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REVIEW ARTICLE

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Infliximab in hidradenitis suppurativa: A systematic review and meta-analysis

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Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory often recalcitrant to treatment. There is a lack of an updated systematic data review for infliximab use in HS. We conducted a systematic review and meta-analysis of literature on infliximab in HS. This study was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was pre-registered on PROSPERO (CRD42021283596). In 9/2021, MEDLINE and EMBASE were systematically searched for articles on infliximab in HS. Non-English, duplicate, and studies with <5 HS patients were excluded. Study quality was assessed utilizing Cochrane Risk of Bias for prospective trials and Newcastle-Ottawa Scale for cohort studies. Random effects meta-analytical model, Cochran's Q statistic, and I squared index were performed. Nineteen articles (314 patients) met inclusion criteria (six prospective, 13 retrospective studies). All patients with HS severity data available ($n = 299$) had moderate-to-severe disease. Outcome measures used for meta-analysis of the pooled response rate were largely based on clinician reported outcomes (16 studies). One utilized both clinician and patient assessment. Two utilized patient-reported response alone. The pooled response rate of HS patients to infliximab was 83% (95% CI, 0.71–0.91). The most common adverse events (AEs) included non-serious infections (13.2%) and infusion reaction (2.9%). The rate of serious AEs was 2.9%. Study limitations include the small number of prospective studies and heterogeneity between studies. Overall, infliximab is an effective treatment for moderate-to-severe HS. Efficacy of infliximab in HS should be compared to other biologics in larger, randomized controlled trials.

KEYWORDS
hidradenitis suppurativa, infliximab, meta-analysis

1 | INTRODUCTION

Hidradenitis suppurativa (HS) is an often-debilitating chronic inflammatory dermatosis that presents as painful lesions in predominantly intertriginous regions. Though several treatment options ranging from topical antibiotics to surgical interventions exist, most treatments lack rigorous efficacy data.[1] In recent years, biologics have been increasingly investigated as a treatment option for moderate to severe

HS. Adalimumab is a fully human monoclonal antibody that binds tumor necrosis factor-alpha (TNF-α). It is currently the only U.S. Food and Drug Administration (FDA)- and European Medicines Agency (EMA)- approved agent for moderate-to-severe HS. Infliximab is anti-TNF-α agent that is an established treatment for HS, but its evidence is more limited when compared to adalimumab.[1] The objective of this study is to systematically evaluate existing literature on infliximab use in HS and examine its efficacy through meta-analysis.

2 | METHODS

2.1 | Search strategy

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was pre-registered on PROSPERO (CRD42021283596). On September 29, 2021, two independent reviewers (TS and KL) searched MEDLINE and EMBASE databases from inception to search date with the following terms: ("hidradenitis suppurativa" OR "hidradenitis" OR "acne inversa" OR "velpeau disease" OR "verneuil disease") AND ("infliximab"). A total of 856 articles were identified. Articles were filtered to remove non-English language and non-human studies. Duplicate articles were excluded. Titles and abstracts were screened for relevance. Full text review was then manually performed on the remaining 298 articles by the two independent reviewers (TS and KL). Studies where infliximab was the primary study intervention and the study population had at least five HS patients were considered eligible for inclusion. Reviews, conference abstracts, meta-analyses, commentaries, and non-relevant articles were excluded. Studies with surgery as a concomitant study intervention or with a duplicate cohort population were also excluded. Any discrepancies were discussed to consensus with a third reviewer (JH). Reference lists of articles that met inclusion criteria were screened for additional articles that may be relevant, and no additional articles were identified.

2.2 | Data extraction

Two reviewers (TS and KL) independently completed data extraction. For each article, the study design, country of study, patient demographics, HS severity, study intervention, efficacy outcomes, safety outcomes, study sponsorship were recorded. The articles were assessed for quality utilizing Cochrane Risk of Bias for prospective trials[2] and Newcastle-Ottawa Scale (NOS) for cohort studies.[3] One author was contacted to confirm that two studies used the same HS patient population, with the resulting exclusion of one of the studies to avoid duplicate reporting.[4]

2.3 | Meta-analysis

A meta-analysis was conducted to assess the pooled estimate of response rate of HS to infliximab. To determine response, pre-determined primary outcome measures were used whenever available, followed by physician assessments, and then patient-reported outcomes. Forest plots were constructed using the proportion of patients with a reported response (including partial response) to infliximab and standard errors/confidence intervals were computed using inverse variance weighting. The Cochran's Q statistic and I squared index (the percentage of variation across studies that is due to heterogeneity rather than chance) were used to assess heterogeneity. Because significant heterogeneity was observed for both analyses, the random effects meta-analytical model was utilized as opposed to the fixed effects pooled estimate. A sensitivity analysis that only included studies with 10 or more patients was also performed to see if the pooled estimates changed with exclusion of smaller studies. Statistical analyses were performed using R V3.6.1 (www.r-131project.org). p values <0.05 were considered statistically significant.

3 | RESULTS

This systematic review and meta-analysis included 19 articles published between 2003 and 2021 that reported the outcomes of infliximab use in HS patients (Figure 1). A total of 314 HS patients were included in this study. Study designs included one randomized controlled trial (RCT) ($n = 15$), four open-label trials ($n = 43$), one prospective cohort study ($n = 58$), 12 retrospective cohort studies ($n = 191$), and one case series ($n = 7$). Study characteristics, patient demographics, disease characteristics, any concomitant treatments, treatment regimen, response to treatment, and study quality are reported in Table 1.

Mean age of patients ranged from 16.4 to 44.4 years across studies.[5–20] Of studies that reported gender, 62.4% (173/277) were female. HS severity was reported as Hurley stage in 13 studies[5–8,11–13,15,16,18,19,21,22] and Hidradenitis Suppurativa Severity Index (HSSI) in one study.[9] Of the 281 patients with HS severity data available, 100% had moderate-to-severe disease. Previously failed treatments prior to infliximab were reported in nine studies, and included adalimumab, topical and systemic antibiotics, systemic corticosteroids, acitretin, isotretinoin, methotrexate, cyclosporine, colchicine, hormonal therapy (e.g., oral contraceptive pill or cyproterone acetate), intralesional corticosteroids, laser treatment, and surgery. Seven studies reported that patients were on concomitant treatments including topical antiseptic wash, topical and systemic antibiotics, and methotrexate, among others (see Table 1). Study locations include the United States ($n = 6$), France ($n = 5$), Spain ($n = 3$), Netherlands ($n = 2$), United Kingdom ($n = 1$), Turkey ($n = 1$), and Denmark ($n = 1$). In terms of funding, only one study was sponsored by industry,[9] and two were supported by National Institute of Health (NIH).[5,7] In terms of study quality, of the five prospective trials, all studies had high risk of bias. Of the 13 cohort studies, 11 were rated as poor quality and two as good quality.

Dosing of infliximab was 5 mg/kg for 10 studies[9,11–17,20,23] and 5–10 mg/kg for five studies.[5–7,18,19] Frequency of maintenance dosing of infliximab ranged from every 4–8 weeks. The time when

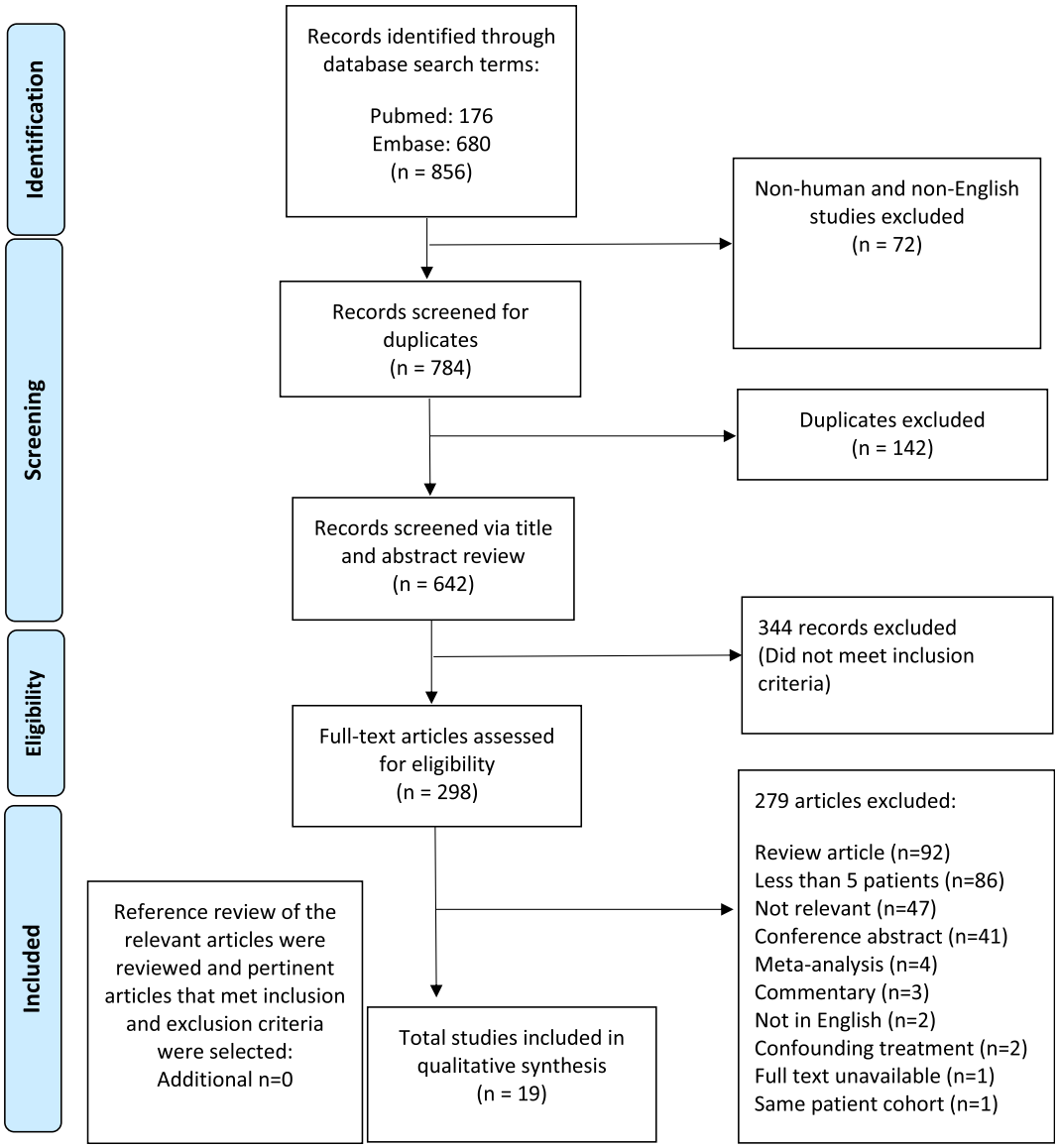

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

treatment response was measured was reported in 10 studies, and the median was 11 weeks (ranges from 3–7 days to 12 months).

The outcome measures used for meta-analysis of the pooled response rate were primarily physician reported outcomes. These included improvement per physician assessment ($n = 9$), Hidradenitis Suppurativa Clinical Response (HiSCR) ($n = 3$), Hidradenitis Suppurativa Physician Global Assessment (HS-PGA) ($n = 2$), Hidradenitis Suppurativa Score (HSS) ($n = 1$), and stable dosing regimen ($n = 1$). One study utilized the Hidradenitis Suppurativa Severity Index (HSSI), which incorporates both physician and patient assessment. Patient reported treatment response was utilized in two studies where physician assessment was not stated.

Based on a meta-analysis of data from all 19 studies, the pooled response rate of HS patients to infliximab was 83% (95% CI, 0.71–0.91) (Figure 2). Significant heterogeneity existed between studies ($I^2 = 89\%$). Seventeen of 19 studies reported a response rate greater than 50%. A sensitivity analysis found no difference in pooled response rate if only studies with 10 or more patients were included (12 studies, response rate 0.83, 0.69–0.92).

Adverse events (AEs) were reported in 18 of the 19 studies, with 94.4% (17/18) reporting AE occurrence, and 5.6% (1/18) reporting that no AE occurred. Information on AEs was available for a total of 273 patients. The most common AEs (occurring at a rate >1%) included non-serious infections (including mucocutaneous/influenza-like symptoms ($n = 24$), secondary infection of HS ($n = 4$), ENT infection ($n = 3$), abscess ($n = 3$), mycobacterial folliculitis ($n = 1$), herpes ($n = 1$), 36/273, 13.2%), infusion reactions (8/273, 2.9%), dermatologic reactions (including psoriasis ($n = 3$), pruritus ($n = 2$), eczema-like eruption ($n = 1$), and photosensitivity ($n = 1$), 7/273, 2.6%), headache (5/273, 1.8%), and elevated liver enzymes (3/273, 1.1%). Serious AEs, each with one patient report, included sepsis, tuberculosis, anaphylactic shock, death from lung malignancy, metastatic squamous cell carcinoma, Hodgkin lymphoma, lupus, and grade three multifocal motor neuropathy.

TABLE 1 Hidradenitis suppurativa and infliximab study characteristics.

Study reference, country, and design	Previously failed treatments before IFX	Concomitant medications	Patient characteristics (gender, age, HS severity, and inflammatory comorbidities)	Intervention	Efficacy	Time point	Study quality[a]
Ghias et al.[5] 2020 U.S. Prospective cohort	None reported	Topical (chlorhexidine, clindamycin) and systemic abx (clindamycin and rifampin or levofloxacin, rifampin, and metronidazole), antiandrogen	$n = 58$ (32F, 26M) Age = 34.5 ± 11.9 Hurley II ($n = 1$), III ($n = 57$)	7.5 mg/kg at weeks 0, 2, 6, then q4w ($n = 42$) 10 mg/kg q4 w ($n = 16$ pts who failed 7.5 mg/kg)	7.5 mg/kg group: HS-PGA improved w0–4 ($n = 42$, $p < 0.001$) and w4–12 ($n = 24$, $p < 0.001$) Clinical response at w4 (20/42, 47.6%) and w12 (17/24, 70.8%) 10 mg/kg group: HS-PGA improved w0–4 ($n = 16$, $p < 0.001$) Clinical response at w4 (6/16, 37.5%) and w12 (6/12, 50%)	Week 4 and 12	Good quality (Newcastle-Ottawa) Total: 8/9 Selection: 3/4 Comparability: 2/2 Outcome: 3/3
Oskardmay et al.[6] 2019 U.S. Retrospective cohort	Adalimumab, abx, surgery	Methotrexate, steroids, abx (not specified)	$n = 52$ (38F, 14M) Age = 35.5 ± 11.4 Hurley II ($n = 4$) and III ($n = 45$), unknown ($n = 3$) Obesity ($n = 40$), depression ($n = 10$), hypertension ($n = 9$), diabetes ($n = 7$)	5–10 mg/kg at week 0, 2, 6, then q4–8 w	Stable dosing regimen (unchanged dose or interval for at least 8 w): 35/52 (67%) HiSCR: 14/22 (64%) Statistically significant improvement in AN count, draining sinuses, and ESR compared to baseline overall	Mean treatment duration 54.4w (3–142 w)	Good quality (Newcastle-Ottawa) Total: 8/9 Selection: 3/4 Comparability: 2/2 Outcome: 3/3
Westerkam et al.[7] 2021 U.S. Retrospective cohort	None reported	None reported	IFX group: $n = 20$ (17F, 3M) Age = 42.2 ± 13.2 Hurley II ($n = 2$), III ($n = 18$) IFX-A group: $n = 14$ (13F, 1M) Age = 35.5 ± 10.9 Hurley II ($n = 3$), III ($n = 11$)	IFX group: IFX 10 mg/kg at week 0, 2, 6 and q4-8w IFX-A group: IFX-A 10 mg/kg at week 0, 2, 6 and q4–8 w	HiSCR (IFX-A): 10/14 (71%) HiSCR (IFX): 12/20 (60%) Both groups achieved statistically significant improved IHS4, AN count, and DLQI score. Only IFX group had statistically significant improved VAS	Minimum follow-up duration 10w	Poor quality (Newcastle-Ottawa) Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3
Van Rappard et al.[8] 2012 Netherlands Retrospective cohort	None reported	IFX followed by surgery	$n = 30$ (13F, 17M) Age = 44 (19–63) Hurley II ($n = 4$, 13%) and III ($n = 26$, 87%)	Dosing not specified Infusions at weeks 0, 2, 6, and q8 w	PGA after IFX: 1 (3%) did not improve, 7 (23%) moderately improved, 18 (60%) improved, 4 (13%) lesion free	Mean treatment duration 9.3 mo (0.5–40 mo) Mean f/u duration 50mo (max 127mo)	Poor quality (Newcastle-Ottawa) Total: 4/9 Selection: 2/4 Comparability: 0/2 Outcome: 2/3
Grant et al. 2010[9] U.S. Prospective, double-blind, placebo-controlled, crossover RCT	None reported	None reported	Intervention: $n = 15$ (12F, 3M) Age = 34 ± 13.44 (16–58) HSSI: severe ($n = 14$), moderate ($n = 1$) Placebo: $n = 23$ (14F, 9M) Age = 33.2 ± 11.4 (17–61) HSSI: severe ($n = 18$), moderate ($n = 5$)	Intervention: 5 mg/kg at weeks 0, 2, 6, then q8w to week 22 Placebo: Placebo at weeks 0, 2, 6 IFX at weeks 8, 10, 14, 22, 30	HSSI (>25% decrease): 13/15, 87% HSSI (25–50% decrease): 60% HSSI (<25% decrease): 13% Significantly improved mean DLQI, VAS, and PGA compared to placebo. HS-PGA after crossover: improved 4.8 (week 8) to 2.0 (week 16, $p < 0.01$)	Week 8 and 16 (crossover)	High risk of bias (Cochrane)
Zhang et al. 2014[10] U.S. Retrospective cohort	None reported	None reported	$n = 15$ on IFX $n = 22$ (13F, 9M) on TNF-a Of entire cohort: Hurley I ($n = 1$) II ($n = 2$), III ($n = 19$) Inflammatory bowel disease and rheumatoid arthritis ($n = 6$)	Not specified	Patient-reported pain/drainage: 11/15 (73%) improved 3 pts maintained improvement on IFX. 1 pt discontinued IFX after 16 infusions and remained stable. Average of two infusions to improve; improvement lasted 2 w–6 mo	Treatment duration 1 mo–3 y	Poor quality (Newcastle-Ottawa) Total: 4/9 Selection: 3/4 Comparability: 0/2 Outcome: 1/3

TABLE 1 (Continued)

Study reference, country, and design	Previously failed treatments before IFX	Concomitant medications	Patient characteristics (gender, age, HS severity, and inflammatory comorbidities)	Intervention	Efficacy	Time point	Study quality[a]
Montaudié et al.[11] 2017 France Prospective trial	None reported	None reported	$n = 13$ (9F, 4M) Age = 36.1 (18–59) Hurley II ($n = 9$), III ($n = 4$)	5 mg/kg at week 0, 2, 6, 14	HS-PGA (≥50% improved): 9/13 (69%) "Objective worsening" 4/13 (31%)	Week 14	High risk of bias (Cochrane)
Moriarty et al.[12] 2014 United Kingdom Retrospective cohort	Systemic abx, retinoids, steroids, cyclosporin, methotrexate, dapsone, surgery, ILK	Chlorhexidine	$n = 11$ (3F, 8M) Age = 44 (28–69) Hurley III ($n = 11$) Acne ($n = 8$), inflammatory arthropathy ($n = 4$), hypertension ($n = 4$), dissecting cellulitis of the scalp ($n = 2$), interstitial keratitis ($n = 1$), ischemic heart disease ($n = 1$), substance abuse ($n = 1$)	5 mg/kg at week 0, 2, 6, then q8 w ($n = 3$) Increased to q4 w ($n = 11$)	Physician's assessment, VAS, DLQI: 11/11 (100%) improved Secondary failure: 2/11 Remained on therapy: 9/11 Mean DLQI: decreased 15.3–12.8, Median VAS: decreased 4.1–3.4	Median treatment duration 49.1 w (18–87 w) Median f/u duration 60.3 w (18–87 w)	Poor quality (Newcastle-Ottawa) Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3
Vural et al.[21] 2019 Turkey Retrospective cohort	None reported	None reported	$n = 11$ Hurley II ($n = 5$), III ($n = 6$) Acne vulgaris ($n = 32$), acne conglobata ($n = 12$), follicular occlusion triad ($n = 16$), inflammatory arthritis ($n = 10$), diabetes ($n = 8$), pyoderma gangrenosum ($n = 5$), rheumatoid arthritis ($n = 4$), PASH ($n = 4$), Behcet's disease ($n = 2$), spondyloarthropathy ($n = 2$), Crohn's disease (n = 2), SAPHO (n = 1)	Dosing not specified	HiSCR: 9/11 (81.8%)	12 mo	Poor quality (Newcastle-Ottawa) Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3
Lesage et al.[13] 2012 France Prospective trial	Retinoids, oral abx, zinc, cyclins, surgery	None reported	$n = 10$ (5F, 5 M) Age = 38.7 (24–54) Hurley II ($n = 6$), III ($n = 4$) Obesity ($n = 5$)	5 mg/kg at weeks 0, 2, 6, then q4 w	Efficacy (HS flares): 20% complete (no HS flares), 80% partial (moderate flares not requiring surgery) Mean DLQI, mean # involved sites, and # annual flares decreased significant. HS severity decreased for all patients (Hurley stage I for 5 pts at 6 mo, 8 pts at 9 mo)	12 mo	High risk of bias (Cochrane)
Mekkes et al.[14] 2008 Netherlands Prospective trial	None reported	None reported	$n = 10$ (6F, 4M) Age = 41 (23–53) Severe HS (≥5 pus-producing lesions and acne severity score > 100)	5 mg/kg at week 0, 2, and 6 (3 infusions total)	Physician assessment: 10/10 (100%) within 2–6 w of treatment Average acne score significantly decreased at 1 mo and 1 y, mean DLQI significantly improved at 1 y, 3/10 pts had no recurrence in 2 y	Weeks 2–6, 1 and 2 y	High risk of bias (Cochrane)

(Continues)

TABLE 1 (Continued)

Study reference, country, and design	Previously failed treatments before IFX	Concomitant medications	Patient characteristics (gender, age, HS severity, and inflammatory comorbidities)	Intervention	Efficacy	Time point	Study quality[a]
Paradela et al.[15] 2012 Spain Prospective trial	Systemic abx, steroids, isotretinoin, OCP, surgical drainage, laser	None reported	$n = 10$ (6F, 4M) Age = 37.9 (23–60) Hurley II and III (specific breakdown unknown) Tabaquism ($n = 6$), obesity ($n = 5$), acne ($n = 4$), anemia ($n = 3$), alcoholism ($n = 2$), Crohn's disease ($n = 2$), gastric reflux ($n = 1$), diabetes ($n = 1$), colitis ($n = 1$), alcoholism ($n = 2$), monoclonal paraproteinemia ($n = 1$)	5 mg/kg at week 0, 2, 6, then q8 w	HSS (≥50% decrease): 8/10 (80%) Relapse: 4/8 (50%) (time to relapse 29–45 w) 2/10 (20%) discontinued after five doses due to absence of response Median disease free period: 16 w	Mean f/u duration 42.7 w (3–181 w) No treatment duration	High risk of bias (Cochrane)
Delage et al.[16] 2011 France Retrospective cohort	Abx, cyproterone acetate, zinc, isotretinoin	None reported	$n = 7$ (4F, 3M) Age = 37 (22–47) Hurley II ($n = 6$), III ($n = 1$)	5 mg/kg at week 0, 2, and 6, then q8 w	DLQI improvement: 6/7 Global improvement: 6/7 Median changed 70% for global improvement, 70% for pain	Mean follow-up duration 72 w	Poor quality (Newcastle-Ottawa) Total: 4/9 Selection: 3/4 Comparability: 0/2 Outcome: 1/3
Fardet et al.[17] 2007 France Retrospective cohort	Oral abx, topical abx, isotretinoin, surgery	No concomitant treatment within 2 mo of infliximab	$n = 7$ (3F, 4M) Age = 44.4 (24–76) Mean sartorius score 82	5 mg/kg at weeks 0, 2, 6 ($n = 7$) and 10 ($n = 5$)	Physician and patient assessment: 5/7 (71%) improved Sartorius score (≥40% improved): (43%) Physician assessment: 2/5 (40%) improved	Week 6 Week 10	Poor quality (Newcastle-Ottawa) Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3
Fougerousse et al.[18] 2020 France Case series	Abx, retinoids, surgery, adalimumab	None reported	$n = 8$ (3F, 5M) Age = 16.4 (14–20) Hurley II ($n = 6$), III (n = 2) Acne ($n = 5$), dissecting cellulitis of the scalp ($n = 2$), pilonidal cyst ($n = 1$), asthma ($n = 1$)	5 mg/kg ($n = 3$) 10 mg/kg ($n = 4$) Not spec ($n = 1$)	HiSCR: 6/7 pts (86%)	Median treatment duration 7 mo (min 4 mo)	
Martin-Ezquerra et al.[22] 2015 Spain Retrospective cohort	None reported	12/19 total received concomitant abx (not specified)	$n = 7$ infliximab Total $n = 19$ (9F, 10M) Hurley II ($n = 8$), III ($n = 11$) Plaque-type psoriasis ($n = 3$), pilonidal cyst ($n = 2$), rheumatoid arthritis ($n = 2$), spondyloarthropathy ($n = 1$), Still's disease ($n = 1$), SAPHO ($n = 1$)	Not specified	IFX as 1st line treatment ($n = 6$): Physician assessment: complete response in 2/6 (33%), partial 3/6 (50%), ineffective 0/6, worse 1/6 (16%) Patient assessment: complete response in 4/6 (66%), partial 0/6, ineffective 1/6 (16%), worse 1/6 (16%) IFX as 2nd line treatment ($n = 1$): Physician assessment: 1/1 partial improvement	Mean treatment duration 12mo (4-32 mo) No f/u duration	Poor quality (Newcastle-Ottawa) Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3

TABLE 1 (Continued)

Study reference, country, and design	Previously failed treatments before IFX	Concomitant medications	Patient characteristics (gender, age, HS severity, and inflammatory comorbidities)	Intervention	Efficacy	Time point	Study quality[a]
Fernández-Vozmediano et al.[19] 2007 Spain Retrospective cohort	Oral abx, steroids, retinoids, surgery, OCP, cyclosporin	Prednisone 1 mg/kg/day +/− cyclosporin 5 mg/kg/day	$n = 6$ (4F, 2M) Age = 34.8 (27–45) Hurley III ($n = 6$)	5 mg/kg at weeks 0, 2, 6, then q4 w	Physician and patient assessment (subjective that is, itching/pain and objective that is, lesion number/size improvements): 6/6 (100%) Hurley stage: III to I ($n = 4$), III to II ($n = 2$) Successive decline in treatment efficacy: 3/6 (50%)	6 months (monitoring period)	Poor quality (Newcastle-Ottawa) Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3
Sand et al.[23] 2015 Denmark Retrospective cohort	Abx, isotretinoin, dapsone, triamcinolone	None reported	$n = 6$ "Severe recalcitrant HS"	5 mg/kg q8 w	Symptoms resolved: 1/6 (16.7%) No response: 5/6 (4/5 on ADA and IFX, 1/5 on IFX and certolizumab)	Mean treatment duration 13 mo (1–50 mo) No f/u duration	Poor quality (Newcastle-Ottawa) Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 2/3
Sullivan et al.[20] 2003 U.S. Retrospective cohort	OCP, oral abx, steroids, ILK, cyclosporin, isotretinoin, Colchicine	Cyclosporin, prednisone, ILK, OCP	$n = 5$ (4F, 1M) Age = 43.4 (28–57)	First infusion of 5 mg/kg ($n = 5$) Second infusion of 5 mg/kg in 4–6 w ($n = 3$)	Physician assessment (decreased induration, sinus drainage and tenderness): 100% (5/5) Self-reported disease activity (scale of 1–10): decreased after IFX infusion ($p = 0.0001$, paired t test)	3–7 days after infusion	Poor quality (Newcastle-Ottawa) Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3

Notes: Fair quality: 2 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome/Exposure domain. Poor quality: 0 or 1 star in Selection domain OR 0 stars in Comparability domain OR 0 or 1 stars in Outcome/Exposure domain. Good quality: 3 or 4 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome/Exposure domain.

Abbreviations: Abx, antibiotic; AN, abscess and inflammatory nodule; DLQI, Dermatology Life Quality Index; ESR, erythrocyte sedimentation rate; F, female; f/u, follow-up; HiSCR, Hidradenitis Suppurativa Clinical Response; HS-PGA, Hidradenitis Suppurativa Physician Global Assessment; HSS, Hidradenitis Suppurativa Score; HSSI, Hidradenitis Suppurativa Severity Index; ILK, intralesional Kenalog; IFX, infliximab; kg, kilograms; M, male; mg, milligrams; mo, months; n, number; OCP, oral contraceptives; PASH, pyoderma gangrenosum, acne, and hidradenitis suppurativa; PGA, Physician Global Assessment; pts, patients; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis; VAS, visual analog score for pain; w, week; y, year.

[a]Cochrane risk of bias used for clinical trials. Newcastle-Ottawa scale (NOS) used for cohort studies. Thresholds for converting the NOS rating to Agency for Healthcare Research and Quality (AHRQ) standards (good, fair, and poor).

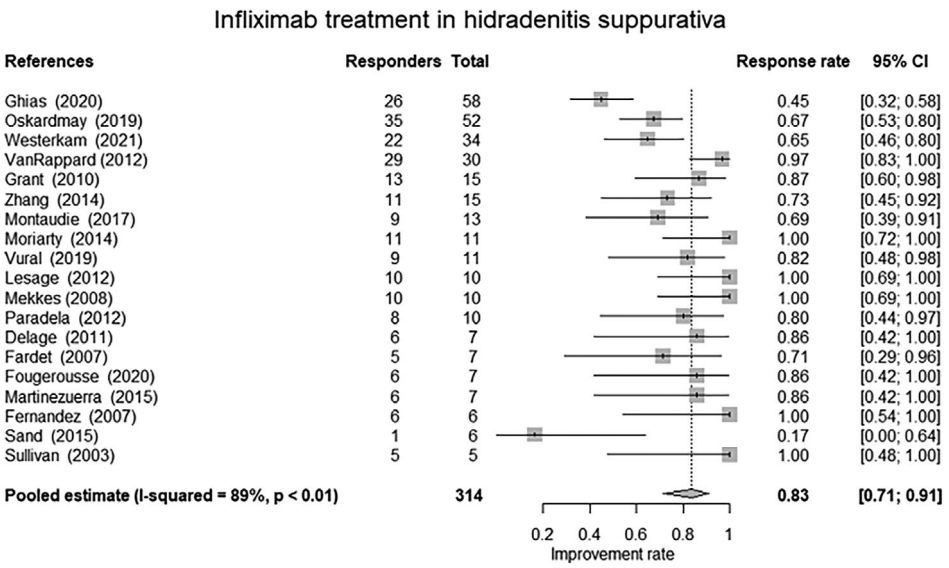

FIGURE 2 Forest plot of random effects meta-analysis among hidradenitis suppurativa patients treated with infliximab.

4 | DISCUSSION

In this meta-analysis, we found that overall infliximab is an effective treatment for patients with moderate-to-severe HS. Random effects meta-analysis showed a pooled response rate of 83%. The rate of serious adverse events was 2.9%. Prospective studies on infliximab in HS are lacking: a majority were retrospective cohort studies, and only 26.3% (5/19) were RCTs or open-label trials.

The pathophysiology of HS is still under investigation. However, multiple inflammatory cytokines have been implicated, including TNF alpha, IL-1, IL-17, IL-12, IL-23, and IL-36,[24] leading to growing investigation of biologics and targeted therapies. HS is oftentimes recalcitrant to multiple therapies, and rigorous data on medications with high efficacy remain lacking. Currently, adalimumab, a TNF-alpha agent, is the only FDA-approved medication for moderate-to-severe HS. Two phase three trials of adalimumab in HS found a HiSCR of 41.8% ($n = 307$) and 58.9% ($n = 326$).[25] A systematic review of randomized controlled trials of adalimumab in HS reported a superior clinical response of adalimumab compared to placebo (relative risk 1.76, 95% CI 1.35–2.29).[26] Other biologics used in HS have been less rigorously studied. For example, anakinra (IL-1 antagonist), had an RCT showing HiSCR of 78% at 12 weeks and an open-label trial where 83% of patients had a significant mean decrease in modified Sartorius score at 8 weeks, however, trial numbers were small ($n = 10$ and 6, respectively).[27,28] A 2020 systematic review of ustekinumab, an IL-12 and IL-23 inhibitor, found that out of 49 patients, a positive response was seen in 38 (78%) of patients.[29] Though data for these agents appear promising, the small numbers of patients limit the ability to broadly generalize these results across HS patients.

Our findings support the findings in previous systematic reviews examining the efficacy of infliximab in HS. Haslund et al. reported a 87% response rate in 52 patients (20 studies),[30] van Rappard et al. reported a 82% response rate of 114 patients (43 studies),[31] and Blok et al. reported a 89% response rate of 147 patients (42 studies).[32] Our study adds to the literature by providing an updated systematic review including studies from the past decade, excluding case reports and series with less than five patients, and performing a meta-analysis of included studies. With over 300 patients included in this meta-analysis, there is stronger evidence to support this high response rate for infliximab. We also examined reported side effects in this HS patient population and found them to be in line with the expected side effect profile for infliximab.

Limitations of this study, common to most systematic reviews on HS treatments, include the small number of prospective studies on infliximab in HS. All but one study took place in North America or Europe, potentially limiting generalizability of our findings. Another limitation is the inability to compare response rates based on presence of different comorbidities. Furthermore, substantial heterogeneity existed between studies with respect to study design and timing and methods for outcome measurement. Thus, caution is warranted when attempting to directly compare the efficacy rate found in this review with that of other HS treatment options.

Future studies on the efficacy of infliximab in HS should include larger RCTs with more diverse study countries and comparative RCTs with other biologic agents. They should also investigate optimal dosing regimen, the impact of combination treatment with antibiotics or other immunomodulators versus monotherapy with infliximab, necessity of concomitant medication such as methotrexate to prevent anti-drug antibodies, and investigation of patient or disease characteristics that may predict treatment response. In addition, use of standardized HS severity and treatment outcome measures in studies will allow for improved measurement of pooled outcomes in meta-analyses.

Overall, infliximab is promising as an efficacious treatment for HS. Larger RCTs are needed to explore the comparative efficacy of infliximab in HS against other biologics as well as the efficacy of infliximab when combined with other treatment modalities.

AUTHOR CONTRIBUTIONS

Terri Shih and Katrina Lee completed data collection, and Tristan Grogan completed data analysis. Terri Shih and Katrina Lee wrote the

manuscript. Katrina Lee, Devea R. De, Vivian Y. Shi, and Jennifer Lin Hsiao edited the manuscript. Vivian Y. Shi and Jennifer Lin Hsiao conceptualized and led the project.

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CONFLICT OF INTEREST

JLH is on the Board of Directors for the Hidradenitis Suppurativa Foundation, has served as a consultant for Boehringer Ingelheim, Novartis, and UCB, and has served as a consultant and speaker for AbbVie. VYS is on the board of directors for the Hidradenitis Suppurativa Foundation (HSF), is a stock shareholder of Learn Health and has served as an advisory board member, investigator, speaker, and/or received research funding from Sanofi Genzyme, Regeneron, AbbVie, Eli Lilly, Novartis, SUN Pharma, LEO Pharma, Pfizer, Incyte, Boehringer-Ingelheim, Aristea Therapeutics, Menlo Therapeutics, Dermira, Burt's Bees, Galderma, Kiniksa, UCB, WebMD, TARGET-Pharmasolutions, Altus Lab, MYOR, Polyfin, GpSkin and Skin Actives Scientific. There was no financial transaction for the preparation of this manuscript. All other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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