Treatment of hidradenitis suppurativa with biologic medications

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Given the absence of significant improvement in the treatment of hidradenitis suppurativa (HS) with traditional medical and surgical therapies, biologics have piqued the interest of research investigators. The efficacy of biologics in the treatment of inflammatory conditions like psoriasis and rheumatoid arthritis is well-documented. More recently, success with biologics has been demonstrated in atopic dermatitis, another dermatological condition associated with inflammatory states. Researchers have begun to probe the utility of biologic agents in less prevalent conditions that feature inflammation as a key characteristic, namely, hidradenitis suppurativa. Five agents in particular adalimumab, anakinra, etanercept, infliximab, and ustekinumab, have been explored in the setting of HS. Results to date put forward adalimumab and infliximab as biologic treatments that can safely be initiated with some expectant efficacy. Other biologic agents require more rigorous examination before they are worthy of addition to the treatment armamentarium. (J Am Acad Dermatol 2015;73:S82-8.)

Key words: acne inversa; adalimumab; anakinra; biologics; etanercept; hidradenitis suppurativa; infliximab; treatment; tumor necrosis factor—alfa; ustekinumab.

INTRODUCTION

Biologic medications—proteins derived from human genes—have been used to treat inflammatory diseases, such as rheumatoid arthritis and psoriasis, for decades. Preliminary success in the management of those conditions served as the impetus to explore the role of biologics in treating other disorders of an inflammatory nature, such as hidradenitis suppurativa (HS).

Though the list of biologic medications has lengthened in recent years, most published results on their use in the setting of HS are based on 5 medications: adalimumab, anakinra, etanercept, infliximab, and ustekinumab. This review will focus primarily on these medications (Table I).[1]

Etanercept

Etanercept is a fully humanized fusion protein composed of the tumor necrosis factor—alfa (TNFα) receptor and receptor protein component of immunoglobulin G1. This protein binds to transmembrane TNFα but unlike infliximab does not bind to soluble TNFα.[2]

Several cohort studies have been conducted on the use of etanercept for patients with HS. Three of these demonstrated mainly positive results.[3-5] Cusack et al[3] found a 61% reduction in disease activity in their open-label study. Giamarellos-Bourboulis et al[4] found that 6 of 10 patients had a significant reduction in their visual analog scale scores, while Sotiriou et al[5] described mean improvement of 68.8% and 66.5% in Dermatology Life Quality Index (DLQI) scores. Lee et al[6] did not confirm these promising results, with just 3 of 15 patients improving.

Only 1 randomized, double-blind trial has been reported to date on the use of etanercept for HS.[7] Patients were enrolled to receive either a 50-mg biweekly injection of the biologic or placebo, with no significant differences uncovered between etanercept and placebo after 12 weeks of treatment, as measured by the primary endpoint (Physician Global Assessment) and secondary endpoints (Patient Global Assessment or DLQI).

Similarly, a recent systematic review on the use of TNFα inhibitors found that etanercept was not

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associated with an improvement in the DLQI.[8] Though the data are not favorable regarding the use of etanercept in the treatment of HS, trials have enrolled relatively few patients, making any conclusions regarding its place in the treatment armamentarium premature. The availability of larger datasets would provide insight into its efficiency.

Infliximab

Infliximab is a chimeric antibody composed of both human and mouse proteins targeting TNFα. Infliximab binds to both soluble and transmembrane TNFα,[2] which may explain its more encouraging results relative to etanercept in the treatment of HS.

Ten cohort studies, with at least 4 and no more than 11 patients in each study, have been published regarding the use of infliximab in patients with HS. The majority of treated patients had moderate to severe disease (Hurley stage II or III), with most treatments consisting of infusions of 5 mg/kg of infliximab at weeks 0, 2, and 6. Outcome measures were often subjective and not validated. Nearly all studies found that some of the patients improved with treatment.

Grant et al[9] performed the only randomized, placebo-controlled trial on the use of infliximab in the treatment of HS. Investigators enrolled 38 patients and found that 26% of patients in the treatment arm experienced a $\geq$50% decrease in disease severity compared to 5% of patients in the placebo group. In addition, DLQI, pain, and Physician Global Assessments all significantly improved from baseline in the treatment arm but not in the placebo arm.

Adalimumab

Adalimumab is a fully humanized monoclonal antibody that corresponds to the human immunoglobulin G1 and has heavy and light chain variable regions exhibiting specificity for human TNFα. It binds with high affinity to both soluble and membrane- bound TNFα.[2]

Retrospective analysis of case reports and case series point to significant efficacy of adalimumab in treating HS. Moreover, it is the most well-studied biologic with multiple, larger-sized, randomized, controlled studies conducted. In a prospective, randomized, double-blind, placebo-controlled study of adalimumab treatment (a subcutaneous dose of 80 mg at week 0 and of 40 mg every second week), patients with HS treated for 3 months experienced significant improvement that was detected as early as 2 weeks after initiation, but the biologic failed to demonstrate significant efficacy at week 12.[2,10] In another prospective, randomized, double-blind, placebo-controlled study of adalimumab treatment (a subcutaneous dose of 40 mg once weekly, 40 mg every other week, or placebo) of 154 patients with moderate to severe disease, 17.6% of patients dosed weekly, 9.6% of patients dosed every other week, and 3.9% of placebo patients achieved clinical response at week 16. Investigators postulated a possible dose-dependent relationship with respect to serious adverse event rates (7.8%, 5.8%, and 3.9%, respectively). Injection site reactions were common in both adalimumab-treated patients and those receiving vehicle (20% and 14%, respectively). Headache was a frequently reported adverse event.[11]

CAPSULE SUMMARY

- Numerous reports suggest that biologic therapies are effective for patients with moderate to severe hidradenitis suppurativa
- The strongest evidence supports the use of adalimumab and infliximab.
- Other biologics might also offer benefit in the treatment of hidradenitis suppurativa, but more data are required to determine which agents will have a role.

Ustekinumab

Ustekinumab, a human, anti-p40 monoclonal antibody, is a biologic used in the treatment of patients with psoriasis. P40 is a shared subunit of human interleukins (ILs) -12 and -23. IL-12 activates T cells, which will secrete the classic T_H1 cytokines interferon-γ and TNFα. IL-23 promotes the survival of T_H17 cells, production of IL-17A and neutrophil recruitment, and downstream TNFα expression.

A study of 3 patients and 3 case reports highlighted treatment with ustekinumab and found that the medication was well-tolerated and produced a partial to complete response in 5 patients, with follow-up exceeding 6 months.[12-15] Of note, the onset of action was not rapid, with improvement described as taking several months before becoming apparent.[16,17] No significant adverse reactions have been reported, but only a handful of patients with HS have been treated with ustekinumab.

Anakinra

Anakinra is a recombinant IL-1-alfa (IL-1α) receptor antagonist that competitively binds to IL-1 receptors and prevents IL-1 accessory protein from interacting with the receptor, resulting in signal blockade. Both the activity of IL-1α and IL-1β are