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ORIGINAL RESEARCH

Ustekinumab in Hidradenitis Suppurativa: A Systematic Review and Meta-analysis

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ABSTRACT

***Introduction*:** Hidradenitis suppurativa (HS) is a frequently debilitating, inflammatory skin condition. Patients may have a limited response to adalimumab, currently the only Food and Drug Administration (FDA)-approved biologic treatment for HS. Ustekinumab is an interleukin-12/23 inhibitor that has been utilized in HS, but there is a lack of an updated systematic review on its efficacy and safety. The aim of this study is to perform a systematic review and meta-analysis of the literature on the efficacy and safety of ustekinumab for HS.

***Methods*:** In October 2022, MEDLINE and Embase databases were searched for articles on ustekinumab in HS. Data extraction was performed on relevant articles by two reviewers. The primary study outcome was the pooled response rate of HS to ustekinumab. A fixed-effects meta-analysis was performed, and Cochran's *Q* statistic and *I* squared index were used to assess heterogeneity. Statistical significance was determined at $p<0.05$. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

***Results*:** From 2012 to 2022, ten articles (nine case series and one prospective trial) with 88 patients met the inclusion criteria. Patients with reported disease severity had Hurley stage II (17.6%, 12/68) or III (82.4%, 56/68) disease. The majority (80.7%, 71/88) had previously failed at least one biologic treatment. A meta-analysis of

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all ten studies showed a pooled response rate of 67% (95% CI 0.57–0.76). Study limitations include a small number of patients and randomized controlled trials (RCTs).
Conclusions: Ustekinumab may be a helpful treatment option to consider for HS that is recalcitrant to first-line biologic therapies, but RCTs are needed to determine optimal dosing regimens and the specific patient populations that would benefit the most from this agent.

Keywords: Biologic treatments; Ustekinumab; Hidradenitis suppurativa; Systematic review; Meta-analysis

Key Summary Points

Although ustekinumab is used to manage hidradenitis suppurativa (HS), there is a lack of comprehensive data regarding its safety and efficacy.

In this systematic review and meta-analysis of ten articles with 88 patients, we found that the pooled response rate to ustekinumab was 67%. The majority of patients had previously failed treatment with one or more biologic agents.

Our study demonstrates the potential efficacy of ustekinumab as a secondary or tertiary treatment option for HS.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, oftentimes debilitating skin condition that presents with abscesses, nodules, sinus tracts, and scarring, typically in intertriginous areas [1]. The pathogenesis of HS is complex and encompasses genetic [2], epigenetic [3], immunological, hormonal, and environmental factors [4]. Though many medical and procedural therapies are used to treat the disease, the condition is often recalcitrant to treatment [5]. Despite recent advances in treatments for HS, there is a substantial unmet need for effective therapeutic solutions [6]. Adalimumab, a tumor necrosis factor (TNF)-alpha inhibitor, and secukinumab, an interleukin (IL)-17 inhibitor, are currently the only FDA-approved biologic agents for the treatment of HS. However, some patients may not have an adequate or durable response to TNF-alpha or IL-17 inhibitors [7]. Ustekinumab is an IL-12 and IL-23 inhibitor that has been utilized in patients with HS, but there is a paucity of data on its efficacy and safety for this disease [8]. The aim of this study is to systematically evaluate existing literature on the efficacy and safety of ustekinumab treatment in HS and conduct a meta-analysis. This information will be useful for clinicians as they counsel patients with HS, particularly those who have inadequate responses to previous biologic treatments, regarding treatment with ustekinumab.

METHODS

Search Strategy

This study was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) and was preregistered on PROSPERO (CRD42022364634). On 5 October 2022, two independent reviewers (R.M. and J.S.) searched MEDLINE and Embase databases from inception to start date with the following terms: ("hidradenitis suppurativa" OR "hidradenitis" OR "acne inversa" OR "velpeau disease" OR "verneuil disease") AND ("ustekinumab"). A total of 361 articles were identified. Articles were filtered to remove non-English-language and nonhuman studies. Duplicate articles were excluded, and the titles and abstracts of the remaining articles were screened for relevance. Full-text review was then performed on the remaining 112 articles by the two independent reviewers (R.M. and J.S.). Studies that described ustekinumab as the primary intervention for HS, contained outcome efficacy data, and had three or more patients were considered eligible for inclusion. Reviews, conference abstracts, meta-analyses, commentaries, and nonrelevant

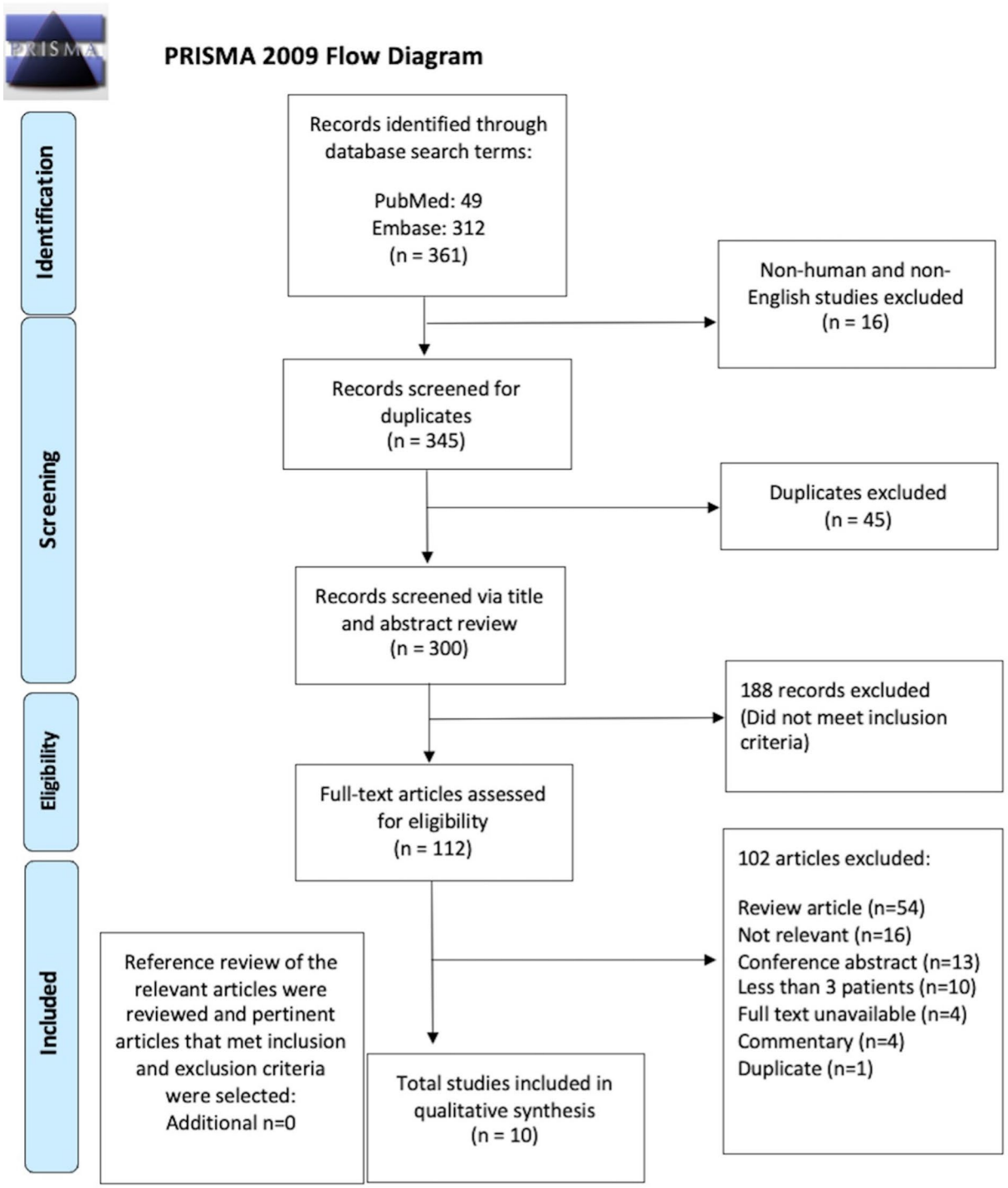

Fig. 1 PRISMA flow diagram. Moher D, Liberati A, Tetziaff J, Altman DG, The PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org

articles were excluded. Any discrepancies were discussed to consensus with a third reviewer (J.L.H.). Reference lists of articles that met the inclusion criteria were screened for additional relevant articles, and none were identified.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The databases used in this study are publicly available: MEDLINE: https://pubmed.ncbi.nlm.nih.gov/ and Embase: https://www.embase.com/search/quick.

Data Extraction

Two reviewers (R.M. and J.S.) independently completed data extraction. Each article was reviewed, and the following information was collected: study design, country of study, patient characteristics, HS severity, regions of the body affected by HS, previously failed treatments, concomitant treatments, inflammatory comorbidities, study intervention, duration of treatment/timepoint of efficacy measurement, treatment response, and adverse effects.

Meta-analysis

A meta-analysis was conducted to determine the pooled estimated response rate of HS to ustekinumab. To determine response, predetermined primary clinician reported outcome measures were used whenever available, followed by physician assessments; the HS Clinical Response (HiSCR) was prioritized if different clinician reported outcome measures were available. Forest plots were constructed using the proportion of patients with a reported response (including partial response) to ustekinumab, and standard errors/confidence intervals were computed using inverse variance weighting (Fig. 2). 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 not observed, a fixed-effects meta-analytical model was utilized as opposed to a random-effects pooled estimate. Statistical analyses were performed using R version 4.1.0 (www.r-project.org). p-Values < 0.05 were considered statistically significant.

RESULTS

Ten articles published between 2012 and 2022 met inclusion criteria. There were 88 patients across nine case series and one prospective trial. Study locations included Spain ($n = 5$), USA ($n = 1$), the Netherlands ($n = 1$), Denmark ($n = 1$), Ireland ($n = 1$), and Germany ($n = 1$). Study characteristics, patient characteristics, treatment regimens, previous treatments,

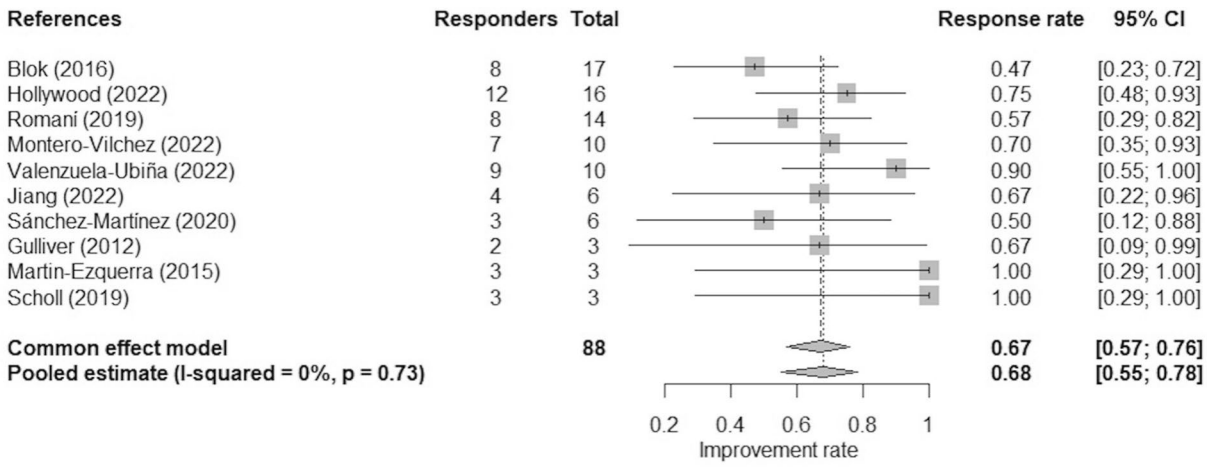

Fig. 2 Forest plot of fixed effects meta-analysis among hidradenitis suppurativa patients treated with ustekinumab

Table 1 Hidradenitis suppurativa and ustekinumab study characteristics

Study reference	Dosing	Patients characteristics (age, gender, affected areas, inflammatory comorbidities, previously failed treatments, concomitant treatments)	Treatment response and adverse effects	Timepoint(s) of efficacy measurement
Blok et al. 2016 [9]; the Netherlands; prospective trial[a]	45 mg SC (90 mg SC for pts > 100 kg) at 0, 4, 16, 28w	$n = 17$ (13F, 4M), mean age = 35 (range 20–53) Comorbidities: obesity ($n = 7$); eczema, acne conglobata ($n = 3$); HTN ($n = 2$); hypothyroidism, diabetes, hyperlipidemia, hypercholesterolemia, CD ($n = 1$) PFT: abx ($n = 16$); topical resorcinol ($n = 12$); deroofing ($n = 11$); I&D ($n = 7$); ILK ($n = 6$); oral retinoids, excision ($n = 5$); topical steroids ($n = 4$); IFX ($n = 3$); systemic steroids, IPL-EPI ($n = 2$); etanercept ($n = 1$) CT: topical resorcinol ($n = 4$); ILK ($n = 2$); I&D ($n = 1$)	40 w HiSCR: 47.1% (8/17) mSS: 112.1 → 60.2 ($p < 0.01$) Marked improvement: 35.3% (6/17) Moderate improvement: 47.1% (8/17) Mild improvement: 5.9% (1/17) No change or worsening: 11.8% (2/17) mHSLASI: 26.3 → 19.6 ($p = 0.01$) Marked improvement: 17.6% (3/17) Moderate improvement: 35.3% (6/17) Mild improvement: 17.6% (3/17) No change or worsening: 29.4% (5/17) DLQI: 41.2% (7/17) VAS pain: 5.8 → 4.6 Skindex-29: 35.3% (6/17) improved 17.6% (3/17) withdrew d/t no response, 5.9% (1/17) withdrew d/t psychological reasons, 5.9% (1/17) withdrew d/t urticaria AE: headache, fatigue, upper respiratory infections (unspecified); urticaria ($n = 1$)	40 w

Table 1 continued

Study reference	Dosing	Patients characteristics (age, gender, affected areas, inflammatory comorbidities, previously failed treatments, concomitant treatments)	Treatment response and adverse effects	Timepoint(s) of efficacy measurement
Hollywood et al. 2022 [10]; Ireland; case series	Not specified	*n* = 16 (12F, 4M), mean age = 37 (22–70) Disease severity: Hurley II (*n* = 4), III (*n* = 12) Comorbidities: CD (*n* = 3); pyoderma gangrenosum, psoriasis (*n* = 2) PFT: ADA, oral abx (*n* = 16); metformin (*n* = 11); IFX (*n* = 9); liraglutide, ANK (*n* = 4); spironolactone (*n* = 2)	Physician assessment Improved: 75% (12/16) Unchanged: 25% (4/16) DLQI: 16.6 (1–25) → 10.25 (range 1–27) Drug survival 6 mo: 93.8% (15/16) 12 mo: 61.5% (8/13) 24 mo: 50% (4/8) 36 mo: 33.3% (2/6) AE: recurrent infections (*n* = 1)	Mean tx duration: 16 mo

Table 1 continued

Study reference	Dosing	Patients characteristics (age, gender, affected areas, inflammatory comorbidities, previously failed treatments, concomitant treatments)	Treatment response and adverse effects	Timepoint(s) of efficacy measurement
Romaní et al. 2019 [22]; Spain; case series	IV loading dose (≤ 55 kg: 260 mg; > 55 to ≤ 85 kg: 390 mg; > 85 kg: 520 mg) → 90 mg q8w SC	*n* = 14, ages = 19–63 AA: axillae (*n* = 8); gluteus, groin (*n* = 7); perineum (*n* = 5); perianal (*n* = 4); genital (*n* = 3); pubis (*n* = 2); scrotum, nape (*n* = 1) Disease severity: Hurley II (*n* = 2), III (*n* = 12) Comorbidities: CD (*n* = 6); psoriasis, DM, HTN, DLP (*n* = 2); spondyloarthropathy (*n* = 1) PFT: ADA (*n* = 14); abx (*n* = 13); surgery (*n* = 10); IFX (*n* = 5); corticosteroids (*n* = 3); cyclosporine, AZA, colostomy, MTX (*n* = 2), ANK, certolizumab, colectomy (*n* = 1) CT: oral/intralesional corticosteroids or abx for flares (*n* = 4)	HiSCR: 21.4% (3/14) at 8 w and 57.1% (8/14) at 16 w IHS4: 76.9% (10/13) improved at 8 w, 83.3% (10/12) at 16 w PGA: 53.8% (7/13) improved at 8 w, 50% (7/14) at 16 w VAS pain: 100% (11/11) improved at 8 and 16 w DLQI: 83.3% (10/12) improved at 8 w, 84.6% (11/13) at 16 w HiSCR and ≥ 30% improvement in DLQI and VAS pain: 50% (7/14) at 16 w Only ≥ 30% improvement in DLQI and VAS pain: 71.4% (10/14) at 16 w 91.6% had minimal clinically important difference in DLQI (reduction of 4) 14.3% (2/14) left study d/t lack of efficacy or patient preference	8 w, 16 w

Table 1 continued

Study reference	Dosing	Patients characteristics (age, gender, affected areas, inflammatory comorbidities, previously failed treatments, concomitant treatments)	Treatment response and adverse effects	Timepoint(s) of efficacy measurement
Montero-Vilchez et al. 2020 [8]; Spain; case series	Induction dose: 45 mg or 90 mg (weight-based) SC → 45 mg q12w SC	$n = 10$ (4F, 6 M), median age = 44 (range 35–44) AA: Groin ($n = 6$); axillae, gluteal ($n = 4$); genital, face, perineum ($n = 2$); pubis, breast ($n = 1$) Disease severity: Hurley II ($n = 2$), III ($n = 8$) Comorbidities: acne conglobate, obesity ($n = 3$); CD ($n = 2$); pilonidal sinus, palmoplantar pustulosis, seborrheic dermatitis ($n = 1$) PFT: retinoids, oral abx, ADA ($n = 8$); surgery ($n = 6$), systemic steroids ($n = 5$); IFX ($n = 4$); ILK ($n = 3$); cyclosporine, interferon, phototherapy ($n = 1$)	HS-PGA Improved (decrease ≥ 1 point): 70% (7/10) Unchanged: 30% (3/10) NPRS Improved (decrease ≥ 2 points): 80% (8/10) Unchanged: 20% (2/10)	Median tx duration: 48 w

Table 1 continued

Study reference	Dosing	Patients characteristics (age, gender, affected areas, inflammatory comorbidities, previously failed treatments, concomitant treatments)	Treatment response and adverse effects	Timepoint(s) of efficacy measurement
Valenzuela-Ubiña et al. 2020 [23]; Spain; case series	90 mg q8w SC ($n = 9$; 3 received an IV loading dose), 45 mg q12w SC ($n = 1$; 1 received an IV loading dose)	$n = 10$ (6F, 4 M), median age = 42.9 Disease severity: Hurley II ($n = 1$), III ($n = 9$) AA: inguinal, genital ($n = 8$); axillae ($n = 7$); thighs, perineal, perianal ($n = 3$); gluteal, intermammary, submammary ($n = 2$) Comorbidities: psoriasis, CD ($n = 3$); UC, spondyloarthropathy, acne, PCOS, SLE ($n = 1$) PFT: oral abx ($n = 10$); ADA ($n = 8$); surgery ($n = 7$); oral steroids, dapsone, IFX ($n = 6$); ILK, oral retinoids, MTX ($n = 5$); ANK ($n = 4$); cyclosporine ($n = 3$); AZA, finasteride, IV abx, IV steroids ($n = 2$); metformin, SFZ, OCPs ($n = 1$)	HiSCR: 90% (9/10), patient on lower dose did not respond Hurley stage decreased in 80% (8/10) HS-PGA decreased by at least 1 point in 90% (9/10) 100% (10/10) had decrease in analytical parameters of systemic inflammation (ASPI) Pt with lower dose did not respond	Mean treatment time: 17.6 mo Mean response time: 4.7 mo
Jiang et al. 2022 [11]; USA; case series	90 mg q4w ($n = 5$), 90 mg q8w ($n = 1$)	$n = 6$ (5F, 1 M), mean age = 53.2 ± 10.2 Disease severity: Hurley III ($n = 6$) PFT: ADA ($n = 6$); IFX ($n = 4$)	IHS4: − 36.1%, 100% (4/4) improved at 8–12 w, 40% (2/5) improved at 13–21 w VAS pain: − 2.5 AN count: 100% (3/3) improved after 8–12 w, 50% (2/4) improved at 13-21w	8–12 w, 13–21 w

Table 1 continued

Study reference	Dosing	Patients characteristics (age, gender, affected areas, inflammatory comorbidities, previously failed treatments, concomitant treatments)	Treatment response and adverse effects	Timepoint(s) of efficacy measurement
Sanchez-Martinez et al. 2020 [24]; Spain; case series	IV loading dose (weight adjusted) → 90 mg q8w SC	*n* = 6 (3F, 3M), median age = 47 (range 31–59) Disease severity: Hurley III (*n* = 6) Comorbidities: DS, RA, autoimmune hypothyroidism, CD, DM (*n* = 1) PFT: abx, ADA, retinoids (*n* = 6); surgery, systemic steroids (*n* = 4); MTX, finasteride, topical steroids (*n* = 2); AZA (*n* = 1) CT: ILK, abx, retinoids (*n* = 2); surgery (*n* = 1)	HiSCR: 50% (3/6) IHS4: 83.3% (5/6) improved	12 w
Gulliver et al. 2012 [25]; Denmark; case series	45 mg SC at 0, 1, and 4mo then q3mo; dose increased to 90 mg at 6 mo in *n* = 1	*n* = 3 (2F, 1M), ages = 32, 32, 30 AA: Axillae, groin (*n* = 3); trunk, R neck, gluteal (*n* = 1) Disease severity: Hurley II (*n* = 2), III (*n* = 1) PFT: oral abx (*n* = 3); topical abx, ADA, retinoids (*n* = 2); steroids, topical resorcinol, IFX, efalizumab, IV abx, ILK (*n* = 1)	Physician assessment Complete response: 33.3% (1/3) Partial response: 33.3% (1/3) after increasing dose to 90 mg No response: 33.3% (1/3) AE: cystitis, psoriasiform dermatitis, arthritis, bacterial infection of axilla (*n* = 1)	6 mo
Martin-Ezquerra et al. 2015 [26]; Spain; Case series	Not specified	*n* = 3 (UST as first-line tx in 2 and second-line tx in 1) PFT: surgery (*n* = 2); TNF-alpha inhibitor (*n* = 1)	Physician and patient assessment UST as first-line tx Complete response: 50% (1/2) Partial response: 50% (1/2) UST as second-line tx Partial response 100% (1/1)	Mean duration of tx: 18 mo (*n* = 2), unspecified (*n* = 1)

Table 1 continued

Study reference	Dosing	Patients characteristics (age, gender, affected areas, inflammatory comorbidities, previously failed treatments, concomitant treatments)	Treatment response and adverse effects	Timepoint(s) of efficacy measurement
Scholl et al. 2019 [27]; Germany; case series	IV loading dose (≤ 55 kg: 260 mg; > 55 to ≤ 85 kg: 390 mg; > 85 kg: 520 mg) → 90 mg SC at week 8 → 90 mg q8w or q12w as tolerated	*n* = 3 (1F, 2M), ages = 31M, 25F, 29M Disease severity: Hurley II (*n* = 1), III (*n* = 2) PFT: Resistant to at least 1 biologic and first- or second-line antibiotic regimens CT: deroofing (*n* = 2); oral abx, local excision (*n* = 1)	100% (3/3) improved after 12 mo Pt 1: increased lesion count and worsened DLQI at 6mo requiring deroofing at 10mo; complete remission at 12 mo Pt 2: 40% improvement of pain, mHSS, SAHS, DLQI Pt 3: required oral abx after 4w; after 6mo, SAHS and mHSS improved by 30% but pain scores and DLQI remained unchanged so required oral abx and deroofing/local excision; after 12 mo, 30% improvement in DLQI, pain scores, stable disease activity, reduced nodule count	q3mo

AA affected areas, *Abx* antibiotics, *ADA* adalimumab, *AE* adverse events, *AN* abscesses and inflammatory nodules, *ANK* anakinra, *AZA* azathioprine, *CD* Crohn's disease, *CT* concomitant treatments, *DLP* dyslipidemia, *DLQI* dermatology life quality index, *DM* diabetes mellitus, *DS* Down syndrome, *d/t* due to, *F* female, *HiSCR* hidradenitis suppurativa clinical response, *HTN* hypertension, *I&D* incision and drainage, *IHS4* international hidradenitis suppurativa severity score system, *IFX* infliximab, *ILK* intralesional Kenalog, *IPL-EPI* intense pulse light plus epilation, *IV* intravenous, *kg* kilogram, *L* left, *M* male, *mg* milligram, *mHSLASI* modified hidradenitis suppurativa lesion area and severity index, *mo* month, *mSS* modified Sartorius Score, *MTX* methotrexate, *N* number, *OCP* oral contraceptive, *PCOS* polycystic ovarian syndrome, *PFT* previously failed treatments, *PGA* physician global assessment, *Pt* patient, *R* right, *RA* rheumatoid arthritis, *SAHS* severity assessment of hidradenitis suppurativa, *SC* subcutaneous, *SFZ* sulfasalazine, *SLE* systemic lupus erythematous, *TNF* tumor necrosis factor, *TX* treatment, *UC* ulcerative colitis, *UST* ustekinumab, *VAS* visual analog scale, *w* week

[a]High risk of bias as per the Cochrane risk of bias assessment used for clinical trials

concomitant treatments, inflammatory comorbidities, responses to treatment, adverse events, and study quality are summarized in Table 1. In terms of study quality, the prospective trial had a high risk of bias.

Across all studies, patient age ranged from 20 to 70 years. The mean age of patients was reported in one prospective trial and two case series as 35, 37, and 53.2 years [9–11], respectively. Of the eight studies that included gender data, 64.8% (46/71) of patients were female. HS severity was reported as Hurley stage in 68 patients across eight studies, and the majority of patients had Hurley stage III disease (82.4%, 56/68) followed by stage II (17.6%, 12/68). Previously failed treatments were described in all studies and included topical resorcinol, topical or systemic antibiotics, steroids (topical, systemic, or intralesional), adalimumab, infliximab, certolizumab, etanercept, anakinra, efalizumab, methotrexate, azathioprine, cyclosporine, sulfasalazine, oral retinoids, dapsone, liraglutide, metformin, spironolactone, finasteride, interferon, intense pulsed light plus epilation, phototherapy, deroofing, incision and drainage, and surgery. The majority (80.7%, 71/88) of patients had previously failed at least one biologic treatment. Nearly three-fourths (71.6%, 63/88) had failed adalimumab, and more than one-third (36.4%, 32/88) had failed infliximab. Comorbidities were reported in 73 patients across six studies; 23.3% (17/73) had Crohn's disease or ulcerative colitis, and 9.6% (7/73) had psoriasis. Concomitant treatments reported in four studies include topical resorcinol, systemic and intralesional steroids, incision and drainage, oral antibiotics, oral retinoids, deroofing, and surgery.

Dosing of ustekinumab was 90 mg (mg) in four studies, 45 or 90 mg in three studies, 45 mg in one study, and unspecified in two studies. Across eight studies, the frequency of the ustekinumab maintenance dosage ranged from every 4 to 12 weeks. The initial loading dose was delivered intravenously in four studies and subcutaneously in three studies. The timepoints for efficacy measurement ranged from 8 weeks to 18 months across all ten studies. Clinician-reported outcome measures used for meta-analysis of the pooled response rate included HiSCR ($n=4$), physician assessment ($n=4$), HS-Physician Global Assessment ($n=1$), and International HS Severity Score System (IHS4) ($n=1$). The overall response rate for weight-based intravenous (IV) loading dose followed by 90 mg every 8–12 weeks subcutaneously (SC) was 65.4% (17/26); the response rate for SC loading dose followed by doses ranging from 45 to 90 mg every 8–12 weeks was 56.7% (17/30).

On the basis of the meta-analysis of the ten included studies, the pooled response rate of patients with HS responding to ustekinumab was 67% (95% CI 0.57–0.76). Nonsignificant heterogeneity was observed between studies ($I^2=0\%$, $p=0.73$) (Fig. 2). Eight out of ten studies reported a response rate greater than 50%. Adverse events were reported in 4.5% (4/88) of patients across studies. These included headache, fatigue, upper respiratory infection, urticaria, cystitis, psoriasiform dermatitis, arthritis, bacterial axillary infection, and recurrent infections.

DISCUSSION

Our study found that ustekinumab may be an effective and safe treatment option for patients with recalcitrant, moderate–severe HS. The fixed-effects meta-analysis showed a pooled response rate of 67%, and over 80% of the patients had previously failed at least one other biologic agent. Adverse events were reported in only 4.5% of patients with HS on ustekinumab treatment.

Although the exact pathophysiology of HS remains unclear, chronic upregulation of inflammatory cytokines is believed to play a vital role in the initiation and propagation of the disease. Disproportionately high levels of IL-12 and IL-23 have been found in HS lesions, suggesting potential benefits from biologic agents that block these cytokines and reduce the downstream maturation of IL-17-producing T-helper cells [12].

The optimal dosing regimen for ustekinumab in patients with HS has not yet been established. Jiang et al.'s 2022 study demonstrated that high-dose, high-frequency ustekinumab may be effective in reducing IHS4 and pain scores in patients with HS, but the study was limited by a small

sample size of six patients [11]. In a 2021 systematic review and meta-analysis by Meserve et al., increasing the frequency of doses to every 4 or 6 weeks instead of 8 weeks, and/or intravenous reinduction, led to a clinical response in 55% of 925 patients with Crohn's disease who previously had an inadequate response to the standard ustekinumab dosing regimen [13]. Increasing the ustekinumab dosing frequency from every 12 weeks to 8 weeks has also been reported to be beneficial in patients with psoriasis [14]. More investigation is needed to understand the potential advantages of dose intensification in patients with HS who are initially nonresponders or partial responders to ustekinumab treatment. Use of ultrasonographic characteristics, such as vascularization and fibrosis [15], may also be considered in the future as adjunct tools to monitor responses to treatment.

In addition, it is currently unclear whether the IV loading dose for HS has benefits over an initial SC loading dose. One study found that ustekinumab trough levels and clinical outcomes were comparable in 17 patients with Crohn's disease who completed SC induction compared with 249 patients with Crohn's disease who received intravenous induction in another clinical trial [16]. At this time, SC induction of ustekinumab may be an appropriate treatment consideration for patients who have personal, financial, or logistical barriers to accessing an infusion center for intravenous induction dosing, but further studies are needed.

There is a paucity of data on the development of antidrug antibodies (ADAs) and therapeutic drug level monitoring for ustekinumab in HS. Tsakok et al.'s prospective cohort study of 491 patients with psoriasis treated with ustekinumab found that ADAs were detected in 3.5% of patients. Higher serum ustekinumab levels during early treatment were associated with better clinical responses after 6 months of treatment, suggesting that appropriate drug levels during the initial phases of treatment may be important for future clinical outcomes [17]. A 2014 systematic review by Hsu et al. reported that ADAs were detected in 3.8–6% of patients treated with ustekinumab for psoriasis compared with 5.4–43.6% of patients on infliximab, 0–18.3% on etanercept, and 6–45% on adalimumab [18]. While these results indicate that ustekinumab may not have as high a risk of ADA development as TNF inhibitors that are commonly used in HS such as adalimumab and infliximab, a more comprehensive understanding of ustekinumab's immunogenicity and optimal serum trough levels could guide clinicians in cases of partial or nondurable response to ustekinumab.

This study contributes to the literature by providing an updated systematic review as well as a pooled response rate on ustekinumab use in HS, which supports the use of ustekinumab in recalcitrant cases of HS. A 2020 systematic review of ustekinumab in HS by Montero-Vilchez et al. found that 78% of 49 patients exhibited a response [8], though of note, case reports were included in this study, which could skew results towards a more favorable response rate. Further support for ustekinumab in HS treatment is seen in recent drug survival studies. Ring and colleagues found that, in a nationwide cohort study of patients with HS, drug survival was comparable between ustekinumab, adalimumab, and infliximab; the median time to discontinuation for ustekinumab was 26 months [19]. Larger studies on the drug survival of ustekinumab in patients with HS may shed further insight on its real-world clinical efficacy. We also found that adverse effects were mild and infrequent among patients with HS treated with ustekinumab and in line with the known side-effect profile of ustekinumab [20]. A retrospective cohort study of 21,821 patients with inflammatory bowel disease found that ustekinumab was associated with a decreased risk of infections compared with TNF-alpha inhibitors [21]. These safety findings may be a potential advantage for ustekinumab as a less immunosuppressive agent compared with TNF-alpha inhibitors.

Study limitations, shared by most systematic reviews on HS treatments, include an overall small number of studies and patients. All studies took place in the USA or Europe, limiting generalizability. Given the small number of patients, we were unable to differentiate the response rates of patients on the basis of inflammatory comorbidities or previously

failed treatments. Another limitation is the risk of reporting bias with the inclusion of case series. Lastly, studies had variable dosing regimens, outcome measures, and timepoints for efficacy measurements.

CONCLUSIONS

Overall, ustekinumab may be a helpful biologic to consider for patients with recalcitrant HS who have failed first-line biologic therapies such as TNF-alpha or IL-17 inhibitors that have robust phase III trial data and, for adalimumab, post-marketing data as well. Large randomized controlled trials are needed to better understand the efficacy, safety, and optimal dosing regimen of ustekinumab in HS. Future investigations should evaluate the benefits of concomitant treatment with ustekinumab and other HS treatments. Studies that investigate patient characteristics that may predict therapeutic responses, drug survival rates, and the potential use of therapeutic drug monitoring are also warranted.

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Declarations

Conflict of Interest. Jennifer L. Hsiao is on the Board of Directors for the Hidradenitis Suppurativa Foundation and has served as a consultant for AbbVie, Aclaris, Boehringer Ingelheim, and Novartis, as a speaker for AbbVie, and as an investigator for Amgen, Aristea, Boehringer Ingelheim, and Incyte. Jennifer L. Hsiao is an editorial board member of *Dermatology and Therapy*. Jennifer L. Hsiao was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Vivian Y. Shi is on the board of directors for the Hidradenitis Suppurativa Foundation (HSF), is an advisor for the National Eczema Association, is a stock shareholder of Learn Health, and has served as an advisory board member, investigator, or speaker for and/or received research funding from Sanofi Genzyme, Regeneron, AbbVie, Genentech, Eli Lilly, Novartis, SUN Pharma, LEO Pharma, Pfizer, Incyte, Boehringer Ingelheim, Almirall, Alumis, Aristea Therapeutics, Menlo Therapeutics, Dermira, Burt's Bees, Galderma, Kiniksa, UCB, Bain Capital, Target-PharmaSolutions, Altus Lab/cQuell, MYOR, Polyfins Technology, GpSkin, and Skin Actives Scientific. Iltefat Hamzavi has served as a consultant to Abbvie, Pfizer, Incyte,UCB,Boerhinger Ingelheim, Sonoma, Union Therapeutics, Novartis, Jansen, Avita, and Galderma, has been an investigator for Lenicura, Pfizer, Incyte, Avita, and Loreal/Laroche Posay, and is a board member and past-president of the HS Foundation and Global Vitiligo Foundation. There was no financial transaction for the preparation of this manuscript. All other authors report no conflicts of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The databases used in this study are publicly available: MEDLINE: https://pubmed.ncbi.nlm.nih.gov/ and Embase: https://www.embase.com/search/quick.

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