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Assessment of the efficacy of biological treatment in acne inversa

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ABSTRACT

Acne inversa is a chronic, progressive inflammatory skin disease. It is characterized by the occurrence of relapsing, painful, deep-seated nodules, abscesses, fistulae, sinus tracts, and scars in the axilla, inguinal area, submammary folds, and perianal area. The disease significantly affects patients' quality of life and is often associated with severe, debilitating pain and depression. Pro-inflammatory cytokines such as TNF-α, interleukin 17 (IL-17), IL-23, IL-12, IL-1α, and IL-1β play a significant role in the pathogenesis of hidradenitis suppurativa. Treatment is difficult and often ineffective, based on both surgical and pharmacological methods. Biologic drugs in hidradenitis suppurativa are the subject of many clinical trials and may be effective in patients for whom other therapies have failed. The first biological drug approved by the Food and Drug Administration for the treatment of hidradenitis suppurativa was the TNF-α inhibitor — adalimumab. The advancement of knowledge of immune mechanisms in the pathogenesis of hidradenitis suppurativa has allowed the development of clinical trials of new therapeutic targets. In 2023, the Food and Drug Administration (FDA) approved the IL-17 inhibitor — secukinumab as the second biological drug in hidradenitis suppurativa. The aim of this review is an update of the biological treatment and its effectiveness in hidradenitis suppurativa.

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Keywords: hidradenitis suppurativa, biological treatment, TNF-α inhibitors, IL-17 inhibitors, IL-23 inhibitors, IL-1 inhibitors

INTRODUCTION

Hidradenitis suppurativa (HS) also known as acne inversa is a chronic inflammatory skin disease. This disease is characterized by chronic deep-seated nodules, abscesses, fistulae, sinus tracts, and scars in the axilla, inguinal area, submammary folds, and perianal area [1]. It significantly impacts patients' quality of life and is accompanied by pain and depression. Mostly it affects adults, but paediatric cases are also known [2]. Prevalence of HS is unknown, but estimates range from 0.00033–4.10%. HS is more than twice as common in women compared to men and is more common in African, Americans and biracial individuals than Caucasians [1]. HS is diagnosed clinically. There are several HS classification systems. The Hurley staging system classifies HS into 3 stages and it was originally developed in choosing treatment for specific areas of the body. The Sartorius system includes 1 — the area of the body, 2 — the number and types of lesions, 3 — the longest distance between two lesions, and 4 — whether all lesions are clearly separated by normal, intact skin. Hidradenitis Suppurativa Clinical Response (HiSCR) is designed to assess treatment response. The International Hidradenitis Suppurativa Severity Score System (IHS4) is the most widely used by physicians. The IHS4 is a validated instrument that scores lesions into three categories: inflammatory nodules, abscesses and draining tunnels. The IHS4 score is qualitatively interpreted as "mild", "moderate" or "severe" [3]. The Hidradenitis Suppurativa Severity Score Index (HSSI) scores disease activity and severity. The Physician's Global Assessment has been adapted into an HS-specific version (HS-PGA). Treatment for HS is multi-directional, including patient education, pharmacology treatment (antibiotics, retinoids, immunosuppressants and anti-inflammatory drugs) and surgical therapy [4].

TNF-α INHIBITORS

Tumour necrosis factor (TNF-α) is a cytokine secreted by macrophages, T lymphocytes and NK cells. There are two forms of TNF-α: soluble (sTNF-α) and transmembrane

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(tmTNF-α) [5]. Higher levels of TNF-α have been shown in the skin lesions and blood serum of HS patients compared to the healthy population [6]. TNF-α plays a significant role in the pathogenesis of acne inversa. It promotes polarization of Th17 lymphocytes leading to increased production of pro-inflammatory cytokines. In addition, it inhibits the secretion of adiponectin, which has anti-inflammatory effects and regulates blood glucose levels [7]. Biological drugs that inhibit TNF-α are used in the treatment of HS.

Adalimumab

Adalimumab (ADA) is a human recombinant IgG1 monoclonal antibody directed against both soluble and trans-membrane TNF-α [6]. Until October 2023, it was the only biologic drug approved for the treatment of HS by the FDA [8]. By binding to TNF-α, it regulates levels of pro-inflammatory cytokines [including interleukin 6 (Il-6), Il-8, Il-1β and soluble tumour necrosis factor receptor (sTNF-R)] and reduces levels of inflammatory white blood cells [9]. ADA is registered for the treatment of moderate to severe acne inversa [10]. ADA is administered subcutaneously, dosing includes a saturating dose of 160 mg, 80 mg in the second week of treatment, and a maintenance dose of 40 mg weekly [11]. Two randomized phase III trials (PIONEER I and II) evaluated the efficacy and safety of ADA in the treatment of HS. The trials included 307 and 326 patients with moderate to severe acne inversa. Treatment efficacy was evaluated by the HiSCR score, described as a reduction of at least 50% in the number of abscesses and inflammatory nodules, with no increase in the number of abscesses or fistulas compared to baseline. Patients treated with ADA and placebo were compared after 12 weeks. Both studies showed that a significantly higher percentage of patients treated with ADA achieved HiSCR compared to placebo (PIONEER I 41.8% *vs.* 26.0%, PIONEER II 58.9% *vs.* 27.6%). In addition, a higher percentage of patients receiving ADA achieved more than 30% pain reduction in the Patient's Global Assessment of Skin Pain (PGA-SP) score [11, 12]. Zouboulis et al. [13] in a study assessing the long-term efficacy of ADA showed a significant improvement in the Dermatology Life Quality Index (DLQI) at week 72 of treatment. Among patients who continued ADA treatment, the HiSCR rate at week 168 was 52.3% [11, 13]. The most commonly reported adverse effects of ADA therapy include injection site reactions, upper respiratory tract infections, headache, rash, and sinusitis [14].

Infliximab

Infliximab is a chimeric human-mouse monoclonal antibody directed against TNF-α. It binds the soluble and transmembrane form of TNF-α [7]. Infliximab has not been approved by the FDA for the treatment of acne inversa; however, its efficacy in this disease is being studied [15]. Shih et al. [16] in a meta-analysis based on 19 clinical trials showed that the overall response rate to infliximab treatment in HS was 83%. In the vast majority of studies, patients received 5–10 mg/kg of infliximab every 4–8 weeks. Adverse effects of therapy mainly include skin reactions at the injection site, pruritus, headache, and nausea [17]. In addition, flu-like symptoms, abscesses, and superinfection of skin lesions have also been described. Very rarely, anaphylactic shock, sepsis, tuberculosis and the development of malignancy have been reported [16].

Certolizumab

Certolizumab is a recombinant humanized Fab fragment of an antibody directed against TNF-α. By binding both the soluble and trans-membrane forms of TNF-α, it reduces the activity of cellular adhesion molecules, chemokines and pro-inflammatory mediators. Because it does not pass through the placenta, it can be used during pregnancy [18]. Shadid et al. [19] summarized 6 case reports in which 7 patients with HS were treated with certolizumab. All of the patients described had previously undergone biological treatment or antibiotic therapy without significant improvement or with only minimal improvement. The dosage of certolizumab varied from case to case, but in general, was based on 200 mg every two weeks or 400 mg every two weeks. In all cases, clinical improvement was reported after the initiation of certolizumab, and no serious side effects were registered. Certolizumab may provide an alternative treatment for pregnant patients with HS. Despite the promising results, further larger studies on the administration of certolizumab in HS are needed [7].

Golimumab

Golimumab is a human IgG1 monoclonal antibody that binds with high affinity to both the soluble and transmembrane forms of TNF-α [5, 6]. In a 2013 case report, a patient with HS was treated with golimumab 50 mg *subcutaneous* (*s.c.*) once a month, and treatment was continued for 8 months. This therapy did not result in clinical improvement [5, 20]. Tursi [21] described a case of a patient suffering from acne inversa stage II according to Hurley. In addition, the patient also suffered from ulcerative colitis (*colitis ulcerosa*) and *pyostomatitis vegetans*. Treatment with golimumab was initiated at an initial dose of 200 mg subcutaneously, followed by 100 mg *s.c.* every 4 weeks. The patient was also receiving amoxicillin with clavulanic acid at a dose of 2 g per day for 2 weeks. After 2 months of treatment, remission of both acne inversa as well as pyostomatitis vegetans and *colitis ulcerosa* was achieved [7, 15]. Ramos et al. [22] presented

a case report of two patients suffering from acne inversa and arthritis in whom golimumab was included after treatment with ADA was not successful. Clinical improvement was achieved in both cases [6, 22]. In a retrospective cohort study by Melendez-Gonzalez et al. [23] in a group of 13 patients with acne inversa and non-response to ADA or infliximab, golimumab was included. In 9 patients, the collected data allowed the evaluation of HiSCR; in this group, 6 patients achieved HiSCR. In addition, the IHS4 score decreased significantly in the described cohort [23]. Golimumab may be an alternative treatment method for HS, especially after the unsuccessful treatment with ADA. However, further studies on the use of this drug in HS are necessary [6].

Etanercept

Etanercept is a recombinant protein that is a combination of two soluble TNF receptor subunits (p75) with the Fc domain of human IgG1 [7]. It binds to TNF-α and inhibits its activity [15]. The use of etanercept in the treatment of HS was evaluated in a randomized, double-blind, placebo-controlled clinical trial. The study included 20 patients with moderate to severe HS. Etanercept was administered 50 mg in a twice-weekly dose. There was no significant difference in Physician Global Assessment PGA (PGA) and DLQI between the etanercept and placebo groups [6, 24].

IL-17 INHIBITORS

Over the past few years, IL-17 has emerged as a key player in many inflammatory diseases [25]. It stimulates neutrophils, monocytes, and Th17 lymphocytes and triggers the expression of other pro-inflammatory factors, further increasing IL-17 production and immune cell infiltration in HS lesions in a feed-forward inflammatory loop [26]. In the lesional dermis of patients suffering from HS, IL-17 is elevated compared to control skin [27]. IL-17 levels are also higher in serum and correlate with disease severity [28]. These findings likely underlie the observed therapeutic effect of IL-17 inhibitors in this disease.

Secukinumab

Secukinumab is a human monoclonal antibody that selectively binds to and inhibits IL-17A. It is approved for the treatment of moderate to severe plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and active non-radiographic axial spondyloarthritis [29]. In October 2023, the FDA approved the drug for the treatment of moderate to severe forms of acne inversa, and it has also been approved by the European Commission [8]. The presence of a second approved biologic therapy alongside ADA offers hope to patients for whom conventional treatment has been ineffective or impossible due to contraindications to previously known drugs. The efficacy of secukinumab has been widely discussed in the literature giving Prussick et al. [30] found that 55.5% (5/9) of patients achieved HiSCR at week 16 and 67% (6/9) at week 24. Casseres et al. [31] reported that 65% (13/20) of patients achieved HiSCR at week 12. Reguiaï et al. [32] showed that 75% of patients (15/20) achieved HiSCR at week 16. Ribero et al. [33] concluded that 26% (8/24) of patients achieved HiSCR at week 16 and 41% (7/17) at week 28. Melgosa et al. [34] recruited 23 patients and 73.9% (17/23) achieved HiSCR at week 16, 71.4% (15/21) at week 24, 71.4% (10/14) at week 36 and 83.3% (10/12) at week 52. Fernandez-Crehuet et al. [35] described patients mainly with stage III Hurley HS, 48.9% (23/47) of whom achieved HiSCR at week 16. In addition, the possible influence of female gender, lower body mass index (BMI) and lower treatment burden on a positive treatment outcome was noted. Promising results were confirmed by two phase III randomised, placebo-controlled, double-blind clinical trials, SUNSHINE and SUNRISE, which compared the efficacy of secukinumab at every 2 weeks and every 4 weeks versus control. In the 541-patient SUNSHINE study, 45% of patients receiving every 2-week dose achieved HiSCR at week 16, which was significant compared to placebo — 34%. In patients receiving the drug every 4 weeks, 42% achieved HiSCR, but this was not significant compared to placebo. The 543-patient SUNRISE study showed HiSCR in 42% of patients receiving the drug every 2 weeks and in 46% of patients receiving the drug every 4 weeks, observed after 16 weeks of treatment and in both cases significantly better than placebo (31%). When reassessed after 52 weeks of treatment in both clinical trials, 76% (SUNSHINE) and 84% (SUNRISE) of patients receiving the drug every 2 weeks and 81% (SUNSHINE) and 77% (SUNRISE) of patients receiving the drug every 4 weeks maintained the therapeutic effect. Side effects can include headache, nasopharyngitis, fungal infections, inflammatory bowel disease and worsening of acne inversa [36]. A multi-centre extension study, continuing both the SUNRISE and SUNSHINE trials, is designed to evaluate the maintenance of HiSCR responses at week 104 with two dose regimens and to assess long-term safety and tolerability as measured by adverse events [37]. However, the results of this large study are still awaited. Martora et al. [8] recently designed a prospective real-life study that confirmed the efficacy and safety of treatment with secukinumab. The trial included 21 patients with severe HS, 17/21 of whom had failed ADA. Results showed that 57.1% of patients achieved HiSCR at week 16, and this increased to 71.4% at week 52. However, real-life studies with large numbers of samples are still limited and a comprehensive study of different clinical outcomes is needed.

Bimekizumab

Bimekizumab is a monoclonal antibody that selectively blocks IL-17A, but also IL-17F, which may result in a broader and therefore more effective therapeutic profile of this drug [38]. Glatt et al. [39] assigned 90 patients with mild to severe HS to bimekizumab, placebo or ADA in a 2:1:1 ratio in a randomised phase II trial. To demonstrate efficacy, they assessed both HiSCR, HiSCR75 and HiSCR90 (≥ 75% or ≥ 90% reduction in total abscess and inflammatory nodule counts from baseline), as well as the PGA-SP and the DLQI. HiSCR was achieved by 57.3% of patients on bimekizumab compared to 26.1% on placebo. HiSCR75 was achieved by 46% and HiSCR90 by 32% compared to 10% and 0% in the placebo group and 35% and 15% in the ADA group. All treatment groups had a similar number of adverse events, most of which were mild or moderate. In the current randomised, placebo-controlled, phase III BE HEARD I and BE HARD II studies, which included 505 and 509 patients respectively, 48% and 52% of patients achieved a significant clinical improvement (HiSCR50) compared to placebo, with an enhancement in quality of life at week 16 that remained high through the 48-week assessment. In both studies, more than 55% of patients who remained on the drug achieved a higher reference level (HiSCR75) at week 48. The most common adverse events were worsening of HS, headache, oral candidiasis and diarrhoea, and the overall safety profile was consistent with previously reported data [40]. A comprehensive meta-analysis by Tsai et al. [41] confirms the efficacy of bimekizumab, placing it in second place behind ADA when HiSCR values achieved by both drugs are considered, and in first place when DLQI scores at weeks 12–16 are considered.

Brodalumab

Brodalumab is a human IgG2 monoclonal antibody that interacts with the A subunit of the IL-17 receptor (IL-17RA), thereby stopping signalling by multiple IL-17 isoforms (IL--17A, IL-17F, IL-17C and IL-17 A/F) [42]. It is currently approved for the treatment of moderate-to-severe plaque psoriasis. Frew et al. [43] in 2020 treated 10 patients with moderate to severe HS and 100% of them achieved HiSCR at weeks 12 and 24. No adverse effects were reported, but 2/10 patients experienced relapse after the saturating dose period. In 2021, the same investigators evaluated the effect of brodalumab in a group of 10 patients with moderate to severe HS, including 7 from a previous report. HiSCR was achieved at week 4 in the entire cohort and no relapses or adverse events were documented during the 24 weeks of treatment [44]. Yoshida et al. [45] described the results of a patient with long-term refractory HS and psoriasis, in whom brodalumab therapy proved effective against both diseases. Arenbergerova et al. [46] described a case of severe extensive gluteal HS after failed anti-TNF-alpha therapy, in which brodalumab was followed by marked clinical improvement, reduction of inflammatory lesions, decrease in IHS4 scores from 62 to 18, DLQI from 17 to 5, and a decrease in exponents indicating systemic inflammation [46]. Kearney et al. [47] described the cases of 8 patients previously treated with biologics without success. They were treated with brodalumab every other week, 7/10 reported a decrease in DLQI from 20.6 to 16.8 at week 16, 1/10 did not respond to the drug, 3/10 experienced secondary treatment failure, and their treatment was changed to guselkumab. Vagnozzi et al. [48] described the case of a patient suffering from HS (Hurley grade III, IHS 56, DLQI 28, VAS 10) and pustular psoriasis of the palms and soles, previously treated unsuccessfully with ADA, infliximab and etanercept. Due to the failure of multiple therapies and the coexistence of two diseases, treatment with brodalumab with acitretin was included. The acitretin was discontinued after 24 weeks due to the rapid resolution of the psoriasis lesions. HiSCR was achieved as early as week 12, and IHS4 was 20. At reassessment at week 48, IHS4 was 10, and improvements in pain (VAS 3/10) and quality of life (DLQI 8) were also achieved. At week 136, complete remission of active HS symptoms in the axillary area and low disease activity in the groin and perineal area was observed, achieving an IHS4 of 5, a VAS of 1, and a DLQI of 4. The study additionally included an MRI evaluation of the lower abdomen and pelvis, which confirmed improvement in acne lesions not seen on clinical examination [48]. Osorio-Gómez et al. [49] recently published a study involving 16 patients with moderate to severe HS. At week 16 of brodalumab treatment, HiSCR was achieved by 50% of them, and IHS4 dropped from 24.13 to 16.81 on average. There were also no serious side effects reported [49]. Brodalumab appears to be effective and safe in patients with moderate to severe HS, even in those who have not responded to previous biologic treatment and therefore represents a promising treatment option for HS.

CJM112

CJM112 is a human IgG1/κ monoclonal antibody with the ability to bind to IL-17A and IL-17AF with similar affinity. The 16-week, double-blind, placebo-controlled Phase II study involved 66 participants with moderate to severe HS. At week 16, 32.3% of the CJM112 group had a reduced HS-PGA score compared to 12.5% of the placebo group. However, a further 16 weeks of follow-up showed a greater-than-expected placebo effect. Finally, there were no significant differences in HS-PGA scores between the groups studied. CJM112 was generally well tolerated, and its safety profile was similar to placebo. The most common adverse events were nasopharyngitis, nausea, diarrhoea and

Table 1. Summary of biologic drugs used in the treatment of hidradenitis suppurativa

Target	Drug	Approved by FDA in HS	Other diseases	Dosage	Pregnancy	References
TNF-α	Adalimumab	+	• Rheumatoid arthritis • Juvenile idiopathic arthritis psoriatic arthritis • Ankylosing spondylitis • Crohn's disease • Plaque psoriasis • Ulcerative colitis • Hidradenitis suppurativa (HS) • Uveitis	160 mg *s.c.* at week 0, 80 mg *s.c.* at week 2, 40 mg *s.c.* at week 4 and 40 mg *s.c.* every week or 2 weeks	–	[10]
TNF-α	Infliximab	–	• Inflammatory bowel disease (IBD) • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis	5–10 mg *i.v.* every 4 or 8 weeks	–	[7]
TNF-α	Certolizumab	–	• Crohn's disease • Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis • Plaque psoriasis	200–400 mg *s.c.* every 2 weeks	+	[7, 19]
TNF-α	Golimumab	–	• Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis • Ulcerative colitis	200 mg *s.c.* at week 0, 100 mg *s.c.* every 4 weeks or 200 mg at week 0, 2 and every 4 weeks	–	[7, 23]
TNF-α	Etanercept	–	• Rheumatoid arthritis • Plaque psoriasis • Psoriatic arthritis • Juvenile idiopathic arthritis • Ankylosing spondylitis	50 mg *s.c.* every 2 weeks	–	[9]
IL-17	Secukinumab	+	• Hidradenitis suppurativa • Plaque psoriasis • Psoriatic arthritis • Ankylosing spondylitis • Axial spondyloarthritis • Juvenile idiopathic arthritis	300 mg *s.c.* every 2 or 4 weeks	–	[7, 36]
IL-17	Bimekizumab	–	• Plaque psoriasis • Psoriatic arthritis • Axial spondyloarthritis	320 mg *s.c.* every 2 or 4 weeks	–	[40, 50]
IL-17	Brodalumab	–	Plaque psoriasis	210 mg *s.c.* every week	–	[7, 44]
IL-17	CJM112	–	–	300 mg *s.c.* for the first 5 weeks and then every 2 weeks	–	[50]
IL-17	Isokibep	–	–	160 mg *s.c.* every week	–	[50]
IL-17	Sonelokimab	–	–	120 mg and 240 mg *s.c.*	–	[50]
IL-23	Guselkumab	–	Plaque psoriasis	100 mg *s.c.* at week 0 and 4 and every 8 weeks	–	[7, 54]
IL-23	Tildrakizumab	–	Plaque psoriasis	100 mg *s.c.* at week 0 and 4 and then 200 mg every 4 weeks	–	[57]
IL-23	Risankizumab	–	• Psoriatic arthritis • Psoriasis	150 mg *s.c.* at week 0 and 4 and every 12 weeks	–	[7]
IL-23/ /IL-12	Ustekinumab	–	• Psoriatic arthritis • Plaque psoriasis • Crohn's disease	45 mg *s.c.* or 90 mg *s.c.* if weight > 100 kg at week 0, 4, 16, 28	–	[10]
IL-1	Anakinra	–	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes • Interleukin-1 receptor antagonist deficiency	100 mg s.c. or 200 mg daily	–	[9, 10, 69]
IL-1	Canakinumab	–	Periodic fever syndromes, active Still's disease, gout flares	Every week/4 weeks/8 weeks — 150 mg *s.c.*	–	[7,74,75]
IL-1	Bermekimab	–	–	7.5 mg/kg every 14 days up to 7 infusions	–	[7,10]

IL — Interleukin; HS — hidradenitis suppurativa; IBD — inflammatory bowel disease; *s.c.* — subcutaneous

headache. The incidence of nasopharyngitis and nausea was higher in the CJM112 group compared to the placebo group [50].

Isokibep

Isokibep is a selective, potent IL-17A inhibitor developed using affibody molecules containing small triple-helical protein domains. It is a novel subcutaneous drug with a small molecular size that greatly enhances biodistribution to inflamed tissue. Isokibep was used in a randomised, double-blind phase IIb study in patients with moderate to severe HS. HiSCR were assessed in 180 patients at weeks 12 and 16, and initial observations at week 12 showed that HiSCR50 was achieved by 71% of participants, HiSCR75 — 57%, HiSCR90 — 38% and HiSCR100 — 33%. Side effects were mainly injection site reactions and one patient was reported to have developed inflammatory bowel disease. Recruitment is ongoing in a double-blind, placebo-controlled Phase III study to assess the proportion of patients with HiSCR75 at week 16 [50].

Sonelokimab

Sonelokimab is a novel trivalent nanobody (a new class of proteins based on single-domain antibodies) that is specific for IL-17A, IL-17F and human serum albumin. Due to the presence of serum albumin, drug concentrations at sites of inflammatory swelling can be increased. A phase II study of 234 participants with severe HS evaluated the efficacy and safety of sonelokimab in two dosing regimens (120 mg and 240 mg) compared to placebo and ADA. The results of the study showed that a higher proportion of patients treated with sonelokimab reached HiSCR75 at week 12 of the study. Additional secondary endpoints, such as HiSCR90 and IHS4, also showed statistically significant results remaining favourable safety profile [50].

IL-23 INHIBITORS

IL-23 is a pro-inflammatory cytokine essential for the differentiation of Th17 lymphocytes [51]. The IL-23/Th17 axis is implicated in the pathogenesis of acne inversa, which contributes to chronic inflammation. Schlapbach et al. [27] showed that skin lesions occurring in acne inversa are characterised by overexpression of IL-23 and IL-12 in macrophages infiltrating the papillary and reticular layers of the skin. Due to the significant role of the IL-23/Th17 signalling axis in acne inversa, anti-IL-23 antibodies may be an effective therapy [52].

Guselkumab

Guselkumab is an IgG1 lambda monoclonal antibody against IL-23, approved for the treatment of psoriatic arthritis and plaque psoriasis, but several studies are showing its efficacy in the treatment of acne inversa [53]. A pilot study by Repetto et al. [54] evaluated the efficacy of HS treatment with antibodies against IL-17 (secukinumab) and IL-23 (guselkumab, risankizumab) after ADA failure or side effects preventing its use. The study included 26 adult patients (16 treated with anti-IL-17 and 10 with anti-IL-23) with Hurley grade ≥ 2 disease severity. The drugs were administered at the dosage approved for the treatment of psoriasis (300 mg at weeks 0–4 and then every 4 weeks for secukinumab, 150 mg at week 0.4 and every 12 weeks for risankizumab, 100 mg at week 0.4 and every 8 weeks for guselkumab). Eight patients taking anti-IL-17 and 1 patient taking anti-IL-23 discontinued therapy due to inefficacy. DLQI, HiSCR and IHS4 were assessed. In the case of anti-IL-23 antibodies, a significant improvement in IHS4 was observed after 12 months. In turn, there was an improvement in DLQI in both groups and no severe side effects were reported. At 6 months of treatment, patients taking anti-IL-23 presented a better response compared to anti-IL-17 (HiSCR for anti-IL-23 was achieved by 90% of patients) [54]. A retrospective study regarding the effectiveness of guselkumab in the treatment of HS was conducted in Spain between 2020 and 2022. It included mostly patients with Hurley III. HiSCR was achieved in more than half of the patients [55]. The literature also presents numerous case reports of HS treatment with guselkumab. One of these is the case of a 17-year-old male suffering from Hurley stage II HS, who received guselkumab at the therapeutic dosage approved for psoriasis (100 mg at week 0 and 4 and every 8 weeks thereafter). The patient achieved HiSCR at week 16 of treatment and clinical response was maintained at follow-up after 52 weeks. No adverse effects associated with guselkumab therapy were observed [53]. In the phase II study by Kimball et al. [55], despite an improvement in HiSCR in patients treated with guselkumab, no statistical significance level was reached.

Tildrakizumab

Tildrakizumab is a humanised monoclonal antibody targeting the p19 subunit of IL-23. Clinical cases are confirming the efficacy of tildrakizumab in the treatment of HS. One of them is the case of a 38-year-old man with HS and plaque psoriasis, who showed a clinical response after treatment with tildrakizumab in a dose of 200 mg [56]. Kok et al. [57] described a case series of 5 patients treated with tildrakizumab 100 mg at weeks 0 and 4 and then 200 mg every 4 weeks. DLQI and number of skin lesions were assessed at week 8 and 20. Quality of life improved in all cases, but further studies including a larger group of patients and parameters such as IHS4 and HiSCR are needed to assess the efficacy of HS therapy with tildrakizumab.

Risankizumab

Risankizumab is also an anti-IL-23 antibody approved by the FDA for the treatment of plaque psoriasis, psoriatic arthritis and Crohn's disease. Studies of its efficacy in the treatment of HS are currently underway. The phase II study by Kimball et al. [58] involved 243 moderate to severe patients. Patients received risankizumab at a dose of 180 mg or 360 mg. After 16 weeks, the efficacy of the treatment was assessed. The percentage of patients taking risankizumab who achieved HiSCR did not differ from patients taking a placebo, which led to the earlier termination of the study [58]. Repetto et al. [59] described a case series of 6 patients treated with risankizumab at the therapeutic dose for psoriasis. The study included 4 patients in Hurley III and 2 patients in Hurley II. All patients achieved clinical improvement and a reduction in IHS4. 3 patients achieved HiSCR after 3 months of treatment and 3 after 6 months. None of the patients reported adverse symptoms. Despite the proven efficacy of risankizumab in the treatment of HS in many case reports, the phase II study does not confirm its effectiveness [58, 59].

IL-12/23 INHIBITOR

Ustekinumab

Ustekinumab is an IgG1κ monoclonal antibody directed against the p40 subunit common to IL-23 and IL-12 preventing their interaction with the β1 subunit of the IL-12 receptor [60]. The interaction of IL-12 and IL-23 with the receptor protein activates the JAK/STAT pathway, which consequently leads to increased inflammation of the skin lesions [61]. It has been shown that certain variants of the IL-12RB1 gene are associated with a more severe form of HS [62]. Montero Vichez et al. assessed the efficacy of treatment of acne inversa with ustekinumab in patients with Hurley II–III. Patients received a dosage of ustekinumab approved for the treatment of psoriasis. Disease severity was assessed with the HS-PGA and pain severity with the Numerical Rating Scale (NRS) before therapy and every four weeks thereafter. The primary endpoint was a > -1 point reduction in HS-PGA and the secondary endpoint was a $> -20\%$ reduction in NRS. Seventy per cent of patients had an improvement in HS-PGA and 80 per cent had an improvement in NRS. Patients did not report any serious adverse effects. The obtained results may prove the efficacy of ustekinumab therapy in patients after unsuccessful first-line treatment [63]. Blok et al. [64] carried out a prospective study including 17 patients who received ustekinumab at a dosage of 45 mg or 90 mg for patients weighing over 100 kg. Ustekinumab was administered at weeks 0, 4, 16, and 28 with follow-up at week 40. The most common adverse effects were headache, fatigue and upper respiratory tract infections. At follow-up after 40 weeks, 82% of patients achieved improvement in modified Sartorius Score (mSS) and 47% of patients achieved HiSCR [64].

IL-1 INHIBITORS

IL-1 receptor antagonists block the inflammatory response of the proinflammatory cytokine IL-1 [17]. IL-1, similarly to TNF-α, is one of the major mediators of the inflammatory response that is also involved in the pathogenesis of HS [65]. This group of drugs includes anakinra, bermekimab and canakinumab.

Anakinra

Anakinra is a recombinant IL-1 receptor antagonist. It blocks the biological activity of naturally occurring IL-1 by competitively inhibiting the binding of both IL-1α and IL-1β to the IL-1 type 1 receptor [66]. So far, this drug has been approved by the FDA for the treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes and interleukin-1 receptor antagonist deficiency. Although the FDA has not approved Anakinra for the treatment of acne inversa, there are studies reporting its effectiveness [67, 68]. In double-blind, randomized, placebo-controlled prospective clinical trial in a group of 20 patients with Hurley stage II/III HS showed 78% efficacy of the drug compared to a placebo group of 30%, and no serious side effects were observed [9, 69]. Failures in the treatment of HS with anakinra have also been described [70–72], so further research is needed on the efficacy of this drug in the treatment of HS. In addition, Anakinra is administered by daily subcutaneous injections, which may reduce patients' willingness to use it.

Canakinumab

Canakinumab is a human IL-1 beta antibody. To date, several case reports have been described in which it has been used to treat HS. The results of these cases are divergent [73]. In several cases, significant improvement and regression of HS lesions are described [74–76]. In contrast, another case report describes that the drug did not show efficacy [77], and another even observed a worsening of the lesions [78]. Due to conflicting observations and a small amount of data, longer (long-term) studies are needed to assess its efficacy.

Bermekimab

Bermekimab also known as MABp1 is a human IL-1α monoclonal antibody. It is currently in phase 2 clinical trials for the treatment of rheumatoid arthritis and colorectal cancer [79]. In one phase II, multicentre, open-leben study of two dose cohorts of bermekimab in patients with moderate-to-severe HS who are naïve to or have failed prior anti-TNF therapy the results bermekimab was effective despite treatment history, with 61% and 63% of patients naïve to and having failed anti-TNF therapy, respectively, achieving HS clinical response after 12 weeks of treatment [80].

In another double-blind study in patients who had failed ADA treatment, the efficacy of bermekimab was 60%, compared to 10% in the placebo group. Ultrasonographically, the drug resulted in a reduction in neovascularization and the depth of skin lesions. No serious side effects were observed [81].

CONCLUSIONS

Biological agents are increasingly used in the treatment of many diseases. They are used to treat acne inversa when other treatments are ineffective. FDA-approved biologic drugs for the treatment of HS are ADA and secukinumab. Numerous clinical trials and case series reports indicate the efficacy of biologic therapy in HS, but further studies involving a larger group of patients are needed. In addition, many agents are in clinical trials. Biologic drugs are mostly well tolerated by patients, and side effects are mostly mild, with isolated cases of severe side effects reported.

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Conflict of interest

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