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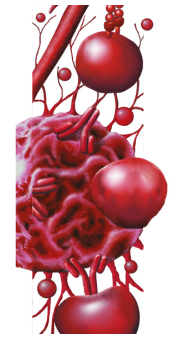

Biologics for hidradenitis suppurativa: an update

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Hidradenitis suppurativa (HS) is a chronic, inflammatory dermatosis characterized by an occurrence of nodules, abscesses, sinus tracks and scarring. Its pathogenesis is multifactorial and still not fully understood, therefore, current systemic therapies still remain a serious challenge. Increased levels of several proinflammatory cytokines have been reported in patients suffering from HS, therefore biologics appear as a new approach to therapy for this condition. Adalimumab is the only one internationally registered agent and should be considered first after the conventional therapies appear insufficient. The efficacy and safety profile of some preparations, like infliximab and etanercept was confirmed so far in randomized trials, but there are some new biologics which are still being evaluated and require more rigorous examination.

First draft submitted: 1 July 2017; Accepted for publication: 4 November 2018; Published online: 7 December 2018

Keywords: acne inversa • biologic drugs • biologics • biologic therapy • hidradenitis suppurativa • management • therapy • treatment

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, recurrent, inflammatory dermatosis characterized by an occurrence of deep, painful lesions like nodules, suppurative abscesses, sinus tracks and scarring [1]. The disease occurs in body areas rich in apocrine glands, including mainly axillae, groin and anogenital region [2]. The changes often spread to the buttocks, the anal area or the woman's interbreast area [1]. The pathogenesis of HS is still not fully understood. The condition is multifactorial and probably results from a combination of genetic, hormonal (mainly hyperandrogenism) and environmental factors. Pilosebaceous unit occlusion, hyperkeratinization and bacterial superinfection are now considered the main pathogenetic mechanisms [2]. Tobacco smoking, drugs and obesity are recognized as the major risk factors for HS development. Moreover, a direct relationship with smoking and the severity of the disease symptoms has been proven [3,4]. The incidence of the disease is around 1% with a female predominance (female to male ratio of 3:1), however, there is also a report suggesting even a 4% prevalence [5,6]. HS has been associated with several comorbid disorders known as immune-mediated inflammatory diseases (IMIDs), such as Crohn's disease, colitis ulcerosa, seronegative arthritis and pyoderma gangrenosum [7,8].

HS is a debilitating disease resulting in patient mutilation, it is also associated with chronic pain sensation. It was documented that HS patients have a poor quality of life (QOL) directly correlated to the severity of the disease. QOL impairment occurs also more frequently than those found in some other dermatoses such as psoriasis, atopic dermatitis and chronic urticarial [9–12].

Due to the multifactorial pathogenesis of the disease, the treatment of HS often occurs as a therapeutic challenge. European S1 guideline for HS has been developed by a group of experts, but an unambiguous treatment algorithm has not been established. Thus, the preparations most commonly used in HS therapy include 1% topical clindamycin, systemic antibiotics (including tetracycline or clindamycin and rifampicin combination), retinoids and hormone therapy [13]. It is important to emphasize that pharmacological therapies should be introduced while treating HS as early as possible, in order to avoid complications such as scars, sinus tracts or malignancies development (Marjolin's ulcer occuring in previously traumatized and chronically inflamed skin areas) [14].

Biologics that have been used for almost 20 years for the treatment of IMIDs, have also proven to be a promising therapeutic option for HS sufferers. They are successfully used in patients with moderate to severe HS when the conventional systemic therapies proved insufficient.

Future Medicine

TNF-α inhibitors

TNF-α is a cell signalling protein (cytokine) produced by many cell types such as activated macrophages, mast cells, $CD4^+$ lymphocytes, NK cells and neutrophils. It plays a key role in the inflammatory response in humans and is involved in various inflammatory responses, including acute phase reaction. TNF-α is generated as a precursor form called tmTNF (transmembrane). Its biological activity is associated with binding two receptors, TNFR1 (found in most tissues) and TNFR2 (expressed typically in cells of the immune system). The cytokine acts by promoting an expression of adhesion molecules, neutrophils migration and phagocytosis of macrophages. It also stimulates production of a number of mediators, including CRP, IL-1 oxidants and the inflammatory lipid PGE_2, as well as activates caspases, intracellular signaling NF-kB and MAPK. Currently, TNF-α is believed also to play an important role in the pathogenesis of HS lesions. This is indirectly confirmed by the fact that TNF-α inhibitors have been successfully used in HS therapy for several years.

The relationship between TNF-α blockade and HS improvement was first noticed in 2001, when Martinez *et al.* [15] observed an improvement in the condition of skin lesions in the course of HS among patients undergoing anti-TNF-α therapy due to co-morbid Crohn's disease. This observation subsequently prompted other researchers to do a deeper analysis of this issue to characterize the proinflammatory and anti-inflammatory cytokines profile in the body of patients suffering from HS.

Matusiak *et al.* [16] showed a significantly elevated level of TNF-α in the blood of HS patients compared with control, whereas the level of cytokine did not correlate with the disease severity, its duration or BMI. In another study, Van der Zee *et al.* [17]. reported increased expression of proinflammatory TNF-α and IL-1β as well as anti-inflammatory Il-10 in patients with HS compared with the healthy controls in both the diseased skin and perilesional area. It was also five-times higher than the values observed in psoriasis. Similar conclusions regarding the level of TNF-α in patients with HS have been reached by Mozeika *et al.* [18] showing elevated levels of cytokine in the skin, apocrine glands and hair follicles.

However, there are also opposite reports that have shown reduced levels of substances associated with innate immune response, including TNF-α in both the blood and tissues of patients suffering from HS. Van der Zee *et al.* [19] when assessing TNF-α levels in the skin of patients undergoing 16-week adalimumab therapy, did not observe any significant differences in cytokine concentration before and after treatment.

Despite contradictory reports, TNF-α seems to play a significant role in the pathogenesis of HS, the best confirmation of which are numerous positive reports on the use of TNF-α blockers in the therapy of this condition.

Adalimumab

Adalimumab (ADA) is a fully human monoclonal antibody against TNF-α. It binds with a high specificity and affinity to soluble and membrane-bound TNF-α and blocks its biological activity. ADA regulates the innate immune response by affecting the levels of proinflammatory cytokines such as Il-6, Il-8, Il-1β and sTNF-RI [20]. Treatment with ADA was also associated with decreased number of inflammatory leukocyte subsets including monocytes, macrophages, dendritic cells, T-helper and B lymphocytes [21].

ADA is administered by subcutaneous injections, and its highest effectiveness, according to European guidelines, is obtained with a dose regimen of 40 mg once weekly. There is no dose adjustment for patients with obesity [13]. The drug is contraindicated in NYHA class III–IV heart failure, history of tuberculosis or other severe infections, severe liver disease, demyelinating processes, malignancies, pregnancy or lactation. Women of childbearing age should therefore receive contraception up to 5 months after treatment [13].

The first reports of scientists about the efficacy of ADA on HS came from several case series. In the majority of studies, ADA was administered with the dosing regimen previously adopted for the treatment of psoriasis (80 mg at week 0, 40 mg at week 1 and then 40 mg every other week) [22]. The effects were satisfactory in accordance to both efficacy and safety of the treatment [21,23–33]. In subsequent years, prospective studies based on larger groups and longer observation of patients were published.

Blanco *et al.* [34] perform a retrospective analysis of a group of six patients treated with ADA for refractory HS. The initial dosage was 40 mg every other week and was increased to 40 mg weekly if the condition was inadequately controlled. All patients reported a marked reduction in the number of affected areas of the body, nodules, fistulas and laboratory parameters, as well as an improvement in the Dermatology Life Quality Index (DLQI). The mean follow-up period in this study was 21.5 months. Arenbergowa *et al.* [35] used ADA in a group of eight patients with severe, recalcitrant HS (Hurley grade III). Patients were treated for 1 year with a standard psoriasis dosing regimen and after that monitored for 1 year. Clinically significant improvement was observed in all patients within 4–6

weeks. Three of them remained stable with no relapse during the follow-up period. The average time to recurrence was 9.5 months.

In another open-label prospective study by Sotiriou *et al.* [36] 15 patients with moderate to severe HS were treated with ADA in a different from previously mentioned dose regimen: 80 mg was administered at week 0, and then 40 mg weekly for 24 weeks. After this time, a significant decrease in Sartorius score was reported. DLQI, as well as disease activity evaluated by visual analogue scale (VAS), also showed a marked reduction at week 24. There was however a significant worsening at week 48, and recurrences after discontinuation of treatment were noticed after mean time of 11 weeks.

In the study by Amano *et al.* [37] the results were not so promising. Ten patients were enrolled in this study and administered ADA for 12 weeks at doses of 160 mg at week 0, 80 mg at week 1 and 40 mg every other week. At week 12, none of the patients were classified as a responder compared with the baseline. There was also no statistically significant improvement in pain and QOL.

The first randomized, double-blind, prospective, placebo-controlled trial evaluating the efficacy and safety of ADA in the treatment of HS was carried out by Miller *et al.* [38] 21 patients suffering from moderate to severe HS (Hurley stage II or III) for at least 6 months were randomized 1:2 (placebo: active treatment). Thus, 15 patients received 80 mg ADA at week 0, followed by 40 mg every other week for 12 weeks, while six patients received placebo. A marked reduction in Sartorius score occurred after 6 weeks and in the ADA group when compared with placebo control. However, no significant change in the Hurley score, VAS or DLQI was seen after 12 weeks.

Kimball *et al.* [39] conducted another larger, randomized, placebo-controlled two-phased study. It included a group of 154 patients with moderate and severe HS (HS Physician Global Assessment [HS-PGA] score of moderate or worse) who had previously reported intolerance or lack of response to oral antibiotics. During period 1 (blinded phase) patients were randomized in a 1:1:1 ratio to ADA 40 mg every week, ADA 40 mg every other week (EOW) and placebo for 16 weeks. Period 2 was open-label and all patients were treated with ADA 40 mg EOW. At weeks 28 or 31 patients with a suboptimal response (HS-PGA score of moderate or worse) were switched to weekly dosing. At week 16, a significantly greater proportion of patients in the weekly group (17.6%) achieved a clinical response (HS-PGA score of clear, minimal or mild with at least a 2-grade improvement relative to baseline) compared with patients in EOW (9.6%) and placebo (3.9%) groups. This group also achieved a significantly greater reduction of pain (assessed by using VAS questionnaire). However, after the switch from weekly to EOW dosing in period 2, a decrease in response was reported. These observations suggest that the most effective dosing regimen for ADA is 40 mg every week. During the study, headaches and injection site reactions were the most frequently reported side effects. Serious adverse event rates in all three groups were: 7.8, 5.8 and 3.9%, respectively, and the worsening of HS, infectious complications and anemia were the most common.

The most recent and most significant Phase III trial for the evaluation of the efficacy and safety of ADA in HS therapy is the PIONEER I and II [40]. These multicenter studies, in which 307 and 326 patients participated, respectively, were similarly designed with two double-blind and placebo-controlled periods. In period 1 (12-weeks), patients were randomized in a 1:1 ratio into two groups – one receiving ADA (160 mg at week 0, 80 mg at week 2 and 40 mg weekly from week 4 through week 12), the second matching placebo. All patients who received ADA in period 1 and continued into period 2, were then re-randomized 1:1:1 to ADA 40 mg weekly, every other week or placebo. Patients who were in the placebo group in period 1 were reassigned to ADA 40 mg weekly (PIONEER I) or placebo (PIONEER II) for 24 weeks. Moreover, in PIONEER II an adjuvant therapy was also allowed (19% of patients received concomitant oral antibiotics).

The primary efficacy end point was HiSCR (Hidradenitis Suppurativa Clinical Response) defined as more than 50% reduction in total abscess and inflammatory nodule count, and no increase in abscess and draining fistula count at week 12 comparing to a baseline.

At week 12, HiSCR achievement rate was significantly higher for patients in the ADA group compared with the placebo group (41.8 vs 26% in PIONEER I and 58.9 vs 27.6% in PIONEER II). The marked improvement was observed in ADA group as early as 2 weeks into therapy.

Moreover, in the PIONEER II, although not in PIONEER I, ADA proved to be significantly more effective than placebo in secondary outcomes including: pain reduction (measured with Patient's Global Assessment of Skin Pain), disease severity (in Modified Sartorius score and Hurley Stage), as well as the number and morphology of skin lesions. This group also had statistically significant improvement in quality of life (DLQI). Also in this study, under ADA treatment tolerance was satisfactory. The most commonly reported adverse effects were headaches and infections (especially upper respiratory tract and the urinary tract infections). During period 1, serious adverse

events were observed in 1.3 ADA versus 1.3% patients in placebo group (PIONEER I) and 3.7 versus 1.8% respectively, in PIONEER II. By period 2, these rates were up to 4.6% with a similar frequency for both groups and studies.

ADA has therefore proved to be a drug with greater efficacy in HS treatment and a similar safety profile compared with a placebo.

In all of the studies, adverse side effects after administration of this preparation were usually mild to moderate. Relatively common adverse drug reactions were injection site reactions and infections, including serious infections such as pneumonia, arthritis, diverticulitis and pyelonephritis. Reactivations of latent tuberculosis or hepatitis B virus, as well as neurological and hematological complications were also reported during the course of a treatment [14]. Very rarely, malignancies (including lymphomas, squamous cell carcinoma or breast cancer) occurred [38,41]. A few cases of paradoxical reactions after ADA administration, due to other diseases therapy, were reported [42].

Therefore, ADA seems to give promising results both in effectiveness of HS therapy and safety of use. According to current evidence it also improves patients' QOL, reduces pain as well as depressive symptoms [43,44]. Three large prospective studies on ADA on a total estimated number of 914 patients are currently underway [45].

ADA is the only biologic drug approved by the US FDA and EMA for therapy of moderate to severe HS in adult patients after failure of classic treatment.

Infliximab

Infliximab (IFX) is a chimeric (mouse/human) monoclonal IgG1 class antibody that works against TNF-α. Similarly, to ADA, it binds to both soluble and transmembrane receptor-bound TNF-α and neutralizes its proinflammatory activity.

IFX is administered by intravenous infusion at a dose of 5 mg/kg body weight at weeks: 0, 2, 6 and then regularly in 8-week intervals for a long-term therapy [13]. Due to the possible infusion reactions, patients should remain under observation during the infusion and 1 hour after the drug administration [13].

A long-term prospective trial was carried out by Paradela *et al.* [46] on a group of ten patients suffering from moderate to severe refractory HS. IFX was administered intravenously in the previously mentioned dose regimen. Response, defined as more than 50% decrease in HSS (hidradenitis suppurativa score) comparing with baseline was achieved in eight patients. However, disease recurrence was noticed in 4 patients after the mean period of 37 weeks.

In another prospective, interventional study by Lesage *et al.* [47] ten patients were treated with IFX 5 mg/kg at weeks 0, 2, 6 and then every 4 weeks. A significant decrease in disease severity (assessed in Hurley score) as well as QOL improvement was noted in all subjects. Complete efficacy (defined as the absence of HS flares) was obtained for two patients and partial efficacy (moderate flares with no need for surgery) for eight.

The only one randomized, double-blind, placebo-controlled study on the efficacy and safety of IFX in HS therapy was performed by Grant *et al.* [48] on a group of 38 patients.

In the first phase of 8-weeks duration, patients with moderate to severe HS (HS Severity Index score greater than 8) were randomized to treatment with IFX 5 mg/kg at weeks 0, 2, 6 or matching placebo. The groups were then unblinded in the second phase of the study, and placebo patients had the opportunity to change therapy to the IFX for another 22 weeks. The last observational phase was followed until week 52. HSSI was used to assess the disease activity. At week 8 it was noted that significantly greater number of patients treated with the active drug achieved at least 50% improvement in skin lesions compared with placebo. Interestingly, a similar effect was achieved by subjects that switched from placebo to IFX in the second phase of the study. Also reduction of DLQI, VAS, PGA (Physician Global Assessment) score and laboratory inflammation markers was significantly greater in IFX-treated patients comparing with placebo. The mean DLQI change from baseline for patients treated with IFX was 10.0 and in placebo group it was 1.6, and the mean VAS change was 39.0 and 0.6, respectively.

Tolerance under IFX treatment was satisfactory, with, most commonly, mild adverse effects observed, including headaches, nausea and infections. Serious adverse events after IFX administration were similar to those reported during ADA therapy and mainly involved: reactivation of latent tuberculosis, Hepatitis B, hepatosplenic T cell lymphoma, hematological complications or neurologic events.

In the retrospective study conducted on two cohorts, each of ten patients, Van Rappard *et al.* [49] compared the effectiveness of IFX and ADA in HS therapy. Ten patients were treated with ADA 40 mg every other week, and the second group with IFX 5 mg/kg at weeks 0–2–6. A significant improvement in skin lesions, as well as reduction of the inflammatory laboratory parameters was obtained in both groups of subjects. The mean decrease

Table 1. Level of evidence and response rate for studies on TNF-α inhibitors.

Biologics	No. of papers	Level of evidence†			Responders (%)‡	Nonresponders (%)
		A	B	C		
Total	69§	4	25	40	55,3%	44,7%
Adalimumab	21	2	7	12	54%	46%
Infliximab	38	1	12	25	82%	18%
Etanercept	10	1	6	3	54%	46%

†The level of the study evidence was defined as: A (randomized controlled trials), B (lower-quality clinical trials), C (case reports and case series).
‡The patients were categorized as 'respoders' or 'non-responders' due to the criteria established for each study.
§References: 36,38,91,92 were not included, due to the lack of precized data about clinical response rate achieved by the patients in these studies.

in Sartorius score compared with baseline was 54% in the IFX group and 66% for the ADA group. However, only the improvement in the IFX group remained significant after one year of observation. Both preparations were beneficial, but IFX happened to be more effective in all aspects than ADA not only in decreasing disease severity, but also in improving QOL, normalizing of laboratory parameters and durability of achieved remission. No serious adverse effects were noticed in both groups.

Etanercept

Etanercept (ETA) is recombinant fusion protein that binds to transmembrane form of TNF-α and inhibits it. It is administrated by subcutaneous injections. It is approved by the US FDA for treatment of rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, juvenile idiopathic arthritis and ankylosing spondylitis [50].

In a series of cases [51–53] as well as open cohort studies [54–59] conducted on groups of 4 to 15 patients who received ETA in doses of 25 mg twice weekly or 50 mg once/twice weekly, promising results regarding the efficacy of the drug in HS therapy were obtained.

Cusack *et al.* [56] reported a significant reduction in self-reported disease activity (mean reduction of 61%) as well as an improvement in the QOL (mean reduction in DLQI scores of 64%). In another study by Giamarellos-Bourboulis *et al.* [55] ETA was administered in a dose of 50 mg once weekly for 12 weeks. More than 50% decrease of disease activity (according to the Sartorius scale) was reported in 6/10 patients at week 12 and 7/10 patients at week 24. The reduction of VAS scores was noticed in 7/10 and 6/10 patients respectively.

Only one randomized, double-blind, placebo-controlled trial assessing the efficacy of ETA in moderate and severe HS has been published, but the results were unsatisfactory. It was carried out by Adams *et al.* [50] on a group of 20 patients. ETA (50 mg) or placebo was administered twice a week for 12 weeks. After that, all subjects received open-label ETA in the same dose regimen for 12 more weeks. At 12 or 24 weeks, there was no significant difference in patient global assessment, physician global assessment or QOL (assessed with DLQI) between ETA and placebo groups.

In most of the published studies, ETA was well tolerated and the most commonly reported adverse reactions were injection site reactions and infections. However, in one patients bilateral *Candida chorioretinitis* followed by septicemia was described [52].

Reports differ as to the ETA efficacy in HS, which, in the light of the more confirmed efficacy of ADA and IFX, argues for the greater utility of these preparations in HS therapy. The dominance of the other two TNF-α inhibitors over ETA can be explained by the fact that these drugs bind to both soluble and transmembrane TNF-α, whereas ETA inhibits only the transmembrane form [14].

Significantly increased expression of TNF-α found in HS sufferers supports the use of TNF-α inhibitors as a therapy of this condition. These preparations are also the most widely investigated biologic agents for the efficacy and safety of use. Both experimental and clinical trials have demonstrated the rationale behind using TNF-α inhibitors in HS treatment. The results of the published studies on ADA, IFX and ETA are summarized in the Table 1.

In total 69 papers were analysed, mostly including case reports and case series, but also randomized controlled trials for each preparation, which were mentioned above. The level of the study evidence was divided into three groups, which were respectively: A (randomized controlled trials), B (lower-quality clinical trials), C (case reports and case series). The patients were categorized as 'responders' or 'non-responders', according to the criteria established for each of the analyzed studies (e.g. decrease in HSSI, PGA score, achieving HiSCR). If no individual results were reported for each subject in a study, all patients were classified according to the mean achieved efficacy. Patients

receiving placebo in the cohort studies were not included. The highest response rate was observed with IFX and the percentage of responders to this preparation was 82% compared with 54% for ADA and ETA. However, it is important to emphasize that the highest quality of evidence was identified for ADA and many more patients were analyzed after its administration than after IFX and ETA, which makes the result of ADA efficacy the most reliable. Smaller studies of IFX and ETA, in which nonvalidated measurements were used to assess the effectiveness of the therapy also do not determine high quality of evidence. Overall, the quality of evidence was much lower for IFX and ETA than for ADA and differed between the preparations, making it difficult to compare these agents directly. Therefore, larger randomized controlled trials are needed to precisely estimate the effectiveness of these preparations in HS therapy.

Other biologics

Anakinra

Anakinra (ANA) is a recombinant IL-1 receptor antagonist. It competitively blocks the binding of naturally occurring IL-1 (IL-1α and IL-1β) to its receptor and inhibits its biological activity. IL-1 (similarly to TNF-α) is one of the major mediators of the inflammatory response that are also involved in the pathogenesis of HS [60].

Due to its immunomodulatory and anti-inflammatory properties, ANA may occur as a new, promising therapeutic approach in the management of HS and an alternative for patients who have failed to respond to other treatment regimens, including TNF-α blockers. ANA was originally registered for the treatment of moderate to severe rheumatoid arthritis. However, a successful off-label use of this drug was also reported in various conditions, often of autoimmune background, including psoriasis, atopic dermatitis, pyoderma gangrenosum, Schnitzler's syndrome, Sweet's syndrome or SAPHO syndrome [61]. In HS, ANA is typically administered by subcutaneous injections in a dose of 100 mg/day, which corresponds to the dosage regimen for rheumatoid arthritis.

Different reports regarding to the efficacy of ANA in the management of HS occurred. In a prospective open-label study, Leslie *et al.* [62] assessed the effectiveness, safety and tolerability of ANA in HS management. The group of six patients with moderate to severe HS were treated with daily ANA (100 mg/day) for 8 weeks, which was the active phase of the therapy, followed by 8-weeks observation phase. Inclusion criteria for this study included minimum modified Sartorius score of 25 or greater and presence of active skin lesions in at least two anatomic areas of the body. As a result, all of the five patients who completed the study (one subject was lost to follow-up because of socioeconomic factors) achieved a clinically meaningful improvement after 8 weeks of therapy. A mean decrease of modified Sartorius score was 34.8 points. Patients' QOL was also improved, and the average decrease in the DLQI was -8.4 points, which is comparable with that obtained under ADA therapy in a study conducted by Kimball *et al.* [39]. However, relapse occurred in HS disease activity as well as others assessed parameters after an 8-week follow-up. ANA was well tolerated – no adverse events were reported in any of the study participants during the entire treatment nor the follow-up period.

A larger randomized double-blind, placebo-controlled clinical trial in a group of 20 HS patients (Hurley stage II or III) was conducted by Tzanetakou *et al.* [63]. Patients were randomized in a 1:1 ratio, to receive placebo or ANA subcutaneously 100 mg once daily for 12 weeks (treatment phase), and then remained under observation for the next 12 weeks. At the baseline visit, the patients were evaluated among the disease activity, number of skin lesions, affected areas and QOL. In addition, peripheral blood samples were also taken from the subjects and mononuclear cells were stimulated to cytokine production. The study confirmed ANA as a potentially efficacious management in HS therapy.

A total of 78% of patients treated with ANA achieved a good clinical response (decrease of disease activity score) after 12 weeks of active therapy comparing to 30% of the placebo group.

After 24 weeks, these results were 67 and 20%, respectively, and the time to disease exacerbation was prolonged in patients treated with ANA. Moreover, there was also a decrease in the production of IFN-γ in ANA group, and the production of interleukin 22 was increased. No serious adverse effects of the therapy were noticed.

Zarchi *et al.* [64] reported the case of a 37-year-old obese patient (BMI = 40) who was successfully treated with ANA 200 mg daily, after the failure of other therapies, including IFX and ADA.

Despite promising reports confirming the efficacy of ANA in the treatment of moderate to severe HS, a few cases of 'nonresponse' to this treatment have also been reported [65–67].

Menis *et al.* [65] described even a worsening of skin lesions as well as DLQI and PGA in one of the two patients administered to with ANA. Due to contradictory reports in previously published studies, there is a need to assess the efficacy and safety of ANA in randomized trials with large groups of patients in the future.

Ustekinumab

Ustekinumab (UST) is a human IgG1 class monoclonal antibody directed against the p40 subunit of IL-12 and IL-23, which regulates specific components of the immune system.

Both IL-12 and IL-23 are involved in differentiation and activation of Th cells subsets (Th1 and Th17 respectively) which release other proinflammatory cytokines [68]. Due to their mechanism of action, IL-12 and IL-23 play a role in the pathogenesis of IMIDs by dysregulation of the immune system, thus UST has been successfully used in the treatment of disorders such as psoriasis, Crohn's disease or HS [69]. Furthermore, Schlapbach *et al.* [70] reported an increased expression of IL-12 and IL-23 in lesional skin of HS sufferers, which was related to infiltration of papillary and reticular dermis by macrophages. These data provide a rationale for UST as a new therapeutic approach for HS therapy.

In a study by Gulliver *et al.* [71] three cases of patients were reviewed to assess the efficacy of UST therapy. All subjects were administered with UST by subcutaneous injections in a previously mentioned dose. Different outcome was achieved in each subject. Complete disease remission in one of the patients was obtained at month 6, while 25-49% improvement was noticed in the second subject and no treatment effect in the third.

According to results of three other case reports, which were published by different authors [72–74], all patients reported a partial or complete response to UST therapy, however the effect of the treatment was not rapid and appeared within several months from the beginning of drug administration.

Blok and colleagues [75] conducted the only uncontrolled open-label clinical trial with prospective design to evaluate the efficacy of UST in HS therapy. 17 patients with moderate to severe HS (Hurley stage II–III) were included and treated with UST according to the further psoriasis dosing regimen: 45 mg s.c. (increased to 90 mg for patients weighing > 100 kg) at week 0, 4, 16 and 28. Results were promising – moderate to marked improvement of skin lesions (according to modified Sartorius score) was achieved in 82% of patients and the HiSCR in 47% at week 40. Moreover, 41% of subjects demonstrated clinically significant improvement in the DLQI. It was also noticed that the milder course of the disease and the lower leukotriene A4-hydrolase serum concentration were associated with a better response to UST therapy. The most commonly reported adverse events in this study were fatigue, headaches and upper respiratory tract infections.

Despite promising effects of UST in HS therapy, other preparations with better evidence for efficacy, such as ADA or IFX, should be considered first [76]. Regarding its unique mechanism of inhibiting IL-12/23, UST may provide a potential new therapeutic approach for HS in some patients after failure of other therapies.

Secukinumab

Secukinumab (SEC) is a fully human monoclonal antibody and is directed against IL-17A.

Recently published data confirmed that the level of IL-17A in the blood of HS patients is significantly elevated, compared with that found in healthy volunteers and directly correlates with the severity of the disease [77]. The expression of IL-17A was also enhanced in lesional as well as perilesional skin of HS sufferers [78]. IL-17A activates neutrophils and lymphocytes and induces the expression of proinflammatory cytokines including IL-1β, IL-6 and TNF-α. SEC binds with a high selectivity to IL-17A and inhibits the inflammatory cascade [77].

Only three cases have been published on SEC in HS treatment after failure of multiple pharmacologic therapies, including biologics. The drug was administered as a subcutaneous injection at a dose of 300 mg weekly (according to scheme 0-7-14-21-28) and then once a month as a maintenance therapy. In a study by Thorlacius *et al.* [79], the number of lesions reported by a patient was reduced from 23 to 7 and pain VAS from 5 to 3 at week 12 comparing to baseline. During the course of the treatment oral candidiasis occurred in the patient.

In the second case that was reported by Schuch *et al.* [80], a significant decrease in inflammatory nodules, as well as white blood cell count and CRP levels were observed. The patient did not experience any adverse effects related to the administered therapy. Jørgensen *et al.* [81] also reported a marked improvement in a patient treated with SEC, expressed by a remarkable reduction in VAS, DLQI, HSS and IHS4 (International Hidradenitis Suppurative Severity Score) after 6 months of therapy.

Currently, SEC is being tested in a randomized placebo-controlled trial in a group of 21 HS patients who receive 300 mg weekly for 4 weeks followed by 300 mg every 4 weeks. Treatment efficacy will be assessed after 24 weeks and the only outcome in this study is achievement of HiSCR. Its results may be helpful in evaluating the therapeutic approach of targeting Il-17 in HS [82].

Table 2. Ongoing trials on other biologic agents in hidradenitis suppurativa treatment (situation as at 20 June 2018).

Drug	Mechanism of action	Phase of study	US NCT number	Study sponsor
MABp1	IL-1α inhibitor	Phase II	NCT03512275	XBiotech, Inc.
CJM112	IL-17A inhibitor	Phase II	NCT02421172	Novartis Pharmaceuticals
Bimekizumab	IL-17 inhibitor	Phase II	NCT03248531	UCB Biopharma S.P.R.L.

IFX-1

IFX-1 is a first-in-class monoclonal antibody directed against complement factor C5a, which is one of the traditional activation products of the complement cascade. C5a is also involved in the activation of neutrophils and the production of proinflammatory cytokines, including TNF-α. Systemic complement activation occurs in HS. In a recent study it was shown that C5a level is significantly increased in the plasma of patients with HS comparing with healthy controls [83]. However, the negative correlation of circulating C5a concentration with HS severity was observed. Interestingly, C5a level in the plasma of HS sufferers was even greater than concentration reported for patients with severe sepsis or multiple organ failure [83]. IFX-1 by blocking C5a may be, therefore, helpful in regulating the inflammatory response in patients with HS.

In an open-label Phase II clinical trial the safety and efficacy of IFX-1 in HS patients were assessed [82,84]. 12 patients with Hurley Stage III HS were treated with IFX-1 at a dose regimen of 800 mg, administered intravenously on days 1, 4, 8, 15, 22, 29, 36, 43 and 50. As a result, HiSCR score was obtained in a rate of 75% in patients at the end of the treatment period (day 50) and 83% after a 12-week follow-up period (day 134). No adverse effects, allergic or anaphylactic reactions after drug infusion were reported during the course of the treatment.

In light of recent data, IFX-1 appears to be a new promising therapeutic approach for patients with HS who have failed to respond to previous conventional therapies or other biologicals. C5a blockade can become a new therapeutic option in diseases where increased systemic complement activation occurs, in particular HS.

A large randomized, double-blind, placebo-controlled, multicenter Phase II study on a group of 175 patients to estimate the efficacy and the safety of IFX-1 is currently under recruitment [45].

Ongoing trials & future perspective

Despite the large progress, HS therapy often remains a serious challenge. There is still an unmet need for a new treatment options which can be achieved by range of potential targets directed against specific mechanisms. A new Phase II trial for HS management has begun in recent years using a inhibition of the targetable inflammatory pathways which are IL-1α, IL-17 and C5a. These cytokines also seem to be involved in HS pathogenesis, therefore their blockade appears as a new approach to therapy of the condition [45]. Currently several new biological preparations are being investigated, including MABp1, CJM112 and bimekizumab. The results failed with the drug MEDI8968 and the trial has been terminated early because of the lack of efficacy [45]. The investigational drugs for HS which are currently in clinical trials are presented in Table 2 [45].

With one approved biologic available, several drugs under investigation and the ongoing development of novel therapeutic agents that act in different specified pathways in the inflammatory cascade, the future of HS management looks promising. The era of targeted treatment will allow for a more 'personalized' approach directed against predictive biomarkers which dysregulation underlies HS pathomechanism. Certain therapies (currently under active investigation), including agents targeting IL-1 or IL-17 may occur as potentially promising options for HS therapy in the future. The current landscape of biologics promises continuous development of these preparations in the next few years with more innovative methods appearing on the market and offering new therapeutic approaches. Therefore, in the coming years, the final goal should be to improve the currently known preparations as well as search for new drugs and finally to find a balance among efficacy, toxicity and cost of therapy. Comparative studies including different preparations and dosing regimens of biologics would be particularly helpful to enhance their therapeutic effect.

Conclusion

Summarizing, conventional treatment options for HS have largely been disappointing and current systemic therapies for this condition still remain a serious challenge, though great progress has been made in HS management within recent years. A substantial therapeutic need still exists in HS because of its high prevalence and the burden it places on affected patients.

Several cytokines have been found to drive inflammation in HS, including TNF-α, IL-1β, IL-17 and IL-23. Due to the role of immune dysregulation in HS pathogenesis, biologic therapy based on a targeted inhibition of these specific cytokines seems to create a promising option for patients with severe and moderate HS after conventional therapies proved insufficient.

According to current evidence, TNF-α inhibitors, especially ADA and IFX were found to be an effective and tolerable treatment modality for HS and appeared to significantly improve patients' QOL. Variable results have been seen with the use of other biologics in HS management, including ETA, ANA, UST, SEC and IFX-1. However, other agents still require more rigorous examination to be established as a therapeutic approach for this condition. Available data report usually good tolerance of biologics with mostly mild adverse events noticed. The results of the published studies on biologics in HS therapy are summarized in the Supplementary tables.

Up to date, ADA still remains as the only FDA/EMA-approved biologic drug in HS treatment and should be considered first, but other biologicals also play a increasing role in off-label therapy. Future large randomized controlled trials are needed to further establish the efficacy and safety profile of biologic agents in HS management.

Executive summary

Background

- Hidradenitis suppurativa (HS) is a chronic, debilitating dermatosis with occurrence of suppurative lesions, sinus tracks and scarring.
- Pathogenesis is multifactorial and a pilosebaceous unit occlusion, hyperkeratinization and bacterial superinfection play a key role.
- Several comorbid disorders (including immune-mediated inflammatory diseases), decreased quality of life and chronic pain appear in HS patients.
- Treatment of the condition is challenging- topical and systemic antibiotics, retinoids and hormone therapy are most commonly used, while biologics create a new promising option.

TNF-α inhibitors

- TNF-α seems to play a significant role in the pathogenesis of HS.
- Increased levels of TNF-α were found both in blood and skin lesions of patients suffering from HS.
- However, no significant difference was found in cytokine concentration before and after treatment with TNF-α inhibitors.

Adalimumab

- By blocking the biological activity of TNF-α, adalimumab (ADA) regulates the innate immune response and affects the levels of other proinflammatory cytokines, including Il-6, Il-8, Il-1β and sTNF-RI.
- The first reports about the efficacy of ADA on HS came from several case series and the effects were satisfactory but in a retrospective studies conducted by different authors, the results were contradictory due to ADA effectiveness.
- In randomized, double-blind, placebo-controlled trials, including one multicenter study, ADA appeared to be well tolerated and effective, especially when administered 40 mg every week.
- ADA is the only biologic agent approved by the and EMA for therapy of moderate to severe HS.

Infliximab

- Infliximab (IFX) is another monoclonal antibody that works against TNF- α and was found to decrease disease severity and improve patients' quality of life.
- In only one randomized, double-blind, placebo-controlled study conducted on a group of 38 patients, a significantly greater number of patients treated with IFX achieved at least 50% improvement in skin lesions compared with placebo.
- In the comparative study, IFX occurred to be more effective in all aspects than ADA with a mean 54% decrease in Sartorius score compared with baseline.

Etanercept

- Promising results regarding the efficacy of etanercept (ETA) (which is another TNF- α inhibitor) in HS therapy were obtained in several case series, as well as, in open cohort studies.
- However, the results were unsatisfactory in only one RCT trial and there was no significant difference in patient global assessment, physician global assessment or quality of life between ETA and placebo groups.

Anakinra

- Anakinra (ANA) is an IL-1 receptor antagonist which was originally registered for the treatment of moderate to severe rheumatoid arthritis.
- One author when assessing the efficacy of ANA in HS therapy in a group of 6 patients reported a clinically significant improvement of disease severity and a mean decrease of modified Sartorius Score in this study was 34.8 points.

- In a larger randomized double-blind, placebo-controlled clinical trial 78% of patients treated with ANA achieved a good clinical response which confirmed ANA as a potentially efficacious management of HS.

Ustekinumab

- Ustekinumab (UST) regulates specific components of the immune system by inhibiting (IL)-12 and IL-23, which were found to be increased in lesional skin of HS sufferers.
- According to results of several case reports including, in total, six patients, different outcomes were achieved from no treatment effect to complete response to UST therapy.
- In the only open-label clinical trial on UST efficacy, moderate to marked improvement of skin lesions (according to mSs) was achieved in 82% and the Hidradenitis Suppurativa Clinical Response in 47% of patients.

Secukinumab

- Secukinumab (SEC) inhibits the inflammatory cascade by working against IL-17A, of which, expression was found to be significantly enhanced both in the blood and the skin of patients with HS.
- Three cases have been published on SEC in HS treatment – the effects were satisfactory and all patients experienced a marked improvement in the course of the disease within a few months.
- Currently, SEC is being tested in a randomized placebo-controlled trial in a group of 21 patients.

IFX-1

- IFX-1 is an antibody directed against complement factor C5a, which is one of the activation products of the complement cascade and is notably increased in the plasma of HS patients.
- In an open-label Phase II clinical trial the efficacy of IFX-1 in HS patients was assessed and as a result Hidradenitis Suppurativa Clinical Response score was achieved in a rate of 75% in patients at day 50 and 83% at day 134.

Ongoing trials & future perspective

- Currently several new biological agents are being investigated in HS therapy, including MABp1, CJM112, bimekizumab and secukinumab.
- Novel biological agents targeted against specific elements of proinflammatory cascade, including IL-1α, IL-17 and C5a may occur as potentially promising options for HS therapy in the future.

Conclusion

- Several cytokines have been found to drive inflammation in HS, including TNF-α, IL-1β, IL-17 and IL-23 and their targeted inhibition appears to create a promising option for patients with severe and moderate HS after a failure of conventional therapies.
- TNF-α inhibitors, especially ADA and IFX were found to be effective and in general well tolerated therapy for HS and still more rigorous evaluation is needed for other agents

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Supplementary data

To view the supplementary data that accompany this article please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2018-0090. References 85–121 refer to the supplementary tables.

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