

# TNF- $\alpha$ inhibitors in the treatment of hidradenitis suppurativa

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**Abstract:** Hidradenitis suppurativa (HS) is a complex disease with a dramatic impact on the quality of life of patients that it afflicts. Despite this, there are few treatment options offering long-term relief. The exact pathophysiology of HS is unclear, although the current theory involves follicular obstruction, rupture, and subsequent inflammation leading to fistula and abscess development in intertriginous skin. Several inflammatory modulators have been implicated in the development of HS, including tumor necrosis factor (TNF)- $\alpha$  as well as interleukin (IL)-1 $\beta$ , IL-10, and IL-17. Initial evidence for the use of TNF- $\alpha$  inhibitors in HS stemmed from recognition that inflammatory bowel disease patients treated with these medications saw a concurrent improvement in their HS symptoms. Early case reports and case series illustrated TNF- $\alpha$  inhibitors' value in the treatment of HS. Later, two phase III clinical trials, PIONEER I and PIONEER II, demonstrated that adalimumab is an efficacious treatment for HS. Infliximab represents another effective HS treatment option with its main advantage being dosing flexibility. In contrast, clinical trials have failed to show evidence for application of etanercept in HS. There is limited data on other TNF- $\alpha$  inhibitors such as certolizumab-pegol and golimumab. This review outlines the history, dosing, response, and adverse effects of TNF- $\alpha$  inhibitors in the treatment of HS.

**Keywords:** adalimumab, biologics, certolizumab-pegol, etanercept, golimumab, hidradenitis suppurativa, infliximab, TNF- $\alpha$  inhibitors

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## Introduction

Hidradenitis suppurativa (HS) is a chronic, debilitating disease characterized by recurrent boils and fistula formation in intertriginous skin that significantly impacts patients' quality of life.<sup>1–3</sup> Despite the large medical and psychosocial burden associated with HS, few therapies offer long-term relief. Traditionally, treatment revolved around use of antibiotics, surgery, and hormonal methods.<sup>4</sup> The application of biologics to HS opened new therapeutic avenues that offer decreased morbidity.

While the etiology of HS is incompletely understood, the prevailing theory is that hyperkeratinization of follicles causes follicular occlusion, subsequent rupture, and inflammation.<sup>5</sup> Tumor Necrosis Factor (TNF)- $\alpha$  is thought to be a primary driver of this inflammatory process, and, indeed, TNF- $\alpha$  concentration is significantly higher

in the serum and skin of HS patients compared with healthy volunteers.<sup>5,6</sup> Lesional HS skin also has significantly higher levels of other pro-inflammatory cytokines including interleukin (IL)-1 $\beta$  and IL-10 compared with healthy skin and psoriatic plaques.<sup>5</sup> Similarly, Kelly *et al.* observed increased TNF- $\alpha$ , IL-1 $\beta$ , and IL-10 levels in HS lesional skin, in addition to elevated IL-17.<sup>7</sup> Despite the wide array of inflammatory cytokines implicated in the pathogenesis of HS, anti-TNF- $\alpha$  therapy seems to offer reductions in the majority of these pro-inflammatory cytokines as well.<sup>8</sup> Cumulatively, this evidence supports the use of biologics targeting TNF- $\alpha$  in the treatment of HS.

## Adalimumab

Adalimumab is the only FDA-approved treatment for moderate-to-severe HS and is a fully human monoclonal IgG1 antibody directed

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toward membrane-bound TNF- $\alpha$ .<sup>9,10</sup> The standard dosing regimen of adalimumab is 160 mg at week 0, 80 mg at week 2, followed by 40 mg weekly starting at week 4.<sup>11</sup> This dosing is higher compared with dosing for other indications such as Crohn's disease and psoriasis.<sup>10</sup> Despite the application of adalimumab to other inflammatory diseases, it was not utilized in HS until recently. Through 2009, for example, in the literature there were only seven references to use of adalimumab in 16 HS patients. In these reports, patients largely demonstrated improvement with adalimumab therapy, with the caveat that many patients relapsed after stopping treatment.<sup>9,12-17</sup>

Several early studies investigated use of adalimumab at less frequent dosing than what was ultimately approved, primarily using various loading doses followed by 40 mg every other week (EOW).<sup>13,17</sup> The results of these studies were inconsistent, but suggested that adalimumab even at EOW dosing may improve HS in appropriate patients. In an open-label clinical trial, severe HS patients ( $n = 10$ ) were initiated on adalimumab at 160 mg at week 0, 80 mg at week 1, followed by 40 mg EOW through week 12. The primary endpoint was defined as a 50% decrease in HS severity index (HSSI) from baseline. No patients were considered responders at the study's conclusion, and four subjects discontinued the study due to lack of effect.<sup>18</sup> Despite the lack of response in this study, some degree of improvement was noticed in patients in similar sized studies of EOW dosing. In a case series, six severe HS patients were treated with 40 mg EOW and uptitrated to 40 mg weekly for unsatisfactory response. Significant improvements were observed in dermatology life quality index (DLQI) score, number of anatomic locations involved, number of fistulas, and number of nodules at both 1 month and 1 year follow ups. Over a mean follow-up of 21.5 months, however, five patients experienced mild relapses including increased pain and drainage.<sup>17</sup> In addition, in a case series of refractory HS patients ( $n = 8$ ) treated with the standard psoriasis dosing of adalimumab for 1 year (80 mg at week 0, 40 mg at week 1, followed by 40 mg EOW), significant reductions were observed in pain, drainage, C-reactive protein (CRP), and leukocyte count. However, after treatment cessation, only three patients were relapse free. Two subjects experienced relapse within 10 months, one within 8 months, and two within 6 months (average time

to relapse: 9.5 months). Disease activity at recurrence, however, remained lower than baseline disease activity in all patients.<sup>19</sup> Finally, a double-blind, placebo-controlled randomized clinical trial (RCT) demonstrated superiority of adalimumab (80 mg at baseline followed by 40 mg EOW for 12 weeks) over placebo in 21 patients. The primary efficacy endpoints were significant changes in Sartorius score and Hurley stage at 12 weeks. A statistically significant reduction in Sartorius score was observed at week 6 and an almost significant reduction was observed at 12 weeks ( $p = 0.07$ ). Improvement in DLQI also neared statistical significance ( $p = 0.06$ ).<sup>20</sup>

Trials implementing more frequent dosing demonstrated improved and more consistent responses. A summary of the results of these clinical trials can be found in Table 1. An open-label clinical trial investigated weekly adalimumab dosing (80 mg at baseline followed by 40 mg weekly) over 24 weeks and observed significant reductions in Sartorius score, disease activity on a visual analog scale (VAS), and DLQI. Patients were subsequently followed for 24 weeks off treatment. Relapse was noted at a mean of 11 weeks and worsening was evident in Sartorius score, disease activity, and DLQI at the 48 week follow-up visits compared with week 24. Despite this, all three measures remained significantly below baseline.<sup>21</sup>

A large-scale RCT later demonstrated superiority of weekly dosing compared with EOW dosing and in 154 HS patients. The study was divided into two periods, including a 16-week placebo-controlled stage followed by a crossover to adalimumab EOW for 3 weeks for all groups. Patients were initially randomized 1:1:1 to 40 mg weekly, 40 mg EOW, and placebo. The primary outcome was defined as an HS physician's global assessment (HS PGA) score of clear, minimal, or mild at week 16 with at least 2-grade improvement relative to baseline. After period 1, a significantly greater proportion of patients in the weekly group, but not the EOW group, achieved the primary endpoint compared with placebo. Lesion counts also improved rapidly and at least half of reduction occurred in the first 4 weeks. Period 2 provided further evidence for weekly over EOW dosing. A majority (63%) of patients in the EOW arm showed suboptimal response at weeks 28 or 31 requiring escalation to weekly dosing; of this

**Table 1.** Clinical trials of adalimumab for HS.

Author (year)	Number of patients	Dose	Endpoint	Results
Amano <i>et al.</i> , <sup>18</sup>	10	160 mg s/c at week 0, 80 mg s/c at week 1, followed by 40 mg s/c EOW	HSSI at baseline <i>versus</i> week 12†	17.0 (baseline) <i>versus</i> 14.5 (week 12), ( $p = 0.40$ )
Miller <i>et al.</i> , <sup>20</sup>	21	80 mg s/c at week 0 followed by 40 mg s/c EOW <i>versus</i> placebo	Sartorius Score at baseline <i>versus</i> week 6†	-10.7 (baseline) <i>versus</i> 7.5 (week 6), ( $p = 0.024$ )*
			DLQI at week 12†	12.40 (adalimumab) <i>versus</i> 9.33 (placebo) ( $p = 0.06$ )
Kimball <i>et al.</i> , <sup>22</sup>	154	40 mg s/c weekly, 40 mg s/c EOW, or placebo	HS PGA of clear, minimal, or mild at 16 weeks†	17.6% (weekly) <i>versus</i> 9.6% (EOW) <i>versus</i> 3.9% (placebo) ( $p = 0.025$ )*
			Mean reduction from baseline at 16 weeks in DLQI‡	6.3 (weekly), 3.2 (EOW), 2.3 (placebo) ( $p = 0.001$ )*
Kimball <i>et al.</i> , <sup>23</sup>	307	160 mg s/c at week 0, 80 mg at week 2, then 40 mg weekly starting at week 4 <i>versus</i> placebo	Achieved HiSCR at 12 weeks†	41.8% (weekly) <i>versus</i> 26.0% (placebo) ( $p = 0.03$ )*
Kimball <i>et al.</i> , <sup>23</sup>	326	160 mg s/c at week 0, 80 mg at week 2, then 40 mg weekly starting at week 4 <i>versus</i> placebo	Achieved HiSCR at 12 weeks†	58.9% (adalimumab) <i>versus</i> 27.6% (placebo) ( $p < 0.001$ )*
			Total abscess and inflammatory-nodule count of 0, 1, or 2 at 12 weeks‡	51.8% (adalimumab) <i>versus</i> 32.2% (placebo) ( $p = 0.01$ )*
			≥30% reduction from baseline in skin pain at 12 weeks‡	45.7% (adalimumab) <i>versus</i> 20.7% (placebo) ( $p < 0.001$ )*
			Improvement in modified Sartorius score at 12 weeks‡	-28.9 (adalimumab) <i>versus</i> -9.5 (placebo) ( $p < 0.001$ )*

†, primary endpoint; ‡, secondary endpoint; \*, significant change; DLQI, Dermatology life quality index; EOW, Every other week; HiSCR, Hidradenitis Suppurativa Clinical Response; HS PGA, Hidradenitis suppurativa physician's global assessment; HSSI, Hidradenitis suppurativa severity index.

cohort, 15% demonstrated clinical response at week 52.<sup>22</sup>

Two large double-blind, placebo-controlled, RCTs, PIONEERI and II, further provided evidence for use of adalimumab. PIONEERI and II followed similar study designs with key differences. In PIONEERI and II, patients were

randomized to receive either adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg weekly starting at week 4) or placebo for 12 weeks. In PIONEERI, patients receiving placebo were crossed-over to adalimumab weekly following a loading dose of 160 mg at week 12, 80 mg at week 14 and 40 mg weekly from week 16 forward. Patients receiving adalimumab weekly were

rerandomized at week 12, 1:1:1 to placebo, adalimumab EOW, or adalimumab weekly, for 24 weeks. PIONEER I also required a 28-day washout of oral antibiotics prior to baseline. In contrast, patients receiving placebo in PIONEER II continued to receive placebo for an additional 24 weeks, while patients receiving adalimumab weekly were rerandomized, 1:1:1 to receive placebo, adalimumab EOW, or adalimumab weekly, for the remaining 24 weeks. PIONEER II also allowed the continuation of stable oral tetracycline antibiotic regimens, which 19% of patients did. Patients that discontinued treatment in either study could enroll in an open-label extension of 40 mg adalimumab weekly.<sup>23</sup>

The primary endpoint in both studies was proportion of patients achieving clinical response according to the Hidradenitis Suppurativa Clinical Response (HiSCR) measure at week 12. HiSCR is defined as a 50% reduction in total abscess and inflammatory nodule count from baseline, with no increase in abscess or draining fistula count; 41.8% and 58.9% of patients in the treatment groups achieved HiSCR at week 12, *versus* 26.0% and 27.6% of patients in the placebo groups, for PIONEER I and II, respectively. PIONEER II also demonstrated significant improvement in lesion count, pain score, and disease severity with adalimumab treatment, although this was not observed in PIONEER I. Adalimumab was well tolerated in both studies.<sup>23</sup> Importantly, while the results of these studies illustrate efficacy of adalimumab in the treatment of HS, the magnitude of improvement is still far less than patients with other dermatologic diseases treated with adalimumab.<sup>24,25</sup>

*Post hoc* analyses of PIONEER I and II demonstrated that adalimumab also alleviates skin pain, especially in the first 2 weeks of treatment. There was a 40.3% and 61.2% overall reduction in pain in patients treated with adalimumab weekly, compared with a 24.9% and 24.8% overall reduction in pain in patients treated with placebo for PIONEER I and II, respectively.<sup>26</sup> In a *post hoc* analysis of a 3-year open-label extension of PIONEER I and II, 52.3% of patients that received adalimumab weekly maintained HiSCR through week 168, illustrating sustained clinical response.<sup>27</sup>

Pharmacokinetic data from the PIONEER I, II, and the initial phase II trial of adalimumab

revealed that steady-state adalimumab concentration was reached by week 2 and maintained through week 12. Further, steady state adalimumab concentration correlated with HiSCR.<sup>22,23,28</sup> Interestingly, the mean steady-state concentration achieved in HS patients was less than that observed in patients with psoriasis, ulcerative colitis (UC), and Crohn's.<sup>29–31</sup> Weight was a significant covariate, potentially explaining why HS patients experienced lower steady state adalimumab concentrations, although BMI was similar to phase III trials of adalimumab for psoriasis.<sup>24</sup>

A Cochrane review lent further evidence to the superiority of weekly dosing over EOW. A meta-analysis was performed combining participants from the phase II trial of adalimumab in HS ( $n = 51$ ) and participants in a smaller randomized trial ( $n = 15$ ) receiving EOW adalimumab compared with placebo. The primary efficacy measures of this analysis included DLQI and adverse events. Secondary outcome measures included pain, number of HS lesions, PGA, and total work productivity index (TWPI)—a measure of the economic impact of HS. The analysis found no statistically significant improvement in primary or secondary outcome measures.<sup>20,22,32</sup> In contrast, an update to the Cochrane review including patients administered weekly adalimumab from the phase II clinical trial, and PIONEER I and II studies demonstrated a 2.8-point reduction in DLQI, with no increase in adverse events compared with placebo.<sup>33</sup>

#### *Adjuvant surgical therapy*

Surgery is one of the most common methods of treatment for patients with HS, and patients are often very satisfied with the results.<sup>34</sup> A study is currently being completed to assess the role of adalimumab in combination with surgery in HS. Patients with HS severe enough to warrant surgery are randomized to receive placebo or adalimumab prior to, and following, surgery on their HS. The purpose of this study is to understand to what degree biologic therapy can optimize severe HS patients in the setting of surgery.<sup>35</sup>

#### *Limitations and side effects*

Despite offering clinical improvement, limitations exist regarding the use of adalimumab to treat HS. HiSCR is only achieved by approximately

**Table 2.** Studies investigating infliximab for the treatment of HS.

Name	Number of patients	Dose	Endpoint	Results
Grant <i>et al.</i> , <sup>47</sup>	38	5 mg/kg IV at weeks 0, 2, 6, then 5 mg/kg every 8 weeks <i>versus</i> placebo	≥50% reduction in HSSI from baseline at 8 weeks†	26.7% (IFX) <i>versus</i> 5.5% (placebo) (not significant)
van Rappard <i>et al.</i> , <sup>48</sup>	19	5 mg/kg IV at weeks 0, 2, 6 <i>versus</i> adalimumab s/c EOW	Reduction in Sartorius score from baseline at one year†	-46% (IFX) ( $p = 0.002$ )* <i>versus</i> -34% (adalimumab) ( $p = 0.02$ )*
DeFazio <i>et al.</i> , <sup>49</sup>	21	3 mg/kg IV at weeks 0, 2, 6, then 5 mg/kg every 6 weeks	Disease-free interval‡	18.5 months (surgery + biologics) <i>versus</i> 6 months (surgery alone) ( $p < 0.001$ )*
			Reoperation for recurrence‡	13.8% (surgery + biologics) <i>versus</i> 38.5% (surgery alone) ( $p < 0.01$ ) *

†, primary endpoint; ‡, secondary endpoint; \*, significant change; EOW, Every other week; HSSI, Hidradenitis suppurativa severity index; IFX, Infliximab.

50% of patients given adalimumab weekly—far less than the magnitude of improvement in patients suffering from other dermatologic diseases.<sup>23–25</sup> Immunogenicity studies demonstrated that 6.5% of patients developed anti-adalimumab antibodies (AAA) during treatment for HS, which, while generally low, may contribute to lack of response in some patients.<sup>28</sup> Adalimumab is also an injection medication that requires weekly self-administered dosing, and is costly without prior authorization by insurance. Lastly, there is an elevated prevalence of obesity in the HS population; higher doses may be required by some patients but are difficult to obtain under current insurance restrictions in the U.S.<sup>36</sup>

Side effects experienced with adalimumab are generally manageable. One small study showed an almost statistically significant increase ( $p = 0.06$ ) in adverse events, including a tenfold increase in mild infections in the adalimumab group ( $n = 21$ ) compared with placebo ( $n = 2$ ).<sup>20</sup> Headache and new-onset psoriasiform eruptions in HS patients treated with adalimumab have also been reported.<sup>22,23</sup> RCTs of adalimumab in HS have not demonstrated any reports of opportunistic infection (excluding oral candidiasis), cancer or tuberculosis (TB)—concerns that have arisen in the psoriasis, rheumatology, and inflammatory bowel disease (IBD) literature.<sup>22,23,27,37,38</sup> The

relatively limited number of patients included in HS clinical trials makes it difficult to comment on the actual risk of these events in HS.

### Infliximab

Infliximab (IFX) is a chimeric anti-TNF- $\alpha$  monoclonal antibody that binds to TNF- $\alpha$  with high affinity, preventing its downstream effects.<sup>39</sup> Efficacy in HS was first observed in patients undergoing IFX treatment for Crohn's who incidentally had improvement in HS.<sup>40,41</sup> Case reports and case series thereafter suggested efficacy for IFX, particularly in patients with severe, recalcitrant disease, both in the setting of concomitant Crohn's<sup>42–44</sup> and without Crohn's.<sup>45,46</sup>

To date, only one RCT of IFX has been performed in HS; a summary of this study can be found in Table 2. IFX was dosed at 5 mg/kg at weeks 0, 2, and 6 followed by maintenance dosing every 8 weeks for 22 weeks; 38 patients participated and the primary endpoint was a ≥50% improvement of HSSI from baseline. IFX was well tolerated and led to improvement in erythrocyte sedimentation rate (ESR), CRP, HSSI, DLQI, pain, and PGA. Of patients treated with IFX ( $n = 15$ ), 26.7% saw a 50% or greater improvement in HSSI, 60% saw a 25–50% improvement in their HSSI, and only 13.3%



demonstrated less than a 25% improvement in their HSSI. Despite the relatively low number of patients meeting the primary endpoint, IFX clearly offered advantage over placebo in which the majority of patients (88.9%) showed less than 25% improvement in HSSI.<sup>47</sup>

Despite the fact that there are few studies, especially RCTs, assessing use of IFX compared with adalimumab, IFX remains a valuable tool. A comparative study of IFX and adalimumab demonstrated that IFX performed better in all assessed categories including DLQI, physician, and patient global assessment, Sartorius score, and duration of efficacy. These results suggest that IFX may be more efficacious than adalimumab for severe HS treatment, likely because of the dosing flexibility.<sup>48</sup> Further, in a cohort study analyzing biologic treatment of HS between 2001 and 2013 at 25 hospitals across France, IFX was the most commonly prescribed biologic.<sup>50</sup>

#### *Adjuvant surgical therapy*

A retrospective study at a single institution reported on use of IFX in conjunction with surgery. IFX prior to surgical therapy was superior to IFX alone as assessed by HS PGA. The authors concluded that administration of IFX to optimize patients prior to surgical intervention was an effective strategy leading to long-term clearance.<sup>51</sup> Another study also investigated biologic therapy (with either IFX or ustekinumab) following surgical resection of HS lesions. Patients treated with IFX (dosed at 3 mg/kg at weeks 0, 2, and 6 followed by 5 mg/kg every 6 weeks) experienced significantly lower rates of recurrence (19%) compared with placebo (38.5%). Further, patients receiving adjuvant biologic therapy experienced lower rates of disease progression for at least 6 months following surgical intervention. Time to recurrence was 4.5 months longer for patients treated with biologics following closure of surgical site compared with patients who did not receive biologic medication.<sup>49</sup>

#### *Biomarkers*

Biomarkers are frequently monitored in patients treated with IFX; however, the utility of monitoring remains unclear. There is some evidence for the role of monitoring IL-6 and high sensitivity CRP (hs-CRP). In one study, responders had lower IL-6 levels compared with nonresponders.<sup>52</sup>

Further, significant reductions in ESR and CRP occur following the initiation of IFX.<sup>48,51,53</sup> The reduction in CRP is not universal, however, as one case series ( $n=7$ ) failed to demonstrate significant change in CRP or neutrophils following treatment with IFX.<sup>54</sup>

#### *Limitations and side effects*

Despite rapid improvement with IFX, relapse commonly follows treatment cessation, occurring anywhere from 10 weeks to 8.5 months, as reported in three studies.<sup>53,55,56</sup> To evade relapses seen in patients dosed with IFX every 8 weeks, Moriarty *et al.* described increasing the dosing frequency to every 4 weeks, which resulted in continued clearance in 11 HS patients for a median treatment duration of 49.1 months.<sup>57</sup> Anti-drug antibody (ADA) formation is a concern with IFX treatment and may contribute to some loss of response and need for dose escalation. Some authors report use of concomitant methotrexate to avoid ADA formation following IFX cessation.<sup>42</sup>

Side effects reported in HS patients receiving IFX include influenza-like illness, headache, neuropathy, anaphylaxis, and serum sickness potentially related to the formation of ADA to IFX.<sup>47,53</sup> In addition, increased dosing of IFX to every 4 weeks led to more adverse events than in patients taking IFX every 8 weeks, including infections and one case of Hodgkin's lymphoma.<sup>57</sup>

#### **Etanercept**

Etanercept is a recombinant human TNF- $\alpha$  receptor p75-Fc fusion protein that competitively binds to membrane bound TNF- $\alpha$  receptors.<sup>58</sup> Etanercept is FDA approved for several inflammatory conditions including rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis.<sup>59</sup> Literature regarding use of etanercept in HS has reported inconsistent efficacy.

Some case reports and small case series support use of etanercept in HS; however, the generalizability of these results is limited by the small number of patients. An early case series of six patients illustrated rapid improvement in abscess number, patient-reported disease activity, and relapse frequency. Patients demonstrated early

**Table 3.** Clinical trials of etanercept for HS.

Name (Year)	Number of patients	Dose	Endpoint	Results
<b>Giamarellos-Bourboulis <i>et al.</i>,<sup>62</sup></b>	10	50 mg s/c weekly	Reduction in disease activity relative to baseline at 12 weeks	Authors noted significant reduction but values not specified ( $p = 0.024$ )*
			Sartorius score reduction at 12 weeks	Authors noted significant reduction but values not specified ( $p = 0.005$ )*
<b>Lee <i>et al.</i>,<sup>64</sup></b>	15	50 mg s/c weekly	HS PGA at 12 weeks†	4.35 (baseline) <i>versus</i> 3.5 (week 12) ( $p = 0.14$ )
			Number of lesions at 12 weeks‡	14 (baseline) <i>versus</i> 12 (week 12) ( $p = 0.69$ )
<b>Adams <i>et al.</i>,<sup>65</sup></b>	20	50 mg s/c twice weekly <i>versus</i> placebo	HS PGA: treatment <i>versus</i> placebo†	Data not included; results not significant per manuscript
			Pain: treatment <i>versus</i> placebo at 12 weeks‡	Data not included; results not significant per manuscript

†, primary endpoint; ‡, secondary endpoint; \*, significant change; HS PGA, Hidradenitis suppurativa physician's global assessment.

improvement (mean: 16 days after treatment initiation), which was sustained, and patient-reported disease activity decreased by 61% at 24 weeks. Two patients (33.3%), however, demonstrated relapse within 3 weeks of cessation of treatment.<sup>60</sup> In addition, in a small case series, four patients with severe recalcitrant HS initiated etanercept 25 mg twice weekly. On average, improvement was noted after 13 days. Patient-reported severity and DLQI improved by 68.8% and 66.5%, respectively. There were no adverse events save for one injection site reaction.<sup>61</sup>

Clinical trials investigating use of etanercept in HS offer varying results and are summarized in Table 3. An open-label phase II trial investigated the efficacy of etanercept (50 mg subcutaneously weekly) in 10 patients and demonstrated decreased local pain at lesion sites as early as 1 month into treatment. A significant reduction in VAS for patient-reported disease severity ( $p = 0.024$ ) and a greater than 30% reduction in Sartorius score were noted by week 12. Disease relapse occurred within 4–8 weeks of discontinuing therapy ( $n = 8$ ), although when patients relapsed, their disease activity was still less than half of their baseline.<sup>62</sup> Participants were followed

in a long-term efficacy study through 144 weeks; patients who experienced disease relapse ( $n = 7$ ) were subsequently restarted on etanercept therapy leading to response in the majority ( $n = 5$ ).<sup>63</sup>

Conversely, an open-label phase II trial failed to demonstrate efficacy of etanercept dosed at 50 mg subcutaneously weekly. Only 3 of 15 patients achieved the primary outcome, defined as 50% or greater improvement in PGA at week 12. While slight decreases were noted in median pain scores and DLQI, only 29% of patients reported even moderate improvement in disease. Of note, patients who achieved the primary outcome had a lower BMI on average than those who did not.<sup>64</sup> Further, the only randomized, double-blind, placebo-controlled trial also failed to show any benefit of etanercept treatment. Patients ( $n = 20$ ) were treated with 50 mg etanercept or placebo twice weekly for 12 weeks, at which point all patients entered a 12-week open-label period of 50 mg etanercept twice weekly. The study's primary endpoint was defined as a PGA of clear or mild at week 12. Secondary endpoints included patient global assessment of lesions, patient-reported pain, and DLQI. At 12 and 24 weeks there were no statistically significant differences

in any of the clinical endpoints assessed.<sup>65</sup> Given its relatively low potency and the effects of weight on efficacy, it may not have been dosed adequately to have the desired therapeutic effect. In summary, there is minimal evidence to support use of etanercept in HS.

### **Golimumab**

Evidence regarding golimumab, a monoclonal anti-TNF- $\alpha$  antibody, is scarce; only two case reports exist in the literature. The first described use of golimumab in a patient with severe HS and psoriatic arthritis who failed adalimumab and anakinra previously. With golimumab, her HS worsened despite improvement in her psoriatic arthritis. She was therefore considered to have failed golimumab.<sup>66</sup> The second report detailed a 42-year-old female with UC, HS, and pyostomatitis vegetans treated with golimumab (200 mg followed by 100 mg every 4 weeks). This patient had remission of her dermatologic symptoms and UC within 2 months of starting therapy.<sup>67</sup> Little can be inferred from these case reports regarding the effectiveness of golimumab in the treatment of HS.

### **Certolizumab-pegol**

Certolizumab-pegol is another biologic targeting TNF- $\alpha$ , and is the only anti-TNF- $\alpha$  agent that does not cross the placenta.<sup>68,69</sup> The inability of certolizumab to cross the placenta may relate to the absence of an Fc region, a factor implicated in placental transfer, due to pegylation.<sup>70</sup> There is a report of certolizumab utilized in a pregnant HS patient as an alternative to adalimumab.<sup>71</sup> With only one mention in the literature, no assessment of certolizumab's efficacy in HS can be ascertained.

### **Safety concerns in patients treated with TNF-inhibitors**

There are several safety concerns to consider when treating patients with TNF- $\alpha$  inhibitors. Data regarding the prevalence of these events in HS patients is scarce given the small number of HS patients treated with TNF- $\alpha$  inhibitors to date and few RCTs in the literature. These factors restrict the ability of researchers to perform meta-analyses—further limiting the study of adverse events in this population. Therefore, safety information is largely borrowed from the

psoriasis, rheumatology, and gastroenterology literature.

TNF- $\alpha$  is heavily implicated in mediating immune response to pathogens. Immunosuppression resulting from anti-TNF- $\alpha$  therapy increases susceptibility to infections, especially concerning is the potential reactivation of latent TB through diminished granuloma integrity.<sup>72–74</sup> In a meta-analysis of 29 RCTs accounting for 11,879 patients, TB reactivation risk was significantly elevated in patients treated with anti-TNF- $\alpha$  medications.<sup>37</sup> Consequently, patients initiating anti-TNF- $\alpha$  therapy should be screened for latent TB and annually thereafter.

Another consideration with anti-TNF- $\alpha$  medications is increased risk of malignancy. One meta-analysis of the RA literature found an increased risk of all-site malignancy associated with anti-TNF- $\alpha$  medications, with an odds ratio (OR) of 3.29 (95% CI: 1.19–9.08).<sup>38</sup> However, in subsequent meta-analyses of RA patients, these results were not replicated.<sup>75–77</sup> Concomitant therapies are also likely important in development of these adverse events. A meta-analysis of the IBD literature also failed to find a significantly increased cancer risk in patients receiving anti-TNF- $\alpha$  therapy, although the authors cited concern that limited follow-up times could lead to less detection and cancer event reporting.<sup>78,79</sup> Importantly, increased risk of nonmelanoma skin cancers (NMSC) associated with anti-TNF- $\alpha$  therapy has been reported. One study reported a relative risk (RR) of 2.02 (95% CI 1.11–3.95), and another demonstrated a RR of 1.45 (95% CI 1.15–1.76).<sup>75,80</sup> Lymphoma risk is also increased in patients treated with anti-TNF- $\alpha$  therapy compared with the general population; but not when compared with RA patients treated with classic disease-modifying anti-rheumatic drugs. Diseases requiring anti-TNF- $\alpha$  therapy inherently involve chronic inflammatory states, which may lead to the development of lymphoma. It is difficult to say whether exposure to anti-TNF- $\alpha$  medications or the chronic inflammatory load experienced by these patients are to blame for the observed increase in lymphoma.<sup>80,81</sup>

Neuropathy has been reported in HS patients taking anti-TNF- $\alpha$  medications.<sup>53</sup> The prevalence of anti-TNF- $\alpha$  related neuropathies is estimated at 0.60% and largely resolve upon withdrawal of anti-TNF- $\alpha$  therapy.<sup>82</sup>



## Conclusion

HS is notoriously difficult to treat. The efficacy of adalimumab and IFX in HS is encouraging despite some limitations. Adalimumab has the highest quality evidence supporting its use in HS, and should be considered as first line therapy. IFX represents another reasonable treatment option, with primary drawbacks including an inconvenient infusion schedule, less robust data, and difficulty obtaining insurance approval. As surgery offers a more permanent solution and may increase time to HS relapse, concomitant use of anti-TNF- $\alpha$  agents in the setting of surgery is an intriguing concept. The etanercept literature lacks convincing data that it can offer benefit in HS. Evidence for golimumab and certolizumab is even further limited. In summary, adalimumab and IFX are mainstays in the treatment of HS; however, as neither offers complete or long-lasting disease remission, continued pursuit of clinical trials investigating novel treatment strategies is paramount.

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