injection, as well as the risk of skin atrophy and systemic adverse effects with repeated treatments, restricts their use, particularly in patients with large areas of alopecia. Contact sensitizers can be effective. As reviewed by Madani and Shapiro,2 response rates of 29% to 87% with squaric acid and 4% to 85% with diphenyl- cyclopropenone have been reported. One third of responders eventually stop responding.2 Potential adverse effects include discomfort from the ensuing contact dermatitis, dissemination of allergic contact dermatitis, and pigmentary abnormalities.5 Other limitations include the need for repeated office visits and the lack of a standardized formulation or application schedule.

Systemic agents, such as corticosteroids and cyclosporine, can be effective, but their long-term use is limited by serious adverse effects, and the response is usually tran-
sient. In a study by Olsen et al,3 30% to 47% of patients attained more than 25% hair regrowth when treated with a 6-week tapering course of oral prednisone, starting at 40 mg daily. In several small case series, treatment with oral cyclosporine led to cosmetically acceptable results in 25% to 50% of patients.4,5 Another treatment option is psoralen–UV-A, although patients often quickly relapse, and long-term use is associated with an increased risk of skin malignancies.1 The limited effectiveness and unfavorable adverse effects of current treatment options warrant investigation of alternative treatments for AA.

SOLUTION

Recently, dermatologists have witnessed a revolution in their therapeutic armamentarium with the development of several novel biologic immunomodulators developed for the treatment of psoriasis. Because psoriasis and AA are thought to be T-cell–mediated diseases,6 we hypothesize that biologic agents effective in the treatment of psoriasis may also be effective in AA. Alefacept (Amevive; Biogen Idec, Inc, Cambridge, Mass) would make an ideal AA treatment given that it interferes with T-cell activation and has an excellent safety profile. Therefore, alefacept was administered in patients as a means of investigating the effectiveness of a biologic treatment for AA.

Four patients with AA or alopecia universalis received 15-mg intramuscular injections of alefacept weekly for 12 weeks at the Washington University Dermatology Clinic and at the Saint Louis University Dermatology Clinic, St Louis, Mo. Three patients received concomitant intralesional triamcinolone to the eyebrows, and 1 patient received intralesional triamcinolone to his scalp. The patients were evaluated every 4 weeks during treatment and then periodically thereafter. Assessments included percentage of scalp affected by AA and an assessment of hair regrowth with the 4-point scale described by Hull and Norris.7 The 4-point scale measures hair regrowth as follows: 1 indicates vellus hair or no hair; 2, sparse pigmented or nonpigmented terminal hair; 3, terminal regrowth with patches of alopecia areata; and 4, terminal regrowth in all areas.7

The results are shown in Table 1 and Table 2. Patient 1 had a decrease in involved scalp surface area from 27% to 22% and an increase in hair regrowth as measured with the 4-point scale from 1 to 2. This improvement was likely because of the intralesional triamcinolone injections (5 mg/mL) that he received on 2 occasions. Patient 2, with alopecia universalis, had approximately 50% regrowth of vellus hair over his scalp, as well as sparse regrowth of terminal pigmented hair 3 weeks after he completed the course of alefacept. Patient 3, with alopecia universalis, had extensive regrowth of nonpigmented terminal hair on her scalp with patches of terminal pigmented hair at 15-week follow-up. She also noted regrowth of terminal hair on her axillae and legs, which required that she shave for the first time in years. Notably, this patient had only sparse regrowth of terminal hair 8 weeks earlier. She elected a second 12-week course of alefacept. Photographs of this patient’s response are shown in Figure 1 and Figure 2. Similarly, patient 4 had a decrease in the affected surface area with patchy regrowth of terminal pigmented hair at follow-up 12 weeks after she completed the course of alefacept. She also had regrowth of her eyebrows and eyelashes. The CD4+ cell counts remained within normal limits in all patients throughout the course of treatment (Table 3). No adverse effects were reported. All 4 patients tolerated the treatment well. Two of the 4 patients elected to repeat a second 12-week treatment course with alefacept, which will be initiated 12 weeks after the first course was completed.

Table 1. Percentage of Scalp Surface Area Involved Affected by AA

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Baseline</th>
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<th>Week 8</th>
<th>Week 12</th>
<th>Follow-up</th>
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<tr>
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</tr>
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</table>

Abbreviation: NA, not available.

Table 2. Hair Regrowth: 4-Point Scale*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Follow-up</th>
</tr>
</thead>
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<td>1</td>
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Abbreviation: NA, not available.

*1, Vellus hair or no hair; 2, sparse pigmented or nonpigmented terminal hair; 3, terminal regrowth with patches of alopecia areata; 4, terminal regrowth in all areas.7

COMMENT

Alopecia areata is a T-cell–mediated autoimmune condition involving the hair follicle and is associated with other autoimmune conditions, including autoimmune
thyroiditis and vitiligo. A family history is present in many instances. Human leukocyte antigens (HLAs) are associated with an individual’s predisposition to autoimmune diseases, and AA is associated with DQB1*03, HLA-B18, and possibly HLA-A2. Gilhar et al demonstrated that AA is a T-cell–mediated disorder. In their study, hair was allowed to regrow on lesional human scalp that had been explanted to severe combined immunodeficiency mice. The mice were then injected with autologous scalp T cells that had been expanded in vitro with homogenates of hair follicles. The transfer of these T cells led to the induction of alopecia. Transfer of autologous T cells that were expanded without homogenates of hair follicles did not lead to alopecia. In a similar mouse model, Gilhar et al showed that CD4+ and CD8+ T cells are necessary to induce AA in explanted lesional human skin. When either T-cell subset is injected alone, AA does not develop. Furthermore, depletion of either CD8+ T cells or CD4+ T cells can reverse AA. A T helper 1 cytokine profile is supported by the increased expression of interferon gamma, interleukin 1β, and interleukin 2 in lesional skin in patients with AA. Neuropeptides also may have a role in the pathophysiological changes of the condition. The antigen to which pathogenic T cells react remains unknown. Paus et al suggest that melanocyte-associated peptides in the hair follicle may act as autoantigens.

Alefacept is a human fusion protein consisting of the first extracellular domain of lymphocyte function–associated antigen 3 fused to the hinge, CH2 and CH3 domains of IgG1. The interaction of lymphocyte function–associated antigen 3 on antigen-presenting cells with CD2 on T cells is a pivotal stimulatory pathway for T-cell activation. Alefacept reduces the T-cell response by means of 2 mechanisms of action. First, the lymphocyte function–associated antigen 3 domain of alefacept blocks the costimulatory interaction between antigen-presenting cells and T cells. Second, the Fc portion of the IgG1 domain of alefacept binds to Fc receptors on accessory cells inducing T-cell apoptosis. Alefacept preferentially targets T cells of the memory subset, which have high expression of CD2 on their surface. A decrease in the number of memory T cells in patients with psoriasis who have received alefacept correlates with clinical improvement.

Although the response to treatment with alefacept was not complete, all 4 patients improved, which suggests that alefacept may be effective, but the dose we used may not have been high enough or the duration of treatment long enough. Moreover, improvement generally was not noted until 3 to 15 weeks after completing the course of alefacept, suggesting that the duration of follow-up may not have been sufficient. The long duration of disease in the patients in our study should also be considered in interpreting the results, since treatment generally is more difficult in patients who have had AA for longer than 1 year.

Alternatively, alefacept may be only partially effective in the treatment of AA because of the complex pathogenesis of the disease. The interaction of lymphocyte function–associated antigen 3 and CD2 could be only partially significant in the costimulation of T cells in patients with AA. Results in 1 animal model showed that antibodies that block costimulatory processes can inhibit the onset of skin graft–induced AA in a mouse but had little effect in mice that already had AA. In addition, alefacept pref-

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<th>Week 12</th>
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*Data are given as amount per microliter.
differentially reduces the number of CD4+ and CD8+ memory T cells (CD45RO+), which have increased expression of CD2 on their surface, by approximately 55% and 67%, respectively. There is no substantial evidence regarding the subset of effector cells in AA. Gottlieb et al20 noted that alefacept resulted in a minimal reduction of naïve (CD45RA+) T cells (13%, CD4+ and 8%, CD8+), and moderate reduction of natural killer cells (39%, CD16+/CD56-) and B lymphocytes (33%, CD19+) during maximal drug effect. These components also may be important in the pathophysiological changes of AA.

Regulation of the immune response in AA could involve elements outside the realm of T-cell stimulation via cytokine signaling. The role of neurotrophins in the pathogenesis of AA is currently being investigated. Nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4 are proteins that bind to the p75 kDa neurotrophin receptor. This receptor is a member of the tumor necrosis factor family of receptors, which has a cytoplasmic death domain that mediates apoptosis.21 Recent evidence shows that neurotrophins stimulate keratinocyte apoptosis in the hair follicle, modulate macrophage activity, and stimulate CD8+ lymphocyte apoptosis.22 Alefacept would not affect this aspect of the immune response.

Because of the small size of this study, final conclusions regarding the effectiveness of alefacept in the treatment of AA cannot be made, and additional studies are warranted. It would be valuable to investigate treatment with alefacept in patients with a more recent onset of AA, as all of the patients in this study had AA for more than 1 year. In addition, a longer follow-up and additional courses of alefacept should also be investigated. Lastly, treatment with other biologic drugs is also warranted to help unfold the pathogenesis and establish safe, effective means of treating AA.

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REFERENCES