Alopecia Areata Universalis Complicating Daclizumab Therapy for Uveitis

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Practice Points

- Biologic therapies have revolutionized the treatment of several immune-mediated conditions, particularly rheumatoid arthritis, psoriasis, and inflammatory bowel disease.
- Manipulation of immune responses, while helpful for one condition, may result in development of unanticipated autoimmune phenomena, including other autoimmune diseases.
- Although tumor necrosis factor antagonist therapies have been implicated in the development of alopecia areata, the condition has now been linked to the use of biologic agents working through different immune pathways.
- The use of agents that modify the effects of IL-2 or bind to CD25 may cause autoimmune diseases, including alopecia areata.

Alopecia areata (AA) is a complication of biologic therapy with several anti–tumor necrosis factor (TNF) inhibitors and efalizumab for the treatment of various autoimmune diseases. We report the case of a 51-year-old woman who developed AA universalis while undergoing treatment with daclizumab, an immunosuppressive biologic therapy, administered for treatment of inflammatory ocular disease. Although immunomodulatory agents that function by interfering with T helper cell stimulation are expected to impede autoimmune-related processes, we believe that daclizumab may be causally related to the development of AA.

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Alopecia areata (AA) is a recurrent nonscarring type of hair loss that affects approximately 2% of the worldwide population.[1] In the United States, AA affects men and women with similar frequency, with a peak incidence at 15 to 29 years of age. Alopecia areata typically presents as limited regions of scalp involvement in 75% of patients but can progress to involvement of the entire scalp (AA totalis) and eventually the entire body (AA universalis).[2] In general, the greater the extent of hair loss, the lower the chance of full recovery.[3] The autoimmune pathogenesis of AA has substantial support, with reports in the literature documenting the co-occurrence of AA with autoimmune disorders such as Hashimoto thyroiditis, pernicious anemia, myasthenia gravis, and vitiligo.[4,5] In our clinical experience, we have seen AA develop in patients with rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus, among other autoimmune conditions.[6] Because keratinocytes in normal anagen hair follicles do not express class I and class II major histocompatibility complex antigens,[7] the abnormal expression of major histocompatibility complex antigens in hair follicle epithelia in patients with AA as well as the

increased expression of various adhesion molecules in blood vessels around the hair follicle are further indications of the autoimmune pathogenesis of AA.[8] Immunohistologic studies indicate that multiple cytokines, such as tumor necrosis factor (TNF) α, IL-1α, and IFN-γ, are relevant to the autoimmune pathogenesis of AA because peribulbar inflammation is believed to inhibit hair growth by the actions of these inflammatory cytokines.

In the last 20 years, biologic therapies have been developed to block various immune-mediated processes involved in the development of autoimmune disorders, primarily using monoclonal antibody technology.[9] Many of these therapies have been demonstrated to have profound efficacy in the treatment of certain autoimmune disorders, such as anti-TNF therapies for the treatment of rheumatoid arthritis and psoriasis. However, many of them also have been associated with paradoxical autoimmune reactions, such as autoimmune hepatitis and drug-induced lupus erythematosus caused by anti-TNF agents.[10] There have been several reports of AA occurring with the use of anti-TNF therapies, including infliximab, adalimumab, and etanercept.[11-13] We report the case of a patient who developed rapidly progressive AA universalis during treatment of inflammatory ocular disease with daclizumab, an inhibitor of the IL-2 receptor that primarily is used to prevent renal transplant rejection.

Case Report

A 51-year-old woman had a history of recurrent scleritis and anterior uveitis since 16 years of age. Initially her disease was well controlled with intermittent use of topical corticosteroids; however, at 38 years of age she developed more persistent severe scleritis with resultant scleromalacia and bilateral iridocyclitis that was refractory to topical therapies. With persistent pain, photophobia, and loss of visual acuity, the patient was started on systemic corticosteroid therapy utilizing prednisone 40 mg daily. Despite the subsequent serial addition of methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil, she continued to require high-dose prednisone to control her condition. She did not demonstrate vitiligo, dyspigmentation of the hair, or vestibuloauditory or neurologic symptoms to suggest Vogt-Koyanagi-Harada syndrome. One year prior to evaluation she developed nodoselike lesions overlying the anterior aspect of both tibias that spontaneously resolved. At that time, evaluation for sarcoidosis, tuberculosis, and inflammatory bowel disease including chest radiography; tuberculin skin test; colonoscopy; and serologies for angiotensin-converting enzyme, anti–*Saccharomyces cerevisiae* antibodies, and antineutrophil cytoplasmic antibodies was unremarkable. Additional serologies for potential infectious causes, such as *Treponema pallidum* infection, *Borrelia burgdorferi* infection, toxoplasmosis, and bartonellosis, were negative. Although the patient reported mild mouth and eye dryness, there was no serologic evidence of Sjögren syndrome, systemic lupus erythematosus, or rheumatoid arthritis. A minor salivary gland biopsy showed minimal lymphocytic infiltration that did not satisfy the histologic focus scoring for Sjögren syndrome.[14] HLA-B27 was negative. The patient's medical history was remarkable for Hashimoto thyroiditis diagnosed 15 years earlier with high titers of anti–thyroid peroxidase and antithyroglobulin antibodies. The patient reported no history of inflammatory rash, alopecia, mucosal lesions, lymphadenopathy, photosensitivity, Raynaud phenomenon, pleurisy, arthritis, spontaneous abortion, spontaneous thrombosis, or renal or neurologic abnormalities. Her family history was remarkable for Raynaud phenomenon in her mother and psoriasis in her daughter.

Physical examination revealed a mildly cushingoid appearance with no inflammatory rash, skin dyspigmentation, or alopecia; palpebral conjunctival injection; marked bulbar injection without limbic blush; hyperpigmented patches of sclerae consistent with scleromalacia; slight pupillary irregularities (reactive to light) with photophobia; and decreased visual acuity of the right eye.

Based on a report on the efficacy of daclizumab in the treatment of uveitis,[15] the patient was started on daclizumab 1 mg/kg via intravenous infusion over a 20-minute period at baseline and every 2 weeks thereafter for a total of 7 infusions. Within 1 month, the ocular symptoms had diminished and the prednisone dose was reduced to 30 mg daily. However, after 4 infusions she began to note patchy hair loss with initial involvement of the parietal regions of the scalp. Within 3 months of starting daclizumab, she noted total loss of scalp hair, eyebrows, and eyelashes. Daclizumab therapy was discontinued after 7 infusions, but the patient continued to lose body hair, including the axillary and pubic regions. A biopsy of the scalp revealed intense perifollicular inflammation and follicular destruction; marked lymphocyte exocytosis, mainly confined to the vellus hairs; and slight perivascular inflammation. No immunoglobulin deposition was noted on immunofluorescent staining.

With improvement of the ocular inflammation, prednisone was tapered over the following 3 months and she was exclusively treated with topical dexamethasone solution and oral cyclosporine. One year after discontinuation of daclizumab, a brief course of intravenous immunoglobulin[16] controlled her recurrent ocular inflammation but had no impact on her

generalized hair loss. Five years after discontinuation of daclizumab, she only noted minimal growth of vellus hairs on the scalp and has only required topical dexamethasone for control of her ocular inflammation.

Comment

Inflammatory ocular diseases, in this case involving the sclera, iris, and ciliary body, have been associated with several autoimmune diseases but also can exist as independent conditions. When topical therapies have been ineffective, multiple systemic agents have been used to try to curtail ocular inflammation, including TNF antagonists and, as in our case, inhibitors of IL-2 function through binding to CD25.[17,18]

The association of uveitis with AA has been seen in Vogt-Koyanagi-Harada syndrome, which results from immune-mediated destruction of melanocytes involving the uvea (uveitis), skin (vitiligo, poliosis, and alopecia), central nervous system (meningitis), and inner ears (vertigo, hypoacusis). Vogt-Koyanagi-Harada syndrome occurs primarily among patients of Asian, Hispanic, and Native American ancestry, typically in those aged 20 to 50 years. Alopecia is seen in 50% to 57% of cases and usually occurs within a few months of ocular or neurologic manifestations.[19] Other than Vogt-Koyanagi-Harada syndrome, there were no known reports of the coincidence of uveitis and AA until 2011 when Ayuso et al[20] reported 3 pediatric cases of AA and intermediate uveitis with onset within 1 year of each other.

CD25, the high-affinity α chain of the IL-2 receptor (IL-2Rα), is a glycoprotein expressed on activated T and B cells as well as macrophages. Resting lymphocytes do not normally express CD25, but activated T cells involved in organ allograft rejection and many T-cell mediated autoimmune diseases do express CD25. There are 2 commercially available anti-CD25 monoclonal antibodies that primarily have been utilized to prevent organ transplant rejection, particularly in kidney transplant patients: daclizumab, a humanized monoclonal antibody, and basiliximab, a chimeric antibody. Daclizumab also has been utilized for off-label treatment of several autoimmune conditions (eg, multiple sclerosis)[21] and has found popularity in the treatment of noninfectious anterior, intermediate, and posterior uveitis and panuveitis (idiopathic or in association with juvenile idiopathic arthritis, birdshot chorioretinopathy, or Behçet disease).[19] In September 2009, production of the only marketed daclizumab preparation was discontinued, not because of safety issues but due to diminishing market demand, according to the manufacturer (L.E. Birgerson, written communication, September 2009). However, due to positive results in the treatment of multiple sclerosis, other companies are seeking approval of daclizumab in the near future, according to a search of clinicaltrials.gov.

The ability to inhibit CD25 to control autoimmune diseases may have paradoxical effects. Because high-affinity IL-2 signaling is important for the development and maintenance of regulatory T cells ($Foxp3^+CD4^+$ T cells) while antagonizing the generation of T_H17 cells, there is theoretical concern that CD25 inhibition may exacerbate autoimmune disorders rather than inhibit them.[22,23] This hypothesis has been supported by the observation that both animals and humans with deletion of CD25 have developed severe autoimmune diseases; additionally, IL-2 neutralization has been associated with in vivo development of organ-localized autoimmune disorders.[24,25] Recently, fatal autoimmune hepatitis was reported in one patient treated with daclizumab for multiple sclerosis.[26] The development of autoimmune diseases is of particular concern because attention has been focused on the role of inhibiting IL-2R as a mechanism for treating AA and other immune-mediated dermatologic conditions.[27,28]

Paradoxical proinflammatory or autoimmune reactions have been seen with several of the biologic agents utilized to treat other autoimmune conditions. Several anti-TNF agents, which have shown impressive results in the treatment of autoimmune conditions such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease, have been linked to the development of AA.[2,11-13,29-33] Development of AA also has been noted with the use of efalizumab, a biologic agent that binds to the CD11a subunit of lymphocyte function–associated antigen 1 previously approved for the treatment of psoriasis.[31]

Conclusion

Although the causality of AA universalis in our patient remains unclear, careful evaluation is necessary in patients developing AA in the setting of biologic therapies used to treat autoimmune diseases until further observations can shed light on the association between daclizumab and AA. Renal transplant immunologists or ophthalmologists and neurologists who will be treating patients in the future with agents that modify the effects of IL-2 or bind to CD25 should be aware of potential paradoxical side effects, including the development of AA.

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