

The New Biologics in Psoriasis: Possible Treatments for Alopecia Areata

Amy J. McMichael

Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

Therapeutics in alopecia areata (AA) have remained relatively unchanged for many years, with few treatments having more than moderate effects in severely affected patients. The advent of the new biologic medications in the dermatologic world, however, particularly in

psoriasis treatment, introduces possibilities of treatment for many other immune-mediated diseases. *Keywords:* biologic response modifiers/psoriasis/alopecia areata. *JID Symposium Proceedings 8:217–218, 2003*

Alopecia areata is one possible candidate disease for biologic modifier application. It is an autoimmune form of hair loss that can cause patchy or complete loss of hair anywhere on the body, though most patients experience this loss on the scalp. AA is mediated by T cells, with a primarily TH1 cytokine profile in active disease. This TH1 profile is a shared characteristic in AA and psoriasis, suggesting that any drug that can target T cells safely and decrease activity in the skin may work for both diseases. So far, the new biologic immunomodulating drugs are an exciting new development for the treatment of psoriasis and associated arthritis. In this short report, the new drugs, called biologic response modifiers, will be evaluated in terms of mechanism, efficacy, and safety. Their possible application in AA warrants a full discussion of their practical considerations and points of therapeutic attack.

PSORIASIS

Psoriasis is a chronic, life-altering, inflammatory skin disease that exhibits erythematous, scaling plaques. It is known to be immune mediated, which leads to an overproduction of keratinocytes. The disease affects more than 2% of the population, and approximately 2 million Americans have moderate to severe involvement. There are complex therapeutic options for psoriasis, many of which attack the immune-mediated portion of the disease as opposed to keratinocyte overproduction.

In dermatology, psoriasis is a prototypic T cell-mediated disease (Bos and Rie, 1999; Nickoloff, 1999). Abundant evidence of its T cell-mediated nature comes from bone marrow experiments, where psoriasis has developed in the recipient of bone marrow from a psoriasis-affected patient. It is also well known that the cells in psoriasis are CD8 and CD4 lymphocytes with TH1 cytokine phenotype, as well as IL-2, IFN- γ and TNF- α . Finally, the role of T cells is clear in psoriasis when the disease improves significantly with drugs that target proliferative T cells, such as methotrexate. Because of this prototype, psoriasis has been the

main target of the new biologic treatments, but it is likely only the first of many dermatologic diseases that will ultimately enter clinical trials for these agents.

THE BIOLOGIC RESPONSE MODIFIERS

The new biologic agents are protein drugs produced *in vitro* through recombinant DNA techniques. They include recombinant cytokines, humanized monoclonal antibodies, and molecular receptors that bind target molecules. When the biologic response modifiers were considered in the treatment of psoriasis, the treatment strategies included moderating or eliminating T cell effects. Four major strategies have been described: targeting pathogenic T cells, inhibiting T cell activation or migration, inducing immune deviation, and inhibiting postsecretory cytokines (Singri *et al*, 2002). The four drugs furthest along in clinical trials for psoriasis are alefacept, efalizumab, infliximab, and etanercept. Each has a varying profile of benefits that can, and likely will, be applied to other dermatologic diseases in the future.

Alefacept Alefacept (Amevive, Biogen Inc., Cambridge, MA) is a human fusion protein that can be intravenously or intramuscularly administered. Pivotal clinical trials are complete, and the drug was approved by the FDA in January 2003 for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. The drug became available for use in February 2003.

Alefacept was designed to bind CD2, inhibit antigen-presenting cell interaction with T cells, and selectively reduce CD45R0+ cells. Mean percent change in psoriasis from the Baseline Psoriasis Area and Severity Index (PASI) has been significant for this drug after even one dose, and continued improvement is observed weeks after a second dose.¹ Safety must be considered before deciding to begin trials with a drug in psoriasis—a nonfatal, albeit very symptomatic and psychologically damaging disease. Alefacept is known to kill

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Correspondence to: Amy J. McMichael, Wake Forest School of Medicine, Winston-Salem, NC 27157-1071, USA. Email: AMCMICHA@WFUBMC.EDU

¹Lebwohl M, Bissonette R, Ellis C, *et al*: Results of a multiple-course, randomized phase III study of alefacept in patients with chronic plaque psoriasis. Presented at the 60th Annual Meeting of the American Academy of Dermatology; February 22–27, 2002; New Orleans, Louisiana, USA. Poster #580.

activated memory T cells, reversibly lowering T cell count. There appears to be no increase in infection rate in subjects taking the medication, nor are there any infusion reactions. Also important is that there is no detectable effect on response to new or old antigen challenge. CD4+ T lymphocytes must be monitored weekly during the 12-week dosing period and used to guide dosing.

Adverse events commonly observed in the first course of placebo-controlled clinical trials with at least 2% or higher incidence in patients treated with alefacept compared to those treated with placebo include pharyngitis, dizziness, increased cough, nausea, pruritus, myalgia, chills, injection site pain, and injection site inflammation. The acquisition price of alefacept will range from \$7000 to \$10,000 per 12-week course depending on dosing. The drug must be administered in a physician's office, as either an intravenous or a subcutaneous injection.

Treatment of AA with alefacept may be a reasonable option if efficacy can be demonstrated in clinical trials, but the weekly in-office dosing may make administration cumbersome. Cost is comparative with other biologic drugs and will require preapproval by insurance carriers for most patients.

Efalizumab Efalizumab (Raptiva, Genentech, Inc., and XOMA, Ltd., Berkeley, CA) is an anti-CD11a molecule that works via several mechanisms as a subcutaneous injection. The first mechanism is inhibition of interaction between T cells and antigen-presenting cells; the second is inhibition of T cell migration from blood. In psoriasis, disease development depends upon the effective rolling of T cells along the endothelium, their binding, and then their migration into the skin. Efalizumab appears to lessen the T cell's immune functions (Gottlieb *et al*, 2002). Its efficacy is demonstrated with 75% improvement in PASI in 30% of subjects in one study and an increase in improvement with increased use. There were no serious infections or injection reactions seen in clinical trial subjects. There was also no reported rebound with continued use, although there is a potential rebound if the drug is abruptly discontinued. Phase III pivotal trials evaluating moderate-to-severe psoriasis have been completed, and a Biologic License Application has been filed with the FDA for efalizumab use in adult moderate-to-severe chronic plaque psoriasis as a once-weekly subcutaneous injection. Like alefacept, efalizumab showed no problems with challenge of new antigens. The drug has been used in trials as a once-weekly subcutaneous injection.

The safety and administration profile of efalizumab may make it ideal for clinical trials in AA. At-home injection of the drug would be preferred by most patients with AA, as would the lack of blood monitoring.

TNF- α Inhibitors The next two agents are both TNF- α inhibitors. Etanercept and infliximab are already on the market, but neither is approved for the treatment of psoriasis or for any other dermatologic condition.

Infliximab (Remicaide, Centocor, Inc.) is an intravenous anti-TNF antibody that kills cells having surface TNF. It is approved for Crohn's disease and rheumatoid arthritis. Significant improvement in mean PASI score can be seen in as few as ten weeks of infliximab treatment (Chaudhari *et al*, 2001). Associated with this drug are serious infusion reactions, rare reported cases of pancytopenia, rare activation of tuberculosis and other granulomatous infections, rare lymphomas, multiple sclerosis, and positive ANA titers thought to be related to the destruction of soluble and fixed

TNF on their surface (cells presumably needed for full immune function against granulomatous infection). Problems with potential use of infliximab in an AA population include the aforementioned side effects and the inconvenience of an intravenous administration.

Etanercept (Enbrel, Amgen, Inc.) is a soluble TNF receptor that works by binding circulation TNF. It is approved for the treatment of psoriatic arthritis and adult and juvenile rheumatoid arthritis. In psoriasis, 75% improvement is seen after etanercept treatment for 24 weeks. There are significant data available on the toxicities of etanercept because the drug has been approved for so long for the above indications. In controlled trials, injection site reactions were reported in 37% of patients; infection of any kind was reported in 52.6% (versus 36.4% of placebo patients) in current indications.² In the current indications, treatment with etanercept is not indicated in patients with active infection. Also, caution must be exercised when using this drug in patients who have congestive heart failure.^{2,3} The pharmacovigilance of etanercept is the most extensive of all the major biologic drugs. Surveillance includes spontaneous safety reports, long-term trials of safety in North America and Europe, the European Safety Registry, and the Juvenile Rheumatoid Arthritis Safety Registry. This agent is administered subcutaneously twice weekly when dosed to treat the approved medical indications. It may show promise for the treatment of AA with favorable at-home administration and long-term safety data.

SUMMARY

The biologic response modifiers are novel agents that are designed to attack one specific part of the immunologic process of psoriasis, much as could be done in the treatment of AA. Their specificity lessens the likelihood of severe and unwanted side effects at the same time allowing the immune system to function in a normal way. Drug-drug interactions can be avoided, as can significant organ toxicity, with these agents.

The likelihood that more biologic drugs will be designed and tested further in psoriasis underscores the need to investigate the full spectrum of their application. When other diseases are considered for treatment with the new biologics, it is important to weigh the likelihood of improvement of the disease and the possibility of serious side effects, as well as drug availability to the average insured patient. There is no doubt that the biologics have not been designed specifically for the treatment of AA; however, there are lessons to be learned from this new arena for all dermatologists interested in treating immune-mediated diseases.

REFERENCES

- Bos JD, Rie MA: The pathogenesis of psoriasis: Immunologic facts and speculations. *Immunol Today* 20:475-476, 1999
- Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB: Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: A randomised trial. *Lancet* 357:1842, 2001
- Gottlieb AB, Krueger JG, Wittkowskin K, Dedrick R, Walicke PA, Garovoy M: Psoriasis as a model for T-cell-mediated disease. Immunologic and clinical effects of treatment with multiple doses of efalizumab, an anti-CD11a antibody. *Arch Dermatol* 138:591-600, 2002
- Nickoloff BJ: The immunologic basis of psoriasis. *Arch Dermatol* 135:1104-1110, 1999
- Singri P, West DP, Gordon KB: Biologic therapy for psoriasis: The new therapeutic frontier. *Arch Dermatol* 138:657-663, 2002

²Enbrel package insert. Seattle, Washington: Immunex Corp, 1999.

³Gottlieb, AB: Efficacy of etanercept in patients with psoriasis. Presented at the American Academy of Dermatology 60th Annual Meeting; February 22-27, 2002; New Orleans, Louisiana, USA. Poster #25.