Biologics: Targets and Therapy

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REVIEW

Systematic review of immunomodulatory therapies for hidradenitis suppurativa

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Background: Greater understanding of the roles of tumor necrosis factor-α, IL-1β, IL-10, and the IL-23/T-helper (Th) 17 and IL-12/Th1 pathways in immune dysregulation in moderate/severe hidradenitis suppurativa (HS) has helped in developing new regimens. We aim to review the use of different immunomodulatory therapies used to manage HS.

Methods: A comprehensive literature search was conducted on the PubMed and Clinicaltrials.gov databases from 1 January 1947 to 31 December 2018. Only clinical trials, case reports, case series and retrospective analyses published in the English language were included.

Results: Our search yielded 107 articles and 35 clinical trials, of which 15 are still ongoing. The tumor necrosis factor-α inhibitors adalimumab and infliximab were the most comprehensively studied agents. Published data from clinical trials support the efficacy of adalimumab, infliximab, anakinra, ustekinumab, bermekimab and apremilast but not etanercept and MEDI8968. Clinical trials for CJM112 have been completed, with results awaiting publication. Trials are underway for secukinumab, IFX-1, INCB054707 and bimekizumab. Biologics used in smaller cohorts include canakinumab, golimumab and rituximab. Most agents are well tolerated and demonstrate a good safety profile, with the most commonly reported adverse event being infections.

Discussion and conclusions: To date, adalimumab is the only biologic which has been approved by the United States Food and Drug Administration for HS. However, other agents also show promise, with further trials underway to evaluate their efficacy, tolerability and safety profiles. Different clinical measurement scores and endpoints used to make direct comparison difficult. Longitudinal surveillance and pooled registry data are paramount to evaluate the long-term safety profile and efficacy of therapy.

Keywords: Hidradenitis suppurativa, biologics, tumor necrosis factor, adalimumab, infliximab, secukinumab

Introduction

Hidradenitis suppurativa (HS), which has an estimated worldwide prevalence of 1%, is a chronic inflammatory follicular occlusive disease predominantly involving the intertriginous areas.[1] Clinically, its manifestations vary from inflammatory nodules and abscesses to the formation of sinus tracts and scarring.[2] It has a profound adverse impact on patients' quality of life, and has been closely linked with physical and psychiatric co-morbidities including obesity, hypertension, dyslipidemia, diabetes mellitus, thyroid disorders, polycystic ovarian syndrome, arthropathies and depression.[3]

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Pathophysiology of HS

Histopathological examination of early lesions in HS demonstrates terminal follicular hyperkeratosis, hyperplasia of the follicular epithelium and perifolliculitis. The occlusion of the terminal hair follicle results in dilation and cyst formation, followed by rupture of the hair follicle. The introduction of follicular contents to the surrounding dermis induces an inflammatory response and subsequent formation of abscess, sinus tracts, fibrosis and scars. This is worsened by biofilm formation and secondary infection.[4,5]

The inflammatory response in HS has in recent years been better characterized, although there are many components that remain to be elucidated. In particular, tumor necrosis factor (TNF)-α, IL-1β, IL-10, and the IL-23/T-helper (Th) 17 and IL-12/Th1 pathways play key roles in immune dysregulation in HS.[6,7] In studies of HS skin, significantly increased frequencies of CD4 T cells expressing Th17-associated cytokines and TNF were found infiltrating HS skin.[7] Treatment with TNF inhibitors was also related with a significant decrease in IL-17 expressing CD4 T cells in HS skin.[7]

Staging of HS and implications on therapy

HS has traditionally been staged according to the Hurley staging system, first proposed in 1989 (Table 1).[8]

The Hurley staging system remains useful for determining the severity of disease in individual patients but is limited in monitoring the dynamic characteristics of disease in clinical trials.[9] Hence, alternative scoring systems have been developed to better evaluate the efficacy of the intervention, as shown in Table 2.

Conventional medical therapy, involving oral antibiotics and topical treatments, is suitable for treatment of mild to moderate HS. However, there are patients where HS remains resistant to conventional treatment. With the discovery of the key inflammatory mediators in HS, the role of biologics and other immunomodulatory therapies in the targeted treatment of moderate-to-severe HS has been closely studied. Of these, adalimumab remains the only Food and Drug Administration (FDA)-approved biologic for the treatment of HS.[10]

We present a review of all biologics and immunomodulatory therapies that have been reported in the treatment of HS.

Table 1 Hurley staging of HS

Stage I (mild)	Abscess formation, single or multiple, without sinus tracts and cauterization.
Stage II (moderate)	Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions.
Stage III (severe)	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

Note: Data from Hurley.[8]
Abbreviation: HS, hidradenitis suppurativa.

Methods

A review of the literature was conducted by multiple PubMed searches using the keywords "hidradenitis suppurativa" or "acne inversa"; with publication date limits from 1 January 1947 to 31 December 2018. Retrieved references were critically appraised. The inclusion criteria were original articles, reports and letters in the English language reporting the treatment of HS with biologic or other immunomodulatory agents, either alone or in combination with conventional drugs or surgery. Articles which were judged to be irrelevant based on the title, abstract or full text, were excluded from the review.

A search of the website Clinicaltrials.gov for planned, in-progress, terminated and completed clinical trials with the terms "hidradenitis suppurativa" and "acne inversa" was also performed up to 31 December 2018.

Results

A total of 2,088 articles were retrieved by multiple PubMed searches conducted until 31 December 2018 using the keywords "hidradenitis suppurativa" or "acne inversa". A total of 107 relevant articles were included in the analysis. A total of 47 case reports, 29 case series, 3 retrospective analyses, 4 cohort studies and 24 articles based on clinical trial data, were selected (Figure 1).

A total of 65 clinical trials were retrieved by a search of the Clinicaltrials.gov database conducted on 31 December 2018, of which 35 were related to immunomodulatory treatment. Twenty of these studies were completed or terminated. To access the results of these trials, the articles retrieved from the PubMed searches were reviewed and matched to their respective clinical trials, using the National Clinical Trial identifier, and the PubMed database was again searched using the terms ("hidradenitis suppurativa" OR "acne inversa") and the medication name. Fourteen of the completed or terminated studies had published articles on PubMed (Figure 2). When trial results were not available in PubMed, results posted on Clinicaltrials.gov were used. In

Table 2 Scoring systems used in grading HS severity

HiSCR[99]	≥50% reduction in inflammatory lesion count (abscesses and inflammatory nodules) **AND** No increase in abscesses or draining fistulas compared to baseline					
HS-PGA[11]	Clear Minimal Mild Moderate Severe Very Severe	No inflammatory or non-inflammatory nodules Only the presence of non-inflammatory nodules 1–4 inflammatory nodules OR 1 abscess or draining fistula AND no inflammatory nodules ≥5 inflammatory nodules OR 1 abscess or draining fistula AND ≥1 inflammatory nodules OR 2–5 abscesses or draining fistulas AND <10 inflammatory nodules 2–5 abscesses or draining fistulas AND ≥10 inflammatory nodules >5 abscesses or draining fistulas				
mSS[100]	**A**	**Number of regions affected (3 points per region)**: Right axilla Left axilla Right groin Left groin Right gluteal region Left gluteal region Other region				
	B	**For <u>each</u>…**: Nodule: 1 point Fistula: 6 points				
	C	**For <u>each</u> affected region, longest distance between two relevant lesions**: <5 cm: 1 point 5–10 cm: 3 points >10 cm: 9 points				
	D	**For <u>each</u> affected region**: If lesions not clearly separated by normal skin: 9 points				
	The mSS is the total of the subtotals of A to D.					
HSSI[101]	Points scored	No. of sites	BSA affected (%)	No. of lesions (erythematous, painful)	Drainage (dressing changes per working or leisure hour)	Pain (VAS)
	0 1 2 3 4	0 1 2 3 ≥4	0 1 2–3 4–5 >5	0 1 2–3 4–5 >5	0 1 >1	0–1 2–4 5–7 8–10
	Sites: Left armpit, right armpit, left side of chest, right side of chest, left groin, right groin, perianal area, sacral area and perineal area. The HSSI is the total of all five assessed domains, with a minimum score of 0 and a maximum score of 19.					
IHS4[102]	**A** **B** **C**	Number of nodules Number of abscesses Number of draining tunnels				
	The IHS4 is derived by the formula: **A** x 1+ **B** x 2+ **C** x 4					

Abbreviations: HiSCR, hidradenitis suppurativa clinical response; HS-PGA, HS physician's global assessment; mSS, modified sartorius score; HSSI, HS severity index; BSA, body surface area; IHS4, International HS Score System.

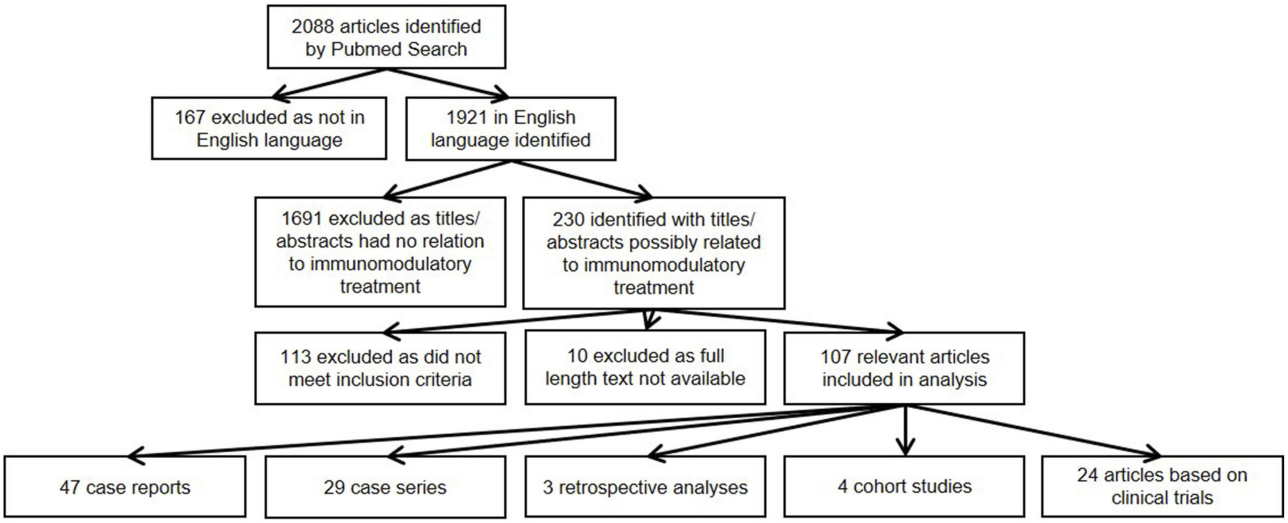

Figure 1 Selection of articles identified by PubMed search.

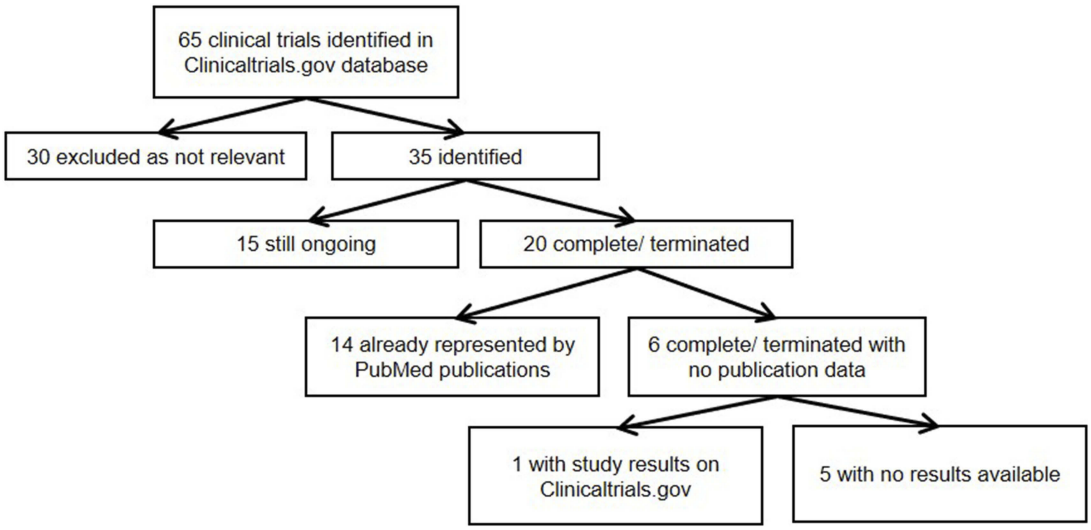

Figure 2 Selection of articles identified by Clinicaltrials.gov search.

five cases, the trials were listed as "completed" on Clinicaltrials.gov, but neither PubMed indexed journal articles nor posted study results on Clinicaltrials.gov were found. A World Wide Web search was then performed to retrieve any study results available.

Biologic and other immunomodulatory therapies

A total of 19 biologic and other immunomodulatory agents reported in the treatment of HS were identified and categorized according to their mode of action (Table 3). Of these, efalizumab has been withdrawn and was thus excluded from this review. Information from individual published articles included in this review is available in Table 4.

TNF-α inhibitors

Adalimumab

Adalimumab is a recombinant human anti-TNF-α IgG1 monoclonal antibody. When used for HS, it is given subcutaneously as an initial dose of 160 mg, followed by a dose of 80 mg 2 weeks later, and a maintenance dose of 40 mg weekly thereafter.[10] In 2015, it became the first and, to date, only FDA-approved biologic agent for the treatment of moderate/severe HS.[10]

A Phase II study by Kimball et al in 2012 first demonstrated that a significantly greater proportion receiving adalimumab weekly (17.6%) compared to placebo (3.9%) achieved the primary clinical endpoint of a HS-PGA score of clear, minimal or mild with at least a two-grade

Table 3 Biologics and other immunomodulatory therapies reported in the treatment of HS

TNF-α inhibitors	Adalimumab*[10,12,14–16,23–27]
	Infliximab[9,31,32]
	Etanercept[51]
	Golimumab[53,54]
	Certolizumab[56]
IL-1 inhibitors	Anakinra[58,60,103]
	Canakinumab[62,63]
	Bermekimab[66]
	MEDI8968[70]
IL-12/-23 inhibitors	Ustekinumab[72]
IL-17 inhibitors	Secukinumab[74-76]
	CJM112[79]
	Bimekizumab[82]
IL-23 inhibitors	Guselkumab[84-86]
Selective PDE-4 inhibitors	Apremilast[89,90,104]
Complement C5a inhibitors	IFX-1[91–93]
CD-11a inhibitors	Efalizumab**[105]
CD-20 inhibitors	Rituximab[95]
JAK-1 inhibitors	INCB054707[96,97]

Notes: [a]FDA-approved for treatment of HS
[b]No longer available, and thus excluded from further review.
Abbreviation: HS, hidradenitis suppurativa.

improvement relative to baseline scores at week 16. This effect was not significantly demonstrated in the group of patients receiving 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).[11] After changing from weekly to every other week dosing, a decreased proportion of patients showed a clinical response.[11]

The subsequent PIONEER I and II Phase III trials involved a total of 633 patients with moderate-to-severe HS with an inadequate response to oral antibiotics. A significantly higher proportion of patients given adalimumab achieved HiSCR, compared to patients given placebo after 12 weeks of treatment (PIONEER I: 41.8% vs 26.0%, p=0.003; PIONEER II: 58.9% vs 27.6%, p<0.001).[12] Most adverse events observed were mild or moderate in severity. Of note, in the group of patients treated with adalimumab, there were new psoriasiform eruptions and psoriasis in ten patients, one case of squamous cell carcinoma of the nose, and one death from cardiorespiratory arrest 42 days after the last dose of adalimumab in a 35-year-old man with a history of diabetes mellitus, smoking and a family history of ischemic heart disease.[12] Secondary efficacy data also showed a greater proportion of subjects achieving a ≥30% reduction in the 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).[13,14]

An open-label extension trial of the PIONEER I and II trials also confirmed that patients who continued to receive weekly adalimumab maintained a long-term response with a HiSCR rate of 52.3% at week 168 and a decrease in the Dermatology Life Quality Index (DLQI) of 5.1–6.8 points at week 72, with no new safety risks identified.[15]

In a study by Ryan et al that analyzed the safety data of adalimumab in HS, there were no new safety concerns identified with the weekly dosing of adalimumab compared with every other week dosing.[16]

In case reports, adalimumab has also shown effectiveness in treating HS associated with pyoderma gangrenosum, acne and psoriatic arthritis.[17–19] However, some case reports and series have drawn caution to the use of adalimumab, reporting adverse events such as erythroderma, melanoma, demyelinating disorders and drug-induced lupus.[20–22]

There are currently post-marketing surveillance trials of adalimumab underway, assessing quality of life, effectiveness of treatment and safety profile.[23–27] In addition, the safety, efficacy and cost-effectiveness of adalimumab in conjunction with surgery are currently under investigation by two Phase IV trials.[28,29]

Infliximab

Infliximab is a chimeric mouse/human anti-TNF-α monoclonal antibody. It is currently FDA-approved for use in inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis;[30] and has been used as an off-label treatment in patients with HS resistant to adalimumab.[9,31,32] It is currently dosed as an intravenous infusion 5 mg/kg body weight on week 0, 2, 6 and thereafter every 8 weeks.[30] However, reports suggest that the dosing regimen for HS requires further refinement.[31]

In a descriptive single-center study involving 10 patients, no long-term curative effect was uniformly seen.[33] In another study evaluating the efficacy of a single course (three infusions) of infliximab in 10 patients, three patients did not have a recurrence at 2 years, whereas the other seven had an average time of 8.5 months to recurrence of lesions (4.3–13.4 months).[34]

In a Phase II randomized study comprising a double-blind placebo-controlled treatment phase, an open-label crossover treatment phase and an observational phase, 38 patients with moderate-to-severe HS as defined by a HSSI

Table 4 Articles included in systematic review

Case reports, case series and retrospective studies

Case reports

Study	Subject characteristics	Therapies	Dose	Treatment duration	Efficacy	Complications
Koilakou S et al[106]	One 38-year-old male	ADA	40 mg EOW	NR	No	None
Benhadou F et al 2018[22]	One 55-year-old female	ADA	160 mg once	1 week	Yes	Erythroderma
Van der Zee HH et al 2013[53]	One 51-year-old female	ADA, GOL, ANK	ADA 40 mg EOW, GOL 50 mg monthly, ANK 100 mg monthly	ADA for 2 years, GOL for 1 year, ANK for 1 year	All ineffective	None
Moul DK et al 2006[107]	One 67-year-old male	ADA	40 mg EOW	5 months	Yes	None
Harde V et al 2008[108]	One 32-year-old male	ADA	80 mg once, then 40 mg weekly	6 months	Yes	None
de Wet J et al 2017[17]	One 42-year-old male	ADA	160 mg at week 0, 80 mg at week 2, and 40 mg weekly for 5 weeks	8 weeks	Yes	None
Samycia M et al[109]	One 48-year-old male	ETA, INF, ADA	ETA 50 mg weekly, then twice weekly, INF 5 mg/kg, then 10 mg/kg every 6 weeks, ADA 80 mg at week 0 then 40 mg EOW then weekly	ETA for 4 months, INF for 1 year 6 months, ADA for 1 year	No Yes, for 1 year Yes	Fatigue (from INF)
Diamantova et al 2014[110]	One 50-year-old female	ADA	80 mg at week 0 then 40 mg EOW	8 weeks	Yes	None
Bosnić et al 2016[111]	One 39-year-old male	ADA	40 mg EOW	1 year	Yes	None
Saraceno et al 2015[18]	One 50-year-old male	ADA	40 mg EOW	36 weeks	Yes	None
Bessaleli et al 2018[112]	One 33-year-old female	ADA	40 mg, then increased to 80 mg weekly	8 months	Yes	Cervical squamous cell carcinoma in situ
Crowley EL et al 2018[113]	One 32-year-old male	ADA	80 mg at week 0 and then 40 mg weekly	3 years	Yes	Oral candidiasis
Molina-Leyva et al 2018[114]	One 39-year-old female	ADA	NR	16 weeks	DLQI reduced from 18 to 0 at week 4 and 16	None

(*Continued*)

Table 4 (Continued).

Case reports, case series and retrospective studies						
Gorovoy et al 2009[115]	One 47-year-old female	INF, ADA	INF NR, ADA 40 mg EOW	15 months for each biologic	Initial response for INF, good response for ADA	Infusion reaction with urticaria (INF)
Murphy et al 2015[19]	One 26-year-old female	INF, ADA	INF 5 mg/kg for 2 doses, ADA 160 mg/80 mg then 40 mg EOW	INF NR, ADA for 2 months	Response to both	Drug hypersensitivity (INF)
Friedman et al 2018[13]	One 48-year-old female	ANK	100 mg/day for 9 months, then 200 mg/day for 15 months	24 months	Moderate response	Drug-induced sarcoidosis
Zarchi et al 2013[116]	One 37-year-old female	ANK	200 mg/day	1 year	Yes	Staphylococcus aureus pustular folliculitis
Jaeger T et al 2013[64]	One 27-year-old male	CAN	150 mg every 3–6 weeks for 8 injections	NR	Yes	NR
Tekin B et al 2017[65]	One 27-year-old male	INF, CAN	INF 5 mg/kg for 8 sessions, CAN 150 mg every 4 weeks for 3 doses	NR	Slight improvement with INF, worsening with CAN	Worsening of HS with CAN
Zangrilli A et al 2008[117]	One 32-year-old male	ETA	50 mg 2x/week for 24 weeks, then 25 mg 2x/week for 24 weeks	48 weeks	Yes	None
Tursi A 2016[54]	One 42-year-old female	GOL	200 mg once then 100 mg every 4 weeks	NR	Yes	None
Roussomoustakaki M et al 2003[38]	One 29-year-old female	INF	5 mg/kg at 0, 2 and 6 weeks	6 weeks	Yes	None
Adams DR et al 2003[118]	One 17-year-old male	INF	5 mg/kg at 0, 2, 6 weeks, and 7 months	7 months	Yes	None
Rosi YL et al 2005[119]	One 30-year-old female	INF	5 mg/kg at 0, 2 and 6 weeks	6 weeks	Yes	None
Husein-ElAhmed H et al 2011[120]	One 47-year-old male	INF	4.6 mg/kg at weeks 0, 2, 6, 10	10 weeks	Yes, but recurrence in 2 weeks	None
von Preussen AC et al 2012[121]	One 42-year-old female	INF	5 mg/kg at 0, 2 and 6 weeks and then every 8 weeks	NR	Yes	None
Montes-Romero JA et al 2008[37]	One 39-year-old male	INF	5 mg/kg at weeks 0, 2, 6 and 14	NR	Yes	None
Goertz RS et al 2008[41]	One 54-year-old male	INF	5 mg/kg for 7 infusions	2 years	Yes, but effect plateaued	New superinfection
Blazquez I et al 2013[39]	One 50-year-old female	INF	INF 5 mg/kg at 0, 2 and 6 weeks and then every 8 weeks	6 months	Yes	None
Groleau PF et al 2015[40]	One 51-year-old male	INF	15 mg/kg at 0, 2 and 6 weeks and then 7.5 mg/kg every 8 weeks for 1 year, then 5 mg/kg every 8 weeks twice, then 2.5 mg/kg every 8 weeks twice Stopped for 7 months, then 5 mg/kg every 8 weeks when relapsed	NR	Yes, relapsed after cessation	None

(*Continued*)

Table 4 (Continued).

Case reports, case series and retrospective studies						
Martínez F et al 2001[42]	One 30-year-old male	INF	5 mg/kg for 2 doses	NR	Yes	Generalized erythema and dyspnea
Lebwohl B et al 2003[122]	One 21-year-old male	INF	NR	NR	Yes, but recurred on prolonged sitting	None
Thielen AM et al 2006[123]	One 48-year-old male	INF	5 mg/kg at 0, 2 and 6 weeks then every 8 weeks	104 weeks	Yes	Limited herpes zoster
Gori A et al 2012[44]	One 19-year-old male	INF	5 mg/kg at 0, 2 and 6 weeks then every 8 weeks	14 weeks	Yes	Acne
Alecsandru D et al 2010[124]	One 47-year-old male	INF	5 mg/kg at 0, 2 and 6 weeks then every 8 weeks	NR	Yes, flared upon stopping	None
Poulin Y et al 2009[125]	One 25-year-old female	ETA, INF	ETA 50 mg twice a week, INF 5 mg/kg at 0, 2 and 6 weeks then every 6 weeks	26 months of ETA, 20 months of INF	Worsened with ETA, improved with INF	ETA caused flare of HS
Staub J et al 2015[36]	One 22-year-old female	ETA, ADA, ANK, INF	ETA, ADA and ANK NR, INF 5 mg/kg at 0 and 2 weeks then every 8 weeks	10 months of ETA, 5 months of ADA, 20 months of INF Not stated for ANK	Improved with INF in combination with dapsone, steroids and cyclosporine but relapsed on tailing cyclosporine	None
Ozer I et al 2016[35]	One 43-year-old male	INF	5 mg/kg at 0, 2 and 6 weeks then every 8 weeks	2 years	Yes	None
Kozub *P* et al 2012[126]	One 53-year-old female	INF	500 mg at 0, 2 and 6 weeks then every 8 weeks	43 weeks	Initial improvement but plateaued until addition of dapsone	None
Vossen MG et al 2011[43]	One 21-year-old male	ETA, INF	ETA 50 mg/week, INF 5 mg/kg	NR	NR	*Gemella morbillorum* bacteremia
Takahashi H et al 2017[95]	One 19-year-old male	RIT	200 mg for 2 doses 1 year apart	1 year	Yes	None
Thorlacius L et al 2017[74]	One 47-year-old male	ADA, INF, ANK, SEC	ADA, INF, ANK NR, SEC 300 mg/week for 4 weeks then every 4 weeks after	7 years	Not improved with ADA, INF, ANK. Responded to SEC	Oral candidiasis (SEC)
Schuch A et al 2017[75]	One 24-year-old male	ADA, INF SEC	ADA, INF NR, SEC 300 mg/week for 4 weeks then every 4 weeks after	NR	Not improved with ADA and INF, responded to SEC	None

(*Continued*)

Table 4 (Continued).

Case reports, case series and retrospective studies						
Giuseppe *P* et al 2018[127]	One 37-year-old male	INF, SEC	INF 5 mg/kg, SEC 300 mg/week for 4 weeks then every 4 weeks after	NR	Partial improvement with INF, improved with SEC	None
Jørgensen AR et al 2018[128]	One 36-year-old female	INF, ADA, UST, SEC	INF, ADA, UST NR, SEC 300 mg/week for 5 weeks then every month	1 year	No response to INF, ADA, UST, improved with SEC but small relapse	Throat infections, fever
Santos-Pérez MI et al 2014[129]	One 50-year-old female	ADA, UST	ADA 80 mg, then 40 mg every 2 weeks, UST 45 mg at weeks 0, 4 and then every 12 weeks	2 years of ADA, 1.5 years of UST	Stable then worsened on ADA, improved with UST but 2 exacerbations reported	None
Sharon VR et al 2012[130]	One 55-year-old male	ADA, UST	ADA NR, UST 45 mg at weeks 0, 4 and 12, then 90 mg every 8 weeks	NR	Did not respond to ADA, improved with UST but flares 2 weeks prior to next dose	None
Scheinfeld N 2014[45]	One 47-year-old male	INF	500 mg for 3 courses	NR	NR	Metastatic cutaneous squamous cell carcinoma
Case series						
Study	**Subject characteristics**	**Therapies**	**Dose**	**Treatment duration**	**Efficacy**	**Complications**
Blanco R et al 2009[131]	Six patients, two males and four females	ADA in six, ETA in one	ADA 40 mg EOW, increased to weekly if inadequately controlled, decreased to 3-weekly if in remission	Mean of 21.5 months	ETA ineffective, ADA effective	Pain at injection site, severe facial cellulitis in one patient
Chinniah N et al 2014[132]	Six patients, four males and two females	ADA in three cases, INF in four cases, ETA in one case**	NR	Mean 25.3 months	Significant response to ADA in two, INF in three, ETA in one	Neurological adverse events in one patient on ADA
Houriet C et al 2017[63]	Two (One male, one female)	CAN	One given 150 mg monthly, one given 150 mg on day 1 and 15 and then monthly	One for 26 months, one for 12 months	Reduction in Sartorius score and VAS for both patients	None

(*Continued*)

Table 4 (Continued).

Case reports, case series and retrospective studies						
Sun NZ et al 2017[62]	Two females	CAN and ANK in one, ADA, INF and CAN in one	INF 5 mg/kg at week 0, 2 and 6, CAN 150 mg every 8 weeks, ANK 100 mg daily for first patient, ADA 40 mg weekly, INF 6 mg/kg and CAN 150 mg weekly for second patient	NR	INF effective in one patient, ADA partial response in same patient	INF - hypersensitivity reaction in first patient, suspicion of drug-related interstitial nephritis in second patient
Sand FL et al 2015[56]	29 patients	ADA in 22, ETA in five, INF in six, CER in two**	ADA 40 mg once weekly, ETA 50 mg once weekly, INF 5 mg/kg every 8 weeks, ADA 40 mg once weekly	Mean of 13 months (1–50 months)	12 out of 22 responded to ADA, two of five to ETA, one of six to INF, none of two for CER	ADA – Meningealia, headache, fever in one patient, pneumonia in two patients, visual disturbances and headache in one patient; ETA – urosepticemia in one patient, sebopsoriasis in one patient; INF –sensory and motor polyneuropathy, myalgia and arthralgia in one patient, recurrent tonsillitis in one patient
Zhao CY et al 2018[21]	Four males	ADA	NR	10–60 months	50–100% improvement	One with development of melanoma in situ, one with worsening of Charcot-Marie-Tooth syndrome, one with drug-induced lupus
Patil 2018[133]	Two males	ADA biosimilar (ZRC-3197)	40 mg weekly for 3 weeks, then EOW for 3 months	3 months and 3 weeks	>50% reduction in abscess and inflammatory nodule count in both patients	None
Menis et al 2014[103]	Two males	ANK	100 mg daily	12 weeks	No	One with worsening of HS
Cusack et al 2006[134]	Six females	ETA	25 mg twice weekly	17–40 weeks	All six improved, between 44% and 73% in DLQI reduction	Increased frequency of upper respiratory tract infections in one patient
Lasocki et al 2010[135]	Four (One male, three female)	INF	5 mg/kg at week 0, 2 and 6, then 8-weekly maintenance infusions.	38–54 weeks	Improvement in all patients, but with recurrence in all after cessation of therapy	Headache and vomiting in one patient
Lozeron et al 2009[20]	One male	INF	5 mg/kg at 0, 2, 6, 12 and 18 weeks	18 weeks	Not effective	Lewis-Summer Syndrome (demyelinating neuropathy)
Elkjaer et al 2008[136]	Two males	INF	5 mg/kg/day at 0, 2 and 6 weeks and then 5 weekly	NR	Effective	Infusion reactions in one patient
Antonucci et al 2008[137]	Two (one male, one female)	INF	5 mg/kg on weeks 0, 2 and 6 and then every 8 weeks	59 weeks	Effective in one, ineffective in one	None

(*Continued*)

Table 4 (Continued).

Case reports, case series and retrospective studies						
Delage et al 2011[32]	Seven (Three males, Four females)	INF	5 mg/kg on weeks 0, 2 and 6 and then every 8 weeks	6–110 weeks	Effective in six	One with eczema-like eruption, one with pretragian abscess
Brunasso et al 2008[138]	Seven (Three males, four females)	INF	5 mg/kg on weeks 0, 2 and 6 and then every 8 weeks	Mean 58.6 weeks (4–72)	Improvements in pain, discharge, area reduction and DLQI. 3 with new lesions during therapy	One with adverse drug reaction, not further specified
Moschella 2007[139]	Three (One male, two females)	INF	5 mg/kg on weeks 0, 2 and 6 and then varying subsequent dosing	54–80 weeks	Effective in all	None
Sullivan et al 2003[140]	Five (One male, four females)	INF	5 mg/kg at week 0 for all five patients, and again at week 4–6 for three patients	0– 6 weeks	Effective in all	Presumed *Mycobacterium tuberculosis* lymph node infection in one patient
Torres et al 2010[141]	Two patients	INF	5 mg/kg on weeks 0, 2 and 6 and then every 8 weeks	7 months	Ineffective	None
Usmani et al 2006[142]	Four patients (two males, two females)	INF	5 mg/kg, varying dosing	Up to 11 months	Two with good response, one with mild response, one with poor response	One with INF-induced lupus, one with infusion reaction
Fernández-Vozmediano et al 2007[143]	Six patients (Two males, four females)	INF	5–10 mg/kg at weeks 0, 2 and 6, then every 4 weeks	6 months	Improvement to stage I in four cases, stage II in two cases	One with headache
Moriarty et al 2014[31]	11 patients (Eight males, three females)	INF	5–10 mg/kg at weeks 0, 2 and 6, then every 4 to 8 weeks	Median 49.1 months	All with initial improvement, two with secondary failure	Nine cutaneous infections requiring antibiotics, four respiratory tract infections requiring antibiotics, one episode of tonsillitis requiring antibiotics, one case of Hodgkin lymphoma 36 months after cessation of INF
Kovacs et al 2018[84]	Three (Two males, one female)	GUS	100 mg at weeks 0 and 4, then 8 weekly	At least 12 weeks	Improvements in IHS4, VAS and DLQI at 12 weeks in all patients	None
Weber et al 2017[88]	Nine patients (Six males, three females)	APR	30 mg twice daily	2 days to 9 months	Improvement in five of six who persisted with therapy	Two with weight loss, one with loose stool, one with dry cough, one with nausea, one with reflux

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Table 4 (Continued).

Case reports, case series and retrospective studies						
Zhang et al 2014[144]	22 (nine males, 13 females)	15 on INF, seven on ADA	NR	1 month to 3 years	14 with improvement (11 with INF, three with ADA)	Three with infusion reactions, two with fatigue, one with anaphylaxis, one with heart failure, one with dyspnea, one with recurrent HSV. One death from lung malignancy, one death from metastatic perianal squamous cell carcinoma (both on INF) but no direct causal relationship established.
DeFazio et al 2016[145]	11 patients	Eight on INF, three on UST	Mean 10.5 months (6 to 15 months)	NR	Effective in seven, local recurrence in four, of which one was after 4 months of INF	None
Monné et al 2014[146]	Four patients	Four on ADA, of which one also tried INF and ETA	Varying doses	NR	ADA effective in three of four, ETA and INF ineffective	None
Gulliver et al 2011[147]	Three (one male, two female)	UST	45 mg at 0, 1 and 4 months	6 months	One ineffective, one 25–49% disease clearance, one complete clearance	One patient with *S. aureus* of right axilla, one patient with cystitis, psoriasiform dermatitis and arthritis
Retrospective analyses						
Study	**Subject characteristics**	**Therapies**	**Dose**	**Treatment duration**	**Efficacy**	**Complications**
van Rappard et al 2012[148]	30 patients (17 males and 13 females)	INF	Weeks 0, 2 and 6 and subsequently every 8 weeks.	Mean 9.3 months	10 free of lesions, 13 improved, 4 moderately improved, 3 no response	Noted in 12 patients, not further specified
Martin-Ezquerra G et al 2014[149]	19 patients (ten males, nine females)	ADA in 11 cases, INF in ten cases, UST in two cases, ETA in two cases**	NR	Mean of 12 months	Physician-judged at least partial responses for ADA in eight, INF in seven, UST in three, none for ETA	Severe infusion reaction and hypertriglyceridemia in two patients
Bettoli, Manfredini et al 2018[150]	34 patients (19 males, 15 females)	ADA	NR	Varying, up to at least 1 year	Among group receiving ADA for >1 year, 60% achieved HiSCR at 3 months and maintained up to 12 months.	NR

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Table 4 (Continued).

Case reports, case series and retrospective studies						
Kyriakou et al 2018[151]	19 (five males, 14 females)	ADA	160 mg at week 0, 80 mg at week 2, 40 mg at week 4 and 40 mg weekly after	At least 24 weeks	63.1% achieved clinical response at 24 weeks (defined by HS-PGA score of clear, minimal or mild with at least two-grade improvement from baseline).	None[#]
Casseres et al 2018[85]	Eight (five males, three females)	GUS	100 mg at week 0, 4 and then 8 weekly	Up to 10 months	Five (63%) with improvement	None
Cohort studies						
Study	**Subject characteristics**	**Therapies**	**Dose**	**Treatment duration**	**Efficacy**	**Complications**
van Rappard et al 2011[152]	19 patients (12 males, seven females)	Ten on INF, nine on ADA	INF 5 mg/kg at weeks 0, 2 and 6. ADA 40 mg EOW.	6 weeks	46% reduction in Sartorius score in INF group vs 34% in ADA group	One on INF with acute arthritis and myalgia, three on ADA with fatigue, one with injection site pain
Sbidian et al 2016[153]	67 patients (30 males, 37 females)	17 on ADA, 63 on ADA, eight on ETA**	INF 5 mg/kg, ADA 40 mg EOW, ETA 50 mg twice a week	NR	Treatment with ADA associated with at least partial response compared to ETA or INF with hazards ratio of 6.6 (p=0.001)	One each with hepatitis, lupus, repeated urinary tract infection and pulmonary embolism
Shanmugam et al 2018[112]	68 patients (23 males, 45 females; 31 ever had biologics, 37 never had biologics)	NR	NR	NR	Ever receiving biologics associated with sharper decline in HS activity, biologic use associated with significant reduction in HSS and Hurley stage, effect of biologics greater in patients who received surgery, combination therapy with surgery and biologics associated with higher probability of achieving 75% reduction in active nodule count.	NR

Clinical trials							
Study	**Trial characteristics**	**Subject characteristics**	**Therapies**	**Dose**	**Treatment duration**	**Efficacy**	**Complications**
Kimball et al 2016,[12] Zouboulis et al 2018[15]	Randomized double-blind placebo-controlled Phase III trial, with open-label extension to 168 weeks	307 for PIONEER I, 326 for PIONEER II	ADA	40 mg weekly vs 40 mg EOW vs placebo	36 weeks	More patients in the weekly ADA group achieved HiSCR [41.8% versus 26.0% in PIONEER I (p=0.003) and 58.9% vs 27.6% in PIONEER II (p<0.001)]. Mean duration of infection-free HiSCR was significantly longer in ADA compared to placebo group (p< 0.001).154 More patients on ADA achieved a ≥30% in the Patient's Global Assessment of Skin Pain, both PIONEER I (ADA [40.3%] vs placebo [24.9%]; OR =2.03, p=0.004) and II (ADA [61.2%] vs placebo [24.8%]; OR=4.78, p<0.001).155 Achievement of HiSCR was maintained through week 168 in 52.3% in weekly ADA group and 57.1% of responders plus partial responders.15	Among ADA group, new psoriasiform eruptions and psoriasis in ten patients, one case of squamous cell carcinoma of the nose, and one death from cardiorespiratory arrest 42 days after the last dose of ADA in a 35-year-old man with a history of diabetes mellitus, smoking and a family history of ischemic heart disease. Adverse events observed during open-label extension were similar to safety profiles observed in PIONEER studies.15 Safety analysis of every week and EOW dosing showed similar adverse event rates.16
Jiménez-Gallo et al 2018[156]	Prospective open label study	19 (11 males, eight females)	ADA	40 mg weekly	36 weeks	HiSCR in 68.42%.	NR
Kimball et al 2012[11]	Phase II parallel randomized, placebo-controlled trial with a blinded 16-week period and an open-label 36-week period	154	ADA	40 mg weekly vs 40 mg EOW vs placebo	52 weeks	17.6% in weekly ADA vs 9.6% in EOW group vs 3.9% in placebo group achieved HS-PGA score of clear, minimal, or mild with at least a two-grade improvement relative to baseline score at week 16 (EOW vs placebo difference, 5.6% [95% CI, 4.0% to 15.3%]; p 0.25; weekly vs placebo difference, 13.7% [CI, 1.7% to 25.7%]; p 0.025). Proportion with clinical response decreased after change from weekly to EOW dosing. A shorter time to achieving HiSCR in weekly ADA vs EOW group.99	24 listed serious adverse events: rectal fissure, inadequately controlled diabetes mellitus, goiter, hidradenitis, interstitial lung disease, pilonidal cyst, viral infection, anemia, bacteremia, vocal cord neoplasm, bacterial genital infection, Escherichia infection, penile swelling, purulent discharge, pustular rash, scrotal swelling, noncardiac chest pain, and cellulitis.

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Table 4 (Continued).

Clinical trials							
Arenbergerova et al 2010[157]	Open label trial	Eight (three males, five females)	ADA	80 mg at week 0, 40 mg at week 1, then 40 mg EOW	12 months	Mean reduction in pain and discharge of 86.5% and 72.8% respectively at 12 months, and 56.6% and 50.1% at 24 months	One case of EBV infection
Amano et al 2010[101]	Open-label Phase II trial	Ten, of which six completed treatment	ADA	160 mg at week 0, 80 mg at week 1, 40 mg EOW	12 weeks	None responded, as defined by at least 50% decrease in HSSI score	No serious adverse events
Leslie et al 2014[60]	Open-label trial	6 (Two males, four females), of which five completed the study	ANK	100 mg daily	8 weeks	Significant improvement in modified Sartorius score during treatment and rebound during follow-up post-treatment	None
Tzanetakou et al 2016[58]	Randomized double-blind placebo-controlled trial	20 patients (ten in anakinraANK arm, ten in placebo arm), of which 19 completed study	ANK	100 mg daily	12 weeks	At week 12, 78% in ANK arm vs 20% in placebo arm had reduction in disease activity score, defined as the sum of scores of all affected areas (two largest diameters in each affected areas multiplied by degree of inflammation at each lesion), and 78% vs 30% achieved HiSCR. At week 24, 10% vs 33% achieved HiSCR.	No serious adverse events
Vossen et al 2018[89]	Randomized double-blind placebo-controlled trial	20 (15 given apremilastAPR and five given placebo) of which 18 completed the study	APR	30 mg BD	16 weeks	Eight of 15 achieved HiSCR in APR arm compared to none in placebo arm (p=0.055) at week 16.	38 adverse events in APR arm vs 11 in placebo arm, none categorized as severe.
Cusack et al 2006[134]	Open-label trial	Six	ETA	25 mg twice weekly	17 to 40 weeks	44 to 73% reduction in DLQI 12 to 24 weeks after starting treatment	Increased incidence of URTIs in one patient
Giamarellos-Bourboulis et al 2007[47]	Open-label Phase II trial	Ten three males, seven females)	ETA	50 mg weekly	12 weeks	>50% decrease in disease activity (defined as sum of lesions with each lesion evaluated with the formula: lesion diameters multiplied by severity) in six patients at week 12 and seven patients at week 24.	No serious adverse events: three patients with self-limited injection site erythema, one patient with right gluteal abscess

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Table 4 (Continued).

Clinical trials							
Sotiriou et al 2008[50]	Open- label trial	Four (one male and three females)	ETA	25 mg twice a week	6 months	54–73% reduction in DLQI	One case of mild injection site reaction
Lee et al 2009[49]	Open-label trial	15, of which ten completed treatment	ETA	50 mg weekly for 12 weeks, then 25 mg weekly for 2 weeks	14 weeks	Only three (20%) of patients achieved 20% reduction in PGA, based on intention to treat analysis.	No serious adverse events reported
Pelekanou et al 2010[48]	Open-label Phase II trial	Ten	ETA	50 mg weekly	Initial 12-week duration, then subsequent 0 to 96-week course depending on recurrence	Three who improved in mSS with no recurrence and 7 who improved and then recurred after stopping treatment, of which five had a positive response to repeat treatment	None
Adams et al 2010[51]	Randomized trial with 12-week double-blind placebo-controlled phase followed by 12-week open-label phase	20 patients (ten in etanerceptETA arm and ten in placebo arm), of which 14 completed entire study	ETA	50 mg twice weekly	24 weeks	No statistically significant difference in physician global assessment between treatment and placebo arms	No serious adverse events
Paradela et al 2012[33]	Open-label trial	Ten (four males, six females)	INF	5 mg/kg at week 0, 2, 6 and then 8-weekly	29 to 181 weeks	Eight with response (defined as 50% reduction in hidradenitis severity score), of which four relapsed (defined as 40% increase in score of initial response)	One case of mycobacterial folliculitis, one case of scrotal abscess, two cases of psoriasis, five cases of positive antinuclear antibodies, two cases of transient hyperlipidemia
Grant et al 2010[9]	Clinical trial with 8-week double-blind placebo-controlled phase followed by 14- to 22-week open label phase	38 patients (15 in infliximabINF arm and 23 in placebo arm)	INF	5 mg/kg at week 0, 2 and 6 and then 8 weekly	22 weeks	At week 8, 60% of patients in INF arm vs 5.6% of patients in placebo arm had 25% to less than 50% reduction in HSSI, and 13.3% of patients in INF arm vs 88.9% in placebo arm had less than 25% decrease in HSSI ($p<0.001$).	Serious adverse events: one pregnancy, one case of hypertension, one infusion reaction requiring hospitalization.
Mekkes et al 2007[34]	Open-label trial	11, of which ten (four males, six females) completed the study	INF	5 mg/kg at week 0, 2 and 6	6 weeks	Improvements in all patients within 2–6 weeks, as defined by reduction in mSS. At one year, improvements in 6 patients, but recurrences in 4.	One with numbness and pain in both legs, one with anaphylactic shock, and one with myalgia and fever

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Table 4 (Continued).

Clinical trials							
Kanni et al 2018[66]	Randomized double-blind placebo-controlled trial	20 patients (10 in bermekimabBER arm and 10 in placebo arm)	BER	7.5 mg/kg every 14 days	12 weeks	60% in BER arm vs 10% in placebo arm achieved HiSCR at week 12, and 40% vs 0% at week 24.	19 HS exacerbations in BER group, of which 2 required hospitalization
Blok et al 2016[72]	Open-label trial	17 (four males, 13 females)	UST	Week 0, 4, 16 and 28–45 mg per dose for participants weighing <100 kg and 90 mg per dose for those >100 kg	28 weeks	Marked improvement of mSS in six (35%), moderate in eight (47%), mild in one (6%), no change/worsening in two (12%) at 40 weeks. Mean mSS of intention-to-treat population decreased from 112.12 to 60.18 at week 40 (46.33% improvement, $p<0.01$). Eight (47%) achieved HiSCR at week 40.	Headache, fatigue, URTI
Guo et al 2017[91]	Open-label phase II trial	12	IFX-1	800 mg on days 1, 4, 8, 15, 22, 29, 36, 43 and 50	50 days	83% achieved HiSCR at Day 134 (95% CI: 0.52–0.98).	NR

Notes: **Overlapping due to switches in therapy. #Study excluded patients who discontinued treatment due to adverse event or had to receive another therapeutic modality.

Abbreviations: ADA, adalimumab; GOL, golimumab; ANK, anakinra; ETA, etanercept; INF, infliximab; CAN, canakinumab; RIT, rituximab; SEC, secukinumab; UST, ustekinumab; CER, certolizumab; GUS, guselkumab; APR, apremilast; BER, bermekimab; EOW, every other week; NR, not reported; PASH, pyoderma gangrenosum, acne and suppurative hidradenitis; NSAID, non-steroidal anti-inflammatory drug; HPV, human papillomavirus; SAPHO, synovitis, acne, pustulosis, hyperostosis and osteitis; HCV, hepatitis C virus; Nd-YAG, neodymium-doped yttrium aluminum garnet; CO_2, carbon dioxide; IHS4, international HS severity score system; HSV, herpes simplex virus; HSS, HS score; HiSCR, HS clinical response; URTI, upper respiratory tract infection; PGA, physician global assessment; mSS, modified sartorius score; EBV, Epstein-Barr virus, HSSI, HS severity index.

score >8 were selected. More patients treated with regular infliximab responded with a 25% to <50% decrease in HSSI compared to placebo (60% vs 5.6%), whereas most patients treated with placebo had a <25% decrease in HSSI compared with infliximab (88.9% vs 13.3%, $p<0.001$).[9] After 8 weeks of treatment, there were significant improvements in the infliximab group compared to the placebo group in terms of mean DLQI change (−10 vs −1.6, $p=0.003$) and mean PGA scores (1.8 vs 4.7, $p<0.001$).[9] Most adverse events were mild and none were considered unexpected.[9]

In case reports, infliximab demonstrated efficacy in treating HS associated with pyoderma gangrenosum, acne, Crohn's disease and systemic amyloidosis.[35–42]

However, infliximab has also in cases been associated with paradoxical worsening of facial acne vulgaris, demyelinating neuropathies, metastatic cutaneous squamous cell carcinoma and a case of *Gemella morbillorum* bacteremia complicated by brain abscesses.[20,43–45]

Etanercept

Etanercept is a dimeric TNF-α inhibitor. It is approved for use in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, plaque psoriasis and psoriatic arthritis.[46]

After showing mixed results in open-label trials,[47–50] it was examined under a double-blind, placebo-controlled study in 20 patients with moderate-to-severe HS. In patients given etanercept 50 mg twice weekly for 24 weeks, no significant improvement in HS was found.[51]

Golimumab

Golimumab is an anti-TNF-α human monoclonal antibody, approved for use in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and ulcerative colitis.[52]

To date, it has been used in two case reports in the treatment of HS. In a case of a patient with concomitant Hurley Stage 3 HS and psoriatic arthritis, the use of subcutaneous golimumab 50 mg once weekly did not result in clinical improvement of HS (after adalimumab and anakinra had failed).[53] However, in a later case report published in 2016 of a 42-year-old female with Hurley Stage 2 HS and pyostomatitis vegetans on a background of ulcerative colitis, golimumab subcutaneously 200 mg once followed by 100 mg every 4 weeks, together with amoxicillin-clavulanate, resulted in complete and sustained remission of HS, pyostomatitis vegetans and ulcerative colitis.[54]

There are no clinical trials underway to further assess golimumab in HS.

Certolizumab

Certolizumab is a PEGylated Fab fragment of a humanized TNF-α monoclonal antibody that is FDA-approved for the treatment of Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis.[55] Its use in HS was described briefly in a case series, where it was used in two patients but found to be ineffective.[56]

IL-1 inhibitors

Anakinra

Anakinra is a recombinant IL-1 receptor inhibitor which is FDA-approved for use in rheumatoid arthritis and neonatal-onset multisystem inflammatory disease.[57] It has been given as a 100 mg subcutaneous daily dose in HS.[57]

It has been studied in a double-blind, randomized, placebo-controlled Phase II clinical trial involving 20 patients. There were significantly more patients with a decreased disease activity score in the anakinra group compared to the placebo group after 12 weeks of treatment (78% vs 20%, $p=0.02$) and achieving HiSCR at the end of 12 weeks (78% vs 30%, $p=0.04$).[58] However, at 24 weeks, the difference in patients achieving HiSCR was not statistically significant (10% vs 33%, $p=0.28$).[58]

In later case reports, there were also experiences of failure of anakinra therapy, or even worsening of HS related to anakinra use, suggesting the need for further clinical trials.[59] Painful injection site reactions are also commonly reported with the use of anakinra, limiting its tolerability for some patients.[60] It was also linked with drug-induced sarcoidosis in one case report.[13]

Canakinumab

Canakinumab is a human monoclonal anti-IL-1β antibody which is FDA-approved for use in cryopyrin-associated periodic syndromes and systemic juvenile idiopathic arthritis.[61] It has been given up to 150 mg subcutaneous weekly dose in the treatment of HS. To date, it has shown mixed results in case reports and series.[62–65]

Bermekimab

Bermekimab (MABp1) is an anti-IL 1α human monoclonal antibody. In a recent Phase II trial involving 20 patients with moderate-to-severe HS either randomized to bermekimab or placebo for 12 weeks, 60% of patients on bermekimab achieved HiSCR at week 12 compared to 10% on placebo ($P=0.035$).[66] Twelve weeks after

cessation of treatment, 40% of patients on bermekimab had a positive HiSCR compared to 0% of patients on placebo.[66] No adverse events related to bermekimab were reported.[66]

MEDI8968

MEDI8968 is a fully human immunoglobulin monoclonal antibody that selectively binds to the IL-1R1 receptor to inhibit activation by IL-1α and IL-1β. It has been studied for use in osteoarthritis, rheumatoid arthritis and chronic obstructive pulmonary disease.[67–69] A Phase IIa study evaluating the safety, tolerability and efficacy of MEDI8968 for the treatment of subjects with moderate-to-severe HS was terminated early due to a lack of efficacy.[70]

IL-12/-23 inhibitors

Ustekinumab

Ustekinumab is a human monoclonal antibody that acts by binding to and inhibiting the p40 subunit on IL-12 and IL-23. It is FDA-approved for use in plaque psoriasis, psoriatic arthritis and Crohn's disease.[71] Patients weighing 100 kg and below receive 45 mg per dose, and those weighing above 100 kg receive 90 mg per dose.[71]

In a Phase II open-label study involving 17 patients on ustekinumab, the majority of patients showed moderate to marked improvement, as defined by a significant decrease in the mSS and modified HS Lesional Area Severity Index.[72] Forty-seven percent of patients achieved HiSCR.[72] Adverse events were mild and temporary, most commonly headache, fatigue and upper respiratory tract infections. The authors of the Phase II study suggested that the dosing regimen in HS may have to be further intensified.[72]

IL-17 inhibitors

Secukinumab

Secukinumab is a human IgG1k monoclonal antibody that acts as an IL-17A inhibitor. It is FDA-approved for moderate-to-severe plaque psoriasis, psoriatic arthritis and ankylosing spondylitis.[73] Given at 300 mg subcutaneously weekly for 1 month followed by 4-weekly maintenance dosing, it has shown dramatic improvement in case reports of patients in whom other biologic therapies failed.[74,75] An exploratory pilot study on the safety and feasibility of secukinumab in HS patients is currently underway,[76] and there are two randomized double-blind multicenter trials to compare the efficacy, safety and tolerability of 2-weekly and 4-weekly secukinumab 300 mg in patients with moderate-to-severe HS.[77,78]

CJM112

CJM112 is a human monoclonal anti-IL-17A antibody. A Phase II study involving 66 patients with moderate-to-severe chronic -HS has been completed, but results are not available at present.[79]

Bimekizumab

Bimekizumab is a humanized anti-IL17A and IL-17F monoclonal antibody which has been studied and found to be effective in patients with psoriasis.[80,81] A Phase II trial is currently underway to investigate its use in moderate-to-severe HS, with no results available at the time of writing.[82]

IL-23 inhibitors

Guselkumab

Guselkumab is an anti-IL-23 monoclonal antibody that has been FDA-approved for use in adults with moderate-to-severe plaque psoriasis. It is given subcutaneously 100 mg at week 0, week 4 and every 8 weeks thereafter.[83] A case series involving three patients with severe HS, given guselkumab, found significant reductions in the IHS4, VAS for pain and (DLQI for all three patients.[84] Another retrospective chart review of eight patients with moderate-to-severe HS given guselkumab found that 63% of patients reported improvements, with suggestions to further intensify the dosing regimen.[85] No adverse events were documented in both articles. A Phase II multicenter randomized double-blind placebo-controlled trial has been initiated to evaluate its efficacy in the treatment of moderate-to-severe HS.[86]

Selective PDE-4 inhibitors

Apremilast

Apremilast is an orally administered PDE-4 inhibitor which is FDA-approved for use in patients with moderate-to-severe plaque psoriasis and active psoriatic arthritis. It is titrated to a target dose of 30 mg twice daily.[87]

In a reported case series of nine patients with Hurley stages II–III HS who had responded poorly to other treatments, five of six patients who persisted with treatment showed a good clinical response, with a significant improvement in the Sartorius score (73.17±67.76 to 56.17±44.89, p=0.028), VAS (7.17±0.98 to 2.00±2.10, p=0.026) and DLQI (21.33±8.91 to 9.33±5.85, p=0.027).[88]

In a double-blind, randomized, placebo-controlled trial involving 20 patients with moderate HS, 8 of 15 patients (53.3%) given apremilast achieved a positive HiSCR at week 16 compared to zero of five in the placebo group (p=0.055). Patients receiving apremilast also showed a significantly lower abscess and nodule count (mean difference −2.6; 95% CI −6.0 to −0.9; p=0.011), numerical rating scales for pain (mean difference −2.7; 95% CI −4.5 to −0.9; p=0.009), itch (mean difference −2.8; 95% CI −5.0 to −0.6; p=0.015) and disease burden (mean difference −1.8; 95% CI −3.7 to −0.01; p=0.049) compared to placebo. There were no major adverse events documented.[89]

Another Phase II open-label trial involving 20 patients has been completed, with no results available at present.[90]

Complement 5a inhibitors

IFX-1

IFX-1 is a human C5a-specific monoclonal antibody. Preliminary data from an open-label clinical study involving 12 patients, 75% of patients achieved HiSCR at day 50 (95% CI 0.43–0.95) and 83% at day 134 (95% CI 0.52–0.98).[91,92]

Another Phase II study is currently underway to determine its efficacy and safety.[93]

CD-20 inhibitors

Rituximab

Rituximab is a chimeric monoclonal antibody against the CD20 protein. It is FDA-approved for use in non-Hodgkin 's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis and pemphigus vulgaris.[94]

In one case report in a kidney transplant recipient with idiopathic carpotarsal osteolysis who suffered chronic active antibody-mediated rejection and also developed HS, low-dose rituximab with two courses of 200 mg each were given with dramatic improvement of HS without remission of rejection.[95]

There are no further studies underway to evaluate the efficacy of rituximab.

JAK-1 inhibitors

INCB054707

INCB054707 is an orally administered inhibitor of the Janus kinase 1 pathway. There are currently two Phase II trials underway, with no other information available at the time of writing.[96,97]

Discussion

The increased understanding of the inflammatory pathways in HS provides many exciting therapeutic opportunities for patients with HS resistant to conventional methods of therapy. As more molecular targets are identified, immunomodulatory therapies can be developed, and their dosing regimens further refined. The efficacy, or lack thereof, of individual therapies also provides key insights into disease pathophysiology.

TNF-α inhibition in HS has been demonstrated to be useful. Adalimumab is presently the only FDA-approved biologic for use in HS and should thus be the drug of choice in moderate-to-severe HS where conventional treatment has proven ineffective. It is worth noting from our systematic review that where HS is associated with pyoderma gangrenosum, acne, Crohn's disease or systemic amyloidosis, infliximab may also be considered as an effective off-label treatment.

Etanercept and MEDI8968 have already proven to be ineffective. Other therapies, involving smaller cohorts, have shown partial or mixed responses, with larger trials underway to further assess their efficacy in HS. The varying clinical measurement scores and endpoints used in these trials to determine treatment responsiveness potentially complicate direct comparison between different agents.

Most biologics and immunomodulatory therapies exhibit a generally well-tolerated safety profile. However, long-term safety concerns, including infection risks, especially latent tuberculosis reactivation, demyelinating disorders, and the development of malignancy from chronic immunosuppression will need to be evaluated through longitudinal surveillance and pooled registry data.[98] These issues are especially pertinent in the treatment of HS, where the dosing regimen for biologics is typically more intensive compared to other inflammatory diseases, such as psoriasis. Patient selection remains important, as complete response is not the norm, not all patients with HS tolerate or respond well to immunomodulatory therapy, and may benefit from other modes of treatment, such as surgery.

In patients with severe HS that does not fully respond even to biologic treatment, we may consider biologics as an adjunct to surgery, where biologics are used to debulk disease to minimize the area required for surgical resection. Results from Phase IV trials to assess the combination of adalimumab with surgery will help refine the treatment approach for this category of severe HS.[28,29]

Ultimately, it is hoped that the use of immunomodulatory therapies will help overcome some of the challenges in treating severe HS, alleviating the impact on sufferers' quality of life and morbidity associated with the disease. However, more quality data is required on their efficacy, safety and use in specific sub-populations before we can achieve truly targeted treatment of HS.

Disclosure

Hazel H Oon is a clinical investigator for Janssen, Novartis and Pfizer. She has also served as a speaker and advisory board member for AbbVie, Janssen, Novartis and Eli Lilly. Hazel H Oon reports grants and personal fees from AbbVie, Eli Lilly, Janssen, Novartis, and Pfizer outside the submitted work.The authors report no other conflicts of interest in this work.

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