Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Adalimumab, Ustekinumab, and Secukinumab in the Management of Hidradenitis Suppurativa: A Review of the Real-Life Experience

Fabrizio Martora, Matteo Megna*, Teresa Battista*, Luca Potestio*, Maria Carmela Annunziata, Claudio Marasca, Alessia Villani, Gabriella Fabbrocini

Section of Dermatology - Department of Clinical Medicine and Surgery, University of Naples Federico II, Napoli, Italy

*These authors contributed equally to this work

Correspondence: Fabrizio Martora, Section of Dermatology - Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Pansini 5, Napoli, 80131, Italy, Tel +39 - 081 – 7462457, Fax +39 - 081 – 7462442, Email fabriziomartora92@libero.it

Abstract: To date, adalimumab (ADA) is the only biotechnology drug approved for the management of hidradenitis suppurativa (HS), an inflammatory skin condition. However, it quickly became apparent that the efficacy of adalimumab in daily practice was highly variable. In our review, we highlighted the current evidence from literature on the use of biologics in HS in a real-life setting, particularly adalimumab, secukinumab and ustekinumab. Data on the effectiveness and safety of biologic drugs in HS management have been analyzed. Even if the results are promising, more studies are needed. In our opinion, the armamentarium of drugs for HS management is increasing, and treatment will be based on a tailored-tail approach, minimizing the risk of adverse events. In this context, we want to point out the reported effectiveness and safety data concerning adalimumab, ustekinumab and secukinumab as well as ixekizumab.

Keywords: hidradenitis suppurativa, adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, real life evidence

Introduction

Hidradenitis Suppurativa (HS) is a chronic, relapsing inflammatory skin condition.[1–3] It is characterized by the occurrence of nodules, often inflammatory, deep and painful, especially at skin regions with a high density of apocrine sweat glands such as the axillary, inguinal, and sub mammary regions.[1]

As regards HS pathogenesis, HS is a multifactorial disease in which genetic and environmental factors play a key role.[4,5] The primary defect in HS pathophysiology involves follicular occlusion of the folliculopilosebaceous unit, followed by follicular rupture, and immune responses (perifollicular lympho-histiocytic inflammation), finally leading to the development of clinical HS lesions.[4,5] Moreover, cutaneous microbiota seems to be involved in HS pathogenesis.[6]

HS is associated with several other pathological conditions. These include Obesity, Metabolic Syndrome, and autoimmune disorders such as Crohn's Disease.[7–10] Patients suffer as much physically as psychologically, with worsening quality of life and a decline in work productivity.[7–10]

To date, adalimumab (ADA) is the only biotechnology drug approved for the condition so registration in 2015 was a major step forward in the treatment of HS. However, it quickly became apparent that the efficacy of adalimumab in daily practice was highly variable.[11–13]

In recent years, studies have been directed toward new therapeutic targets for this condition; bimekizumab and secukinumab drugs are still being studied and would appear to show promising results.[11,12]

Several real-life studies on the use of ADAs in routine clinical practice have been published in the literature.[14–16] Indeed, real-life data are mandatory to improve decision-making in the field of dermatology, as these studies also include

Received: 17 November 2022
Accepted: 12 January 2023
Published: 19 January 2023

patients typically excluded from clinical trials, such as subjects suffering from various comorbidities, subjects on polytherapies and multi-failure patients.[17]

In this review, we conducted a comprehensive literature review of real-life data on adalimumab, ustekinumab, and secukinumab; and a brief report of miscellaneous indicating small experiences with biologic drugs.

Methods

A comprehensive review of the English-language medical literature was performed using the PubMed, Ovid, Scopus, Embase, and Cochrane Library databases from their inception to October 1, 2022, using Medical Subject Headings (mesh) (if applicable) and medical terms for the concepts of adalimumab, ustekinumab, and secukinumab use in a real-life setting. Studies were identified, screened and extracted for relevant data following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1). The search strategy to identify articles was performed using the following search terms: "IL-17 inhibitors", "adalimumab", "secukinumab", "ustekinumab", "ixekizumab", "guselkumab" AND "real life", AND "real world evidence", AND "hidradenitis suppurativa", and combinations thereof. The search involved all fields, including title, abstract, keywords, and full text. Clinical and epidemiological

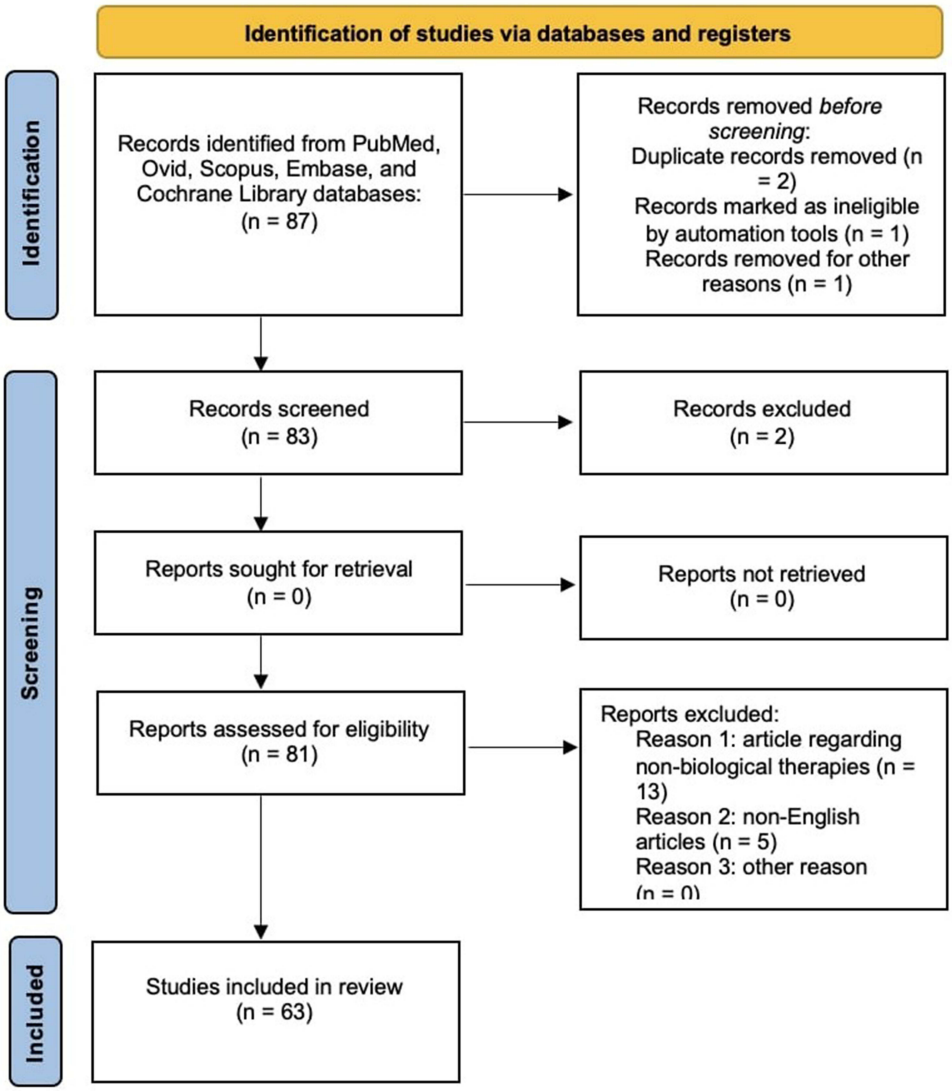

Figure 1 Prisma checklist.

Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372: n71. doi: 10.1136/bmj.n71. Creative Commons.

studies, reviews, and systematic reviews on the use of adalimumab, secukinumab, ustekinumab, and other biologic drugs in a real-world setting were included. Articles published from the first papers published until October 2022 and from any source were considered. Non-English literature was excluded. The article is based on previously conducted studies.

Adalimumab

Adalimumab is an anti-TNF-α IgG1 monoclonal antibody, the only drug currently approved by the FDA in 2015 for hidradenitis suppurativa (HS), administration includes as initial dose 160 mg subcutaneously, followed by an 80 mg dose 2 weeks later and a maintenance dose of 40 mg weekly thereafter.[18]

A Phase II study by Kimball et al showed for the first time that a significantly greater proportion of patients receiving adalimumab weekly (17.6%) than placebo (3.9%) achieved the primary clinical endpoint of an HS-Physician's Global Assessment (PGA) score with at least a two-grade improvement over baseline scores at week 16. This finding was not significantly confirmed in the group of patients who received adalimumab every other week (9.6%) (weekly vs placebo difference 13.7%, p = 0.025; every other week vs placebo difference 5.6%, p = 0.25).[19]

The subsequent Phase III PIONEER I and II studies involved a total of 633 patients with moderate to severe HS with inadequate response to oral antibiotics. A significantly higher percentage of patients administered adalimumab achieved a clinical response to suppurative hidradenitis (HiSCR), defined as a ≥50% reduction in abscess and inflammatory nodule counts, with no increase in abscess and draining fistula counts compared to baseline, compared to patients given placebo after 12 weeks of treatment (PIONEER I: 41.8% vs 26.0%, p = 2 weeks). Eight percent vs 26.0%, p = 0.003; PIONEER II: 58.9% vs 27.6%, p < 0.001).[14] Secondary efficacy data also showed a higher percentage of subjects achieving ≥30% reduction in Patient's Global Assessment of Skin Pain (PGA-SP) in both PIONEER I (adalimumab vs placebo [24.9%]; OR = 2.03, p = 0.004) and PIONEER II (adalimumab [61.2%] vs placebo [24.8%]; OR = 4.78, p < 0.001).[14,20]

An open-label extension study of the PIONEER I and II trials also confirmed previous data-in fact, patients who continued to receive adalimumab weekly had a HiSCR of 52.3% at week 168 and a decrease in Dermatology Life Quality Index (DLQI) of 5.1–6.8 points at week 72, with no new safety risks.[21]

Ryan et al analyzed safety data of adalimumab in HS, no new safety issues were identified with weekly dosing of adalimumab compared with dosing every other week.[22]

In 2021, Marzano et al conducted a multicenter real-life study to evaluate the impact of different clinical parameters on the clinical response to adalimumab in a large cohort of patients with moderate-severe HS at week 16 and week 52 after the initiation of adalimumab.[23] In this multicenter retrospective real-life study, 21 Italian dermatology units were involved and provided demographic and clinical data of patients with moderate-severe HS being treated with adalimumab from January 2016 to December 2018. Data included gender, age at HS onset (≤30, >30–50, >50 years), age at diagnosis (≤29, >29 years), age at adalimumab initiation (≤30, >30–50, >50 years), body mass index (BMI; ≤25, >25–30, >30 kg m-2), smoking (never smoked, current smoker, former smoker), family history of HS, comorbidities, previous and concomitant treatments with adalimumab, and HS phenotypes according to van der Zee and Jemec classification.[23]

Adalimumab response rate was measured at week 16 and week 52 by HiSCR.[23]

Bettoli et al have previously stated that HS duration and diagnostic delay have a negative impact on disease severity.[24] It has been suggested that early treatment with adalimumab positively affects the clinical response to the drug (window of opportunity).[25]

The group of 389 patients with moderate to severe HS treated with adalimumab analyzed by Marzano et al showed a significant inverse correlation between treatment delay and clinical response to the drug at week 16 of treatment 17. This finding confirms that early use of adalimumab in HS increases response to therapy and therefore provides evidence of a "window of opportunity" in this disease.[24,25]

Regarding ultrasound, it can be said that it is useful for diagnosis and treatment monitoring in patients with HS, in this regard Chiricozzi et al[20] conducted a study to evaluate clinical response to adalimumab using ultrasound findings. The study included a total of 41 HS patients on treatment who were treated with adalimumab for a mean period of 50.8 ± 32.2 weeks; range 6–108 weeks).[14] Clinical improvement was observed during adalimumab therapy, with progressively more patients achieving a HiSCR50 response (36.4% at week 52).[26]

HARMONY 21 is a multicenter, postmarketing observational study conducted in adult patients with moderate to severe HS. Disease severity and QoL parameters were assessed using validated measures at 12-week intervals for 52 weeks of treatment. The primary endpoint was the percentage of patients achieving HiSCR at 12 weeks.[27] Secondary endpoints were HiSCR at 24, 36 and 52 weeks and changes in QoL parameters and work productivity ratings. Treatment of moderate to severe HS with adalimumab resulted in a reduction in disease severity and improvements in QoL and productivity.[20] The response to adalimumab was rapid (within 12 weeks) and durable (52 weeks). No unexpected safety signals were reported.[27]

In the study conducted by Gulliver et al[28] in 23 Canadian centers, 138 adults with moderate to severe HS who required modification of current therapy were treated with adalimumab for up to 52 weeks according to physician practice. Patient-reported outcome measures (PROMs) were obtained at baseline, weeks 24 and 52 to measure overall HRQoL, HS severity, anxiety and depression levels, HS impact and symptoms, work productivity, and activity impairment.[28]

From baseline to weeks 24 and 52, all overall PRO scores improved significantly ($P \leq 0.0023$). The number of patients reporting "good disease control" and "complete disease control" increased from 9.7% to 66.4% over the 52 weeks.[22] At week 24 and maintained at week 52 in a real-world setting, adalimumab significantly improved HRQoL, work productivity, and activity impairment in patients with moderate-to-severe HS.[28]

Muralidharan et al conducted a retrospective cross-sectional study to determine the effects of adalimumab on HS-PGA and DLQI scores in patients with HS who had been treated for at least 6 months.[29] Approximately 77% (n = 78/101) of patients demonstrated improvements in HS-PGA scores. Significant improvements were also demonstrated in the DLQI scores of the patient cohort ($P = 0.0001$, 95% CI −12.8 to −5.9). A total of 31.7% (32/101) of patients experienced adverse effects (including fungal rash, worsening liver function tests, and depression) affecting multiple organ systems, with 27.7% (28/101) requiring discontinuation of treatment.[29] Adalimumab was effective in reducing HS-PGA and DLQI scores.[29]

A retrospective observational study was conducted in 19 patients with clinically evident moderate to severe HS who were treated with adalimumab for at least 24 weeks.24 HS-PGA, modified Sartorius scale, and DLQI scores at baseline, week 4, week 12, and week 24 were retrieved from medical records. Both the modified Sartorius score and DLQI decreased significantly during the weeks of assessment ($P < 0.001$).[30] The percentage of patients achieving a clinical response was 10.5% (n = 2) at week 4, 42.1% (n = 8) at week 12, and 63.2% (n = 12) at week 24. Treatment with adalimumab was associated with both clinical remission of HS and improvement in patients' quality of life.[30]

Roccuzzo et al[31] recently presented a retrospective real-world study designed to evaluate the safety and efficacy of switching from adalimumab originator to biosimilars in 37 patients, evaluated for 12 months in terms of IHS4 (International Hidradenitis Suppurativa Severity Score System) and HiSCR. Overall, no significant differences emerged between originator and biosimilar adalimumab in terms of clinical response following nonmedical switch.[31]

Another real-life study is this trial (ClinicalTrials.gov: NCT03894956) where the authors evaluated the safety and efficacy of adalimumab in routine clinical practice in Japan from March 2019 to May 2021.26 The primary endpoint was safety.[32] Secondary endpoints assessed efficacy, reporting HiSCR and DLQI data. Eighty-three patients were enrolled. At week 12, 57.4% of patients achieved HiSCR and significant reductions from baseline in DLQI were observed ($p < 0.0001$).[32]

The treatment was well tolerated with no adverse events reported.[32]

Neves et al[26] conducted a retrospective study in Lisbon to analyze HS patients treated with adalimumab between 2016 and 2019. Epidemiological, clinical, and therapeutic information was collected. HS activity and adalimumab response were monitored at baseline and at weeks 16 (W16), 24 (W24), and 52 (W52) 0.27 At W16, HISCR was achieved in 27 patients (75%). The iHS4 mean was reduced from 16.7 to 7.2 ($p < 0.001$). At W24, the mean iHS4 was 4.7 ($p < 0.001$) and HISCR was still achieved in 76.7% (n = 23/30) of patients. Between baseline and W52, DLQI and VAS pain increased from a mean value of 15.4 to 10.5 ($p = 0.001$) and 4.4 to 1.8 ($p < 0.001$), respectively. The results showed a greater response to adalimumab in patients with Hurley II compared to Hurley III. Also, in this study, the diagnostic delay was determined in fact these data confirm the hypothesis of the "window of opportunity".[25]

This study showed superiority in terms of HISCR results at W12/16, W24 and W52 compared to the PIONEER I and II clinical studies[14] and the multicenter study Marzano et al.[23] However, the authors conclude that these improved results could be associated with the use of adjuvant intralesional, and systemic therapies taken by patients during treatment.[33]

Another hypothesis put forward was that the flare-up outbreak could be a possible predictor of response to adalimumab.[34]

Caposiena et al showed a positive correlation between relapse of exacerbation and non-response to adalimumab ($P < 0.001$).[34] Among the identified causes associated with poor response to therapy was the onset of an exacerbation before week 12 which showed the highest risk of no response ($P < 0.001$).[34]

Nazzaro et al conducted a 12-week prospective study. There were 32 patients enrolled, two main parameters were evaluated at baseline and week 12: International Hidradenitis Suppurativa Severity Score System score (IHS4) and ultrasound (according to US HS-PGA)/Color Doppler. Regarding IHS4 the authors conclude by saying that it was 22.4 at baseline while at week 12 it had dropped to 14.7. Regarding IHS4 the authors conclude by saying that it was 22.4 at baseline while at week 12 it had dropped to 14.7.[35] There were 78 (81.3%) intensely vascular lesions at baseline while at week 12 there were 25 (26.04%), which confirms the importance of ultrasound as a parameter for evaluating adalimumab therapy.[35]

In clinical cases, adalimumab has also been shown to be effective in treating HS.[36–39] There are also cases of HS associated with ankylosing spondylitis, Crohn's disease, pyoderma gangrenous, acne and psoriatic arthritis successfully treated with adalimumab.[40–46] Main articles regarding the use of adalimumab for the management of hidradenitis suppurativa in real-life setting are reported in Table 1.

Table 1 The Use of Adalimumab for the Management of Hidradenitis Suppurativa in Real-Life Setting

Authors	Study Design	Patient Enrolled	Effectiveness	Safety
Kimball et al[19]	Phase 2, parallel, randomized, placebo-controlled trial consisting of a blinded 16-week period (period 1) and an open-label 36-week period (period 2)	154 adult patients with moderate to severe HS who were unresponsive or intolerant to oral antibiotics.	At week 16, 3.9% of placebo patients (2 of 51), 9.6% of EOW patients (5 of 52), and 17.6% of weekly patients (9 of 51) achieved clinical response	Serious adverse event rates were 3.9%, 5.8%, and 7.8% for placebo, EOW, and weekly patients, respectively (EOW vs placebo difference, 1.8% [CI, −6.4% to 10.1%]
Kimball et al[14]	PIONEER I and PIONEER II. phase 3 multicenter trials of adalimumab for hidradenitis suppurativa, with two double-blind, placebo-controlled periods. In period 1, patients were randomly assigned in a 1:1 ratio to 40 mg of adalimumab weekly or matching placebo for 12 weeks. In period 2, patients were reassigned to adalimumab at a weekly or every-other-week dose or to placebo for 24 weeks.	307 patients in PIONEER I and 326 patients in PIONEER II.	Clinical response rates at week 12 were significantly higher for the groups receiving adalimumab weekly than for the placebo groups: 41.8% versus 26.0% in PIONEER I (P=0.003) and 58.9% versus 27.6% in PIONEER II (P<0.001). Patients receiving adalimumab had significantly greater improvement than the placebo groups in rank-ordered secondary outcomes (lesions, pain, and the modified Sartorius score for disease severity) at week 12 in PIONEER II only.	Serious adverse events in period 1 (excluding worsening of underlying disease) occurred in 1.3% of patients receiving adalimumab and 1.3% of those receiving placebo in PIONEER I and in 1.8% and 3.7% of patients, respectively, in PIONEER II.
Zouboulis et al[21]	An open-label extension study of the PIONEER I and II trials	//	HiSCR of 52.3% at week 168 and a decrease in Dermatology Life Quality Index (DLQI) of 5.1–6.8 points at week 72	No new safety risk reported

(*Continued*)

Table 1 (Continued).

Authors	Study Design	Patient Enrolled	Effectiveness	Safety
Marzano et al[23]	Retrospective real-life multicentre cohort study	389 patients with HS treated with Adalimumab in 21 Italian centers. Response to adalimumab and its impact on quality of life (QoL) were evaluated using the Hidradenitis Suppurativa Clinical Response (HiSCR) and the Dermatology Life Quality Index (DLQI) or the Visual Analogue Scale for pain (VAS pain), respectively.	HiSCR was achieved in 43·7% and 53·9% patients at week 16 and 52, respectively. Significant reductions in both DLQI and VAS pain were found between week 16 vs baseline (P < 0·0001 for both) and week 52 vs baseline (P < 0·0001 for both).	Adverse events most frequently have included asthenia, headache, upper respiratory tract infection and nausea. Three serious infections have been 2 cases of septicemia and 1 case of pneumonia sustained by Aspergillus fumigatus.
Chiricozzi et al[26]	A Real-life Monocentric Experience	A total of 41 patients with hidradenitis suppurativa who were treated with adalimumab for a mean period of 50.8 ± 32.2 weeks: range 6–108 weeks	Clinical improvement was observed during adalimumab therapy, with a progressively greater number of patients achieving HiSCR50 response (36.4% at week 52)	No data reported
Hafner et al[27]	HARMONY is a multicentre observational study. Primary enpoint was HiSCR at week 12. Secondary endpoint was HiSCR at 24, 36 and 52 weeks.	A total of 231 patients at 59 sites were enrolled in this observational study, and 147 (64%) completed the study.	The proportion of patients reaching the primary HiSCR endpoint was 70.2% (n = 132/188 enrolled) and remained ≥70% until study completion. HiSCR rates remained at >70% at weeks 24 (75.7%; 131/173), 36 (71.3%; 102/143) and 52 (72.1%; 106/147)	No unexpected safety signals were reported
Gulliver et al[28]	Real word experience. Patient-reported outcome measures (PROMs) were obtained at baseline, weeks 24 and 52 to measure overall HRQoL, HS severity, anxiety and depression levels, HS impact and symptoms, work productivity, and activity impairment	138 patients in 23 Canadian centres.	The number of patients reporting "good disease control" and "complete disease control" increased from 9.7% to 66.4% over the 52 weeks	The HS symptoms skin "tenderness" and "itchiness" improved the most
Muralidharan et al[29]	A retrospective cross-sectional study to determine the effects of adalimumab on HS-PGA and DLQI scores in a period of 6 months of treatment.	101 patients enrolled.	77% (n = 78/101) patients demonstrated improvements in their HS-PGA scores. Significant improvements in the DLQI scores of the patient cohort (P = 0.0001, 95% CI −12.8 to −5.9)	A total of 31.7% (32/101) patients experienced adverse effects spanning multiple organ systems, with 27.7% (28/101) requiring treatment discontinuation.
Hayashi et al[32]	A multicenter open-label observational study in Japan.	83 patients enrolled. Primary endpoint was safety. Secondary endpoint was HS Clinical Response (HiSCR), skin pain, Dermatology Life Quality Index (DLQI), and C-reactive protein (CRP)	At week 12, 57.4% of patients achieved HiSCR, and significant reductions from baseline in skin pain, DLQI (both p < 0.0001), and CRP (p = 0.0029) were observed	The treatment was well tolerated with no adverse events reported. One patient died from a serious adverse event of cardiac failure unrelated to adalimumab

(*Continued*)

Table 1 (Continued).

Authors	Study Design	Patient Enrolled	Effectiveness	Safety
Neves et al[33]	A retrospective study to analyze HS patients treated with adalimumab during 2016 to 2019 in Lisbon.	36 patients were in treatment with Adalimumab. Adalimumab responses were monitored at baseline and at weeks 16 (W16), 24 (W24), and 52 (W52).	At W16, HISCR was achieved in 27 patients (75%). The iHS4 mean was reduced from 16.7 to 7.2 ($p < 0.001$). At W24, the mean iHS4 was 4.7 ($p < 0.001$) and HISCR was still achieved in 76.7% of patients.	No data reported
Nazzaro et al[35]	Prospective Study	32 patients. International Hidradenitis Suppurativa Severity Score System score (IHS4) and ultrasound (according to US HS-PGA)/Color Doppler were evaluated	IHS4 was 22.4 at baseline while at week 12 was 14.7. Vascular lesions were 78 at baseline while at week 12 were 25	No adverse events reported

Ustekinumab

Ustekinumab is a human monoclonal antibody generally used to treat the following conditions: moderate to severe plaque psoriasis, psoriatic arthritis, moderate to severe Crohn's disease or moderate to severe ulcerative colitis (inflammatory bowel disease).[47] Ustekinumab is an interleukin-12 (IL12) and interleukin-23 (IL23) antagonist. FDA approval is indicated for use in moderate to severe plaque psoriasis (Ps) for patients 6 years of age and older.[48,49] Main articles regarding the use of ustekinumab for the management of hidradenitis suppurativa in real-life setting are reported in Table 2.

To date ustekinumab has not received FDA approval for many other inflammatory-mediated diseases, however, there are studies and case reports in the literature where the drug is used off label for the treatment of hidradenitis suppurativa.[50]

Hollywood et al have conducted a retrospective review of patients treated with ustekinumab,[51] sixteen patients received ustekinumab between January 2017 through September 2020, all the patients had failed the first lines treatments according HS guidelines, subjective clinical improvement was found in 9 patients (56%), the parameters that were used

Table 2 The Use of Ustekinumab for the Management of Hidradenitis Suppurativa in Real-Life Setting

Authors	Study Design	Patient Enrolled	Effectiveness	Safety
Montero-Vilchez et al[52]	Case series	10 patients Average treatment was 48 (32–167) weeks Disease severity was evaluated HS-PGA and NPRS	A one-point reduction in HS-PGA is was appreciated in seven (70%) patients and a ≥2-point reduction in NPRS in eight (80%) patients.	No adverse events have been reported
Hollywood et al[51]	Retrospective Study	16 patients All the patients have failed the first-line therapies.	Subjective clinical improvement was seen in 9 patients (56%)	No adverse events have been reported
References[53–62]	Case report and Case series	49 patients Clinical improvement was measured using the International Hidradenitis Suppurativa Severity Score System (IHS4), the HS-PGA, the Hidradenitis Suppurativa Clinical Response (HiSCR) or the modified Sartorius Scale (mSS)	Of a total of 49 patients, a reduction in IHS4, HS-PGA, HiSCR or mSS was observed in 38 (78%). Of a total of 49 patients, a reduction in VAS or DLQI was observed in 42 (86%).	No adverse events have been reported

being reduction in the number of flares and improvement in quality of life. Four patients (25%) showed no improvement and the remaining 3 (19%) had good disease control.[51]

T Montero-Vichez et al have evaluated the therapeutic outcomes of 10 patients with HS treated with ustekinumab.[52] All patients had moderate to severe HS (Hurley stage II–III) and had failed to respond to previous treatment. Disease severity was evaluated according to the physician's global assessment (HS-PGA) and pain was assessed with the Numerical Pain Rating Scale (NPRS). The average duration of treatment was 48 (32–167) weeks.

A one-point reduction in HS-PGA was appreciated in seven (70%) patients and a ≥2-point reduction in NPRS in eight (80%) patients. In patients who did not respond to therapy, no worsening of HS severity or symptoms was observed.[52]

We reviewed all available literature on real-life studies with ustekinumab; in total, between case reports and case series there were 49 patients treated.[53–62]

Out of a total of 49 patients, the most encountered comorbidities were: 33 (67%) smokers or former smokers, 11 (22%) were obese, and 8 (16%) had additional components of the follicular occlusion tetrad: pilonidal sinus (n = 2) and acne conglobata (n = 6). Nine (18%) patients also had Crohn's disease.[53–62]

Among the 49 patients, 32 (65%) had previously undergone biologic treatment; 27 (55%) had been treated with adalimumab and 14 (28%) with infliximab, while 17 (35%) had not received any biologic drug treatment prior to ustekinumab administration.[53–62]

The average duration of treatment was 40 (16–44) weeks. The instruments used to assess disease severity and treatment outcomes were different for the different cases.

Clinical improvement was measured using the International Hidradenitis Suppurativa Severity Score System (IHS4), the HS-PGA, the Hidradenitis Suppurativa Clinical Response (HiSCR) or the modified Sartorius Scale (mSS).[63] Symptomatic improvement was assessed using the Visual Analog Scale (VAS) and the Dermatologic Quality of Life Index (DLQI). Of a total of 49 patients, a reduction in IHS4, HS-PGA, HiSCR or mSS was observed in 38 (78%). Of a total of 49 patients, a reduction in VAS or DLQI was observed in 42 (86%).

The real limitation of all reported real-life cases is the sampling number, which is very low to be able to establish the efficacy and safety of the drug.

Secukinumab

Secukinumab is a biological agent that acts selectively on interleukin 17 (IL-17).[64] To date, several clinical studies confirm its efficacy in the management of plaque psoriasis and psoriatic arthritis and ankylosing spondylitis.[64]

FDA approved the drug for the following indications: moderate to severe psoriasis, hypertrophic palmoplantar psoriasis, generalized pustular psoriasis, psoriatic arthritis and ankylosing spondylitis.[65] It has been used off-label for rheumatoid arthritis and hidradenitis suppurativa.[66] Main articles regarding the use of secukinumab for the management of hidradenitis suppurativa in real-life setting are reported in Table 3.

There is a lack of real-life data on HS or at least very few are available.

An open-label exploratory study evaluated the efficacy of secukinumab 300 mg per week for five weeks and then every four weeks thereafter in nine patients with moderate to severe HS (Hurley stage II or III).[67] The authors conclude that six patients on nine (67%) achieved an improvement of at least 50% in total inflammatory nodule and abscess counts.

Table 3 The Use of Secukinumab for the Management of Hidradenitis Suppurativa in Real-Life Setting

Authors	Study Design	Patient Enrolled	Effectiveness	Safety
Prussick et al[67]	Open-label exploratory study	9 patients enrolled and 4 patients completed study after 24 weeks	Six patients on nine (67%) achieved an improvement of at least 50% in total inflammatory nodule and abscess counts	No serious adverse events reported
Ribero et al[68]	Multi-center retrospective study	31 patients HiSCR was evaluated at week 28	HiSCR was achieved by 41% of patients	No adverse events reported

Ribero et al[68] conducted a multi-center retrospective study with 31 patients treated with secukinumab, all patients had failed or had contraindications to at least one anti-TNF-alpha. In this study, the Hidradenitis Suppurativa Clinical Response Score (HiSCR) was achieved by 41% of patients at week 28. No adverse events were reported.[68]

Our research found no other monometric or multicenter real-life or open-label studies. We found several case reports and case series.

Marasca et al reported two cases;[69] the first case involved a 63-year-old man with a history of Hurley's stage III HS, initially treated with adalimumab who developed a bilateral psoriasiform rash on his lower limbs following treatment with adalimumab. The patient was treated with secukinumab 300 mg per week for the first four weeks and then 300 mg every four weeks, which resulted in complete resolution of the psoriasiform rash and partial resolution of the HS lesions.

The second reported case involved a 46-year-old man with a history of psoriasis for whom he had initiated secukinumab therapy and who subsequently paradoxically developed HS after therapy, this is one of the very few cases of secukinumab-induced HS.[69]

Thorlacius et al[70] reported a case of a 47-year-old man with Hurley's stage III HS treated with secukinumab with substantial disease improvement, particularly a decrease in the number of lesions from 23 to seven and on the analog pain scale visual score five to three after 12 weeks of therapy.[70]

Another case report of a 24-year-old man with recalcitrant HS reported by Schuch et al[71] the authors indicate that the patient showed almost complete resolution of the inflammatory nodules, the authors however do not show scoring data but only clinical and photographic data.

Jørgensen et al[72] reported the case of a 36-year-old woman with stage II Hurley HS treated with secukinumab 300 mg per week for the first four weeks and 300 mg every four weeks thereafter.

This patient was shown to have improved dermatological quality of life Index Score (DLQI) from 17 out of 30 to 5 out of 30, HSS from 76 to 19, Visual Analogue Score (VAS) from 10 out of 10 to 7 out of 10, International Hidradenitis Suppurativa Severity Score (IHS4) from 19 to 1, and the disappearance of most inflammatory lesions after six months of treatment. No adverse events were observed.[72]

Considering that serum levels of Il-17 are increased in patients with HS,[69–73] the data emerging from these case reports would be confirmed by this hypothesis, however the sampling is still very scarce to demonstrate efficacy and safety, in large-scale studies are needed in the future.

Miscellaneous

We did not find real-life studies but only case reports or case series that involved the use of two other biologic drugs for HS: ixekizumab, guselkumab and brodalumab. Ixekizumab (an IL-17A antagonist) is a biologic therapeutic licensed for use in moderate-to-severe plaque psoriasis and psoriatic arthritis,[73] represent a new generation of biologic therapy with rapid and high response rates, quickly becoming a crucial part of the psoriasis treatment armamentarium.[74,75]

Cotter et al[76] reported two cases of Hurley's stage III HS treated with ixekizumab 160 mg starting dose, 80 mg every 2 weeks for 3 months and 80 mg every four weeks thereafter.

The first case was a 42-year-old woman with Hurley's stage III HS who achieved subjective improvement in the disease; she reported a reduction in swelling and suppuration of the lesions. Similar was the second case of a 34-year-old woman with Hurley's stage III HS and Crohn's disease who experienced a subjective improvement in disease severity and a reduction in groin swelling after treatment. We would like to point out, however, that the authors do not report accurate IHS4 or HSS score data.[76]

Esme et al reported on a case series of five patients with severe HS (Hurley stage III) who had been on adalimumab treatment for 3 months with poor results, these patients were switched to ixekizumab according to the psoriasis therapeutic schedule of administration.[77] The primary endpoint was HiSCR after 12 weeks. The secondary endpoints were DLQI and VAS. Four out of 5 patients (80%) achieved HiSCR. While improvement was observed in VAS and DLQI scores of 4 patients. No adverse events to treatment were recorded.[77]

Megna et al[69] reported the case of a 50-year-old man with HS and Psoriasis. Regarding HS lesions, the patient achieved HiSCR (Hidradenitis-Suppurativa-Clinical-Response) at week 10 of treatment and maintained it at the last

follow-up visit (week 24). In addition, the pain analog-visual scale (VAS) score decreased from 4 to 1 and the pain/utility/handicap score decreased from 1 to 2.[78]

As regards anti-IL17, promising data have been reported also for brodalumab.[79]

Another interesting finding, we found in the literature was the article by Montero-Vichez et al, the authors reported a case series of 4 patients treated with Guselkumab, a fully human monoclonal antibody specifically targeting the p19 subunit of IL-23.[80] The primary endpoint involved assessment of IHS4, DLQI and VAS after the 12 weeks of treatment. Two patients achieved 50% improvement while all had moderate improvement after treatment.[80] No adverse events were recorded.[80] The authors also conducted a systematic review of the literature where they reported another 16 case reports with discordant results-in fact, they conclude that further studies will be needed to establish and clarify the potential role of anti-IL-23 antibodies in this disease.[80]

Discussion

HS is a chronic, relapsing inflammatory skin condition that needs long-term management and frequent follow-ups.[81] Unfortunately, current conventional available drugs (eg antibiotics), are ineffective for the severe forms of the disease as well as their use is contraindicated in several situations. In this scenario, the introduction of biologic drugs in HS treatment opened a new era in HS management. Indeed, these drugs have already been used in other dermatological conditions such as psoriasis and atopic dermatitis,[82–86] reporting a high profile in terms of effectiveness and safety for these diseases,[87–91] also during COVID-19 era.[92–104] Since then, several clinical trials have been carried out to assess their use in HS management. Currently, adalimumab is the only drug approved for HS, but clinical trials and real-life experiences reported promising results also for other biologics.

In our review, we highlighted the current evidence from literature on the use of biologics in HS in a real-life setting, particularly adalimumab, secukinumab and ustekinumab. Data on the effectiveness and safety of biologic drugs in HS management have been analyzed.

In our opinion, the armamentarium of drugs for HS management is increasing, and treatment will be based on a personalized approach in order to choose the right treatment for the right patient at the right moment and to minimize the risk of adverse events. In this context, we want to point out the reported effectiveness and safety data concerning adalimumab, ustekinumab and secukinumab as well as ixekizumab. Of note, many data deriving from real-life, particularly for non-approved biologic drugs, are limited to few case reports and patients were usually affected by HS and other dermatological conditions (eg, psoriasis), requiring biologic treatment for the second one. Thus, the possible coincidence of HS resolution cannot be ruled out.

To sum up, the landscape of HS treatment is changing, also for the introduction of new personalized approaches (eg, telemedicine),[105–107] and clinicians must be prepared for the revolution of HS treatment. Biological drugs seem to represent an extraordinary weapon among the armamentarium of HS treatment. Certainly, more studies, more clinical trials and more real-life experiences are required to confirm these promising data. Moreover, the introduction of new biologics for HS and the emerging data will lead to the need for new guidelines.

It is important to set new guidelines to well establish the "therapeutic window" for the biologic treatment because from all these data we can take out that previous is the treatment higher is the response. For this reason, ecografic panelist must set up new criteria that can be associated with the classification of severity of HS based on the real-life data.[108–110]

Strengths and Limitations

Main strengths of our review are the systematic method during the literature research and the elevated number of investigated articles. Main limitations should be reported. First, only adalimumab is currently approved for HS management. Thus, data from real-life for other biologics are limited. Moreover, several case reports reported the use of biologics for other diseases in patients also affected by HS. Therefore, the casual coincidence of HS improvement during treatment cannot be excluded.

Conclusion

New knowledge on HS pathogenesis is leading to the development of new selective and effective drugs, with a high profile in terms of safety. In this scenario, the introduction of biologic drugs is revolutionizing HS management. However, data based on real-life experiences are limited as only adalimumab is currently approved for HS. Fortunately, several studies on different biologic drugs are ongoing and the results are promising. Certainly, more data are needed.

Data Sharing Statement

Data are reported in the current study and are on request by corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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