Introduction: Pain is experienced by most patients with hidradenitis suppurativa (HS) and has a severe impact on their quality of life. Its management still presents a challenge. Adalimumab, a TNF-α antagonist, has shown promising results in HS-related pain reduction.

Objectives: To aggregate and synthesize all existing evidence regarding the effect of adalimumab on HS-associated pain.

Methods: We identified original controlled and uncontrolled studies with participants receiving adalimumab, which included change in pain score post-treatment compared to baseline as an endpoint. We searched MEDLINE, ScienceDirect, the Cochrane Library, ClinicalTrials.gov and International Clinical Trials Registry Platform. The primary endpoint of our study was the mean change (continuous variable) of pain scores at week 12 compared to baseline.

Results: We performed a meta-analysis of 4 randomized controlled trials (282 patients in the intervention group and 266 patients in the control group). Adalimumab brought about a 0.418 reduction in mean pain score at its worst with 95%CI [–0.588, –0.248] and P = 0.000 at 12 weeks after treatment commencement. Four more studies were included in a qualitative synthesis, 2 of which reported statistically significant reduction in pain scores at week 12.

Conclusions: Adalimumab could be prescribed more readily in cases of HS associated with significant pain.
Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease (of the terminal hair follicle) that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly in the axillary, inguinal, and anogenital regions [1]. Pain is experienced by the majority of HS patients [2–4]. HS-related pain is greater than the one associated with other skin diseases, such as eczema, psoriasis, skin tumors and acne, and constitutes one of the major reasons for the seriously impaired patient quality of life [4,5]. Among other things, pain is responsible for the poor sleep quality, impaired general activity, negatively affected inter-personal relationships and reduced life enjoyment of this population [2,6]. Perception of HS pain is influenced by depression and anxiety, which are frequent comorbidities, as well as by gender and age [3].

HS-related pain derives from deep-seated skin lesions and is of two types: acute/episodic, attributed to disease flares (newly formed and/or old recurring nodules and abscesses), and chronic, which is the result of longstanding inflamed lesions such as sinuses, dermal nodules and contracted scars [7–9]. Acute-pain relief is usually facilitated through abscess rupture or acute surgical interventions [7,9]. HS pain is most commonly described as “shooting” (83%), “itchy” (79%) and “blinding” (75%) and is more intense when more anatomic areas are involved or when disease is more severe (Hurley stage III) [3]. The 3 most common self-reported pain aggravators are friction from tight clothing (47%), heat (40%) and stress (13%) [10].

According to Ring et al HS patients tend to desperately seek for ways to alleviate their pain [10]. The majority of them make use of analgesics (77%) [11]. Common pain relief strategies include non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol received either topically or systemically, as well as cold baths and wraps [9,10,12]. It is worth noting that this data has originated from European studies. When pain is very severe, careful administration of opioids in collaboration with a pain specialist should be considered [9,13]. Self-reported use of tramadol was 37% in a 2016 study and opioids were reported the most efficient in offering relief [11]. Other options may include antidepressants, anticonvulsants, specialist psychological support and patient support groups [9,12].

Only a small number of studies have looked into the prevalence and impact of pain or strategies for its alleviation in HS populations [5,14]. What is more, it seems that the analgesics most commonly used by HS patients are inadequate [10]. Adalimumab, a tumor necrosis factor antagonist, has been approved for the treatment of moderate-to-severe HS, based on the results of 2 clinical trials (PIONEER I and II) [15,16]. A number of studies have reported that adalimumab can effectively reduce pain. This is the first systematic review and meta-analysis to aggregate and synthesize all existing data concerning adalimumab efficacy in alleviating HS-related pain.

Methods

Study Design

This systematic review aimed at examining the effect of adalimumab on HS-related pain. It was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and was registered with PROSPERO (ID: CRD42021229190).

Eligibility Criteria

To answer the research question, we identified original studies with participants receiving adalimumab, which included change in pain scores compared to baseline as an endpoint. We imposed no restrictions on adalimumab dose, language and year of publication and publication status. We included both clinical trials and controlled and uncontrolled observational studies in our review.

Literature Search

A comprehensive electronic search of 5 databases was conducted, namely MEDLINE, ScienceDirect, the Cochrane Library, ClinicalTrials.gov and International Clinical Trials Registry Platform, from November 5–20, 2020, to source studies pertaining to the research question. We also searched Google Scholar and the archives of the major recent dermatology conferences to identify gray literature. Finally, we contacted AbbVie, the major sponsor of adalimumab trial projects, requesting unpublished material. The “Reference” section of manuscripts relevant to the research question was hand-searched, to maximize the sensitivity of our search. As this study was a review of existing research projects, neither informed consent nor ethics approval was required.

The comprehensive database search was performed independently by 2 authors (A.T. and E.S.). We used the following free-text terms for the MEDLINE database search: (hidradenitis suppurativa) OR (acne inversa) AND (adalimumab) OR (biologic) OR (Humira®) OR (anti-TNF) OR (monoclonal antibody) AND (pain) OR (skin pain) OR (ache). Appropriate modifications were applied to the above search strategy, so that it would comply with the search rules of the rest of used databases.

Study Selection

After removing duplicates, A.T. and E.S. initially, independently, read titles and abstracts to eliminate records out of the scope of this review. They subsequently went through the full details of each record and settled disputes through consensus, having a set of predetermined inclusion and
exclusion criteria as a guide. Studies adhering to the following criteria were considered for inclusion: 1) trial or observational study, controlled or not, 2) recruited patients with a clinical diagnosis of HS, 3) patients (all of them or intervention arm) received adalimumab subcutaneously, 4) pain intensity was assessed with a validated pain measuring scale at baseline and 12 weeks after commencing treatment, 5) change in pain scores and/or proportion of patients achieving a certain reduction in such scores was documented, 6) included patients were adults of any age, gender and background population. A study was excluded if it included: 1) non-human subjects, 2) pregnant or lactating females. All selected studies were included in the qualitative synthesis, but only controlled ones were included in the quantitative synthesis.

**Data Extraction**

Eligible studies were subjected to data extraction using a pre-formulated extraction sheet. This process was performed independently by two researchers (A.T. and E.S) and any discrepancies were settled through discussion and agreement. The following data was retrieved from each one of the selected studies: general characteristics (study identifier, ClinicalTrials.gov identifier, study design, phase, number of study sites, countries included, study period, funding, inclusion criteria, exclusion criteria, intervention, comparator, follow-up duration, primary endpoint(s), secondary endpoints) and outcome data.

**Data Items**

Pain intensity is measured with scales assigning increasing value to increasing pain intensity. In dermatology, both generic visual analogue scales (VAS) and specific tools, such as the Patient’s Global Assessment of Skin Pain Numeric Rating Scale (NRS), are commonly used [17]. The former represents a 100 mm-long scale, with 0 corresponding to “no pain” and 100 to “worst possible pain” [17]. NRS consists of successive numbers (the actual length of the scale is not important), usually presented on a horizontal linear configuration, from 0 (no pain) to 5 or 10 (worst possible pain) [17]. The patient is asked to mark the point/length that best corresponds to his/her pain intensity and this value is documented [17]. Mean change and the proportion of patients achieving a certain score reduction are common efficacy endpoints. NRS30 is a 30% and at least 1 unit reduction in the PGA skin pain NRS score compared to baseline. We imposed no restrictions to our search regarding the pain measuring tools used, on the basis that VAS data can be turned into NRS data through dividing by ten. The primary endpoint of our study was mean change (continuous variable) of pain scores at week 12 compared to baseline. In the absence of published statistical measures needed, we contacted authors and requested said data. Secondary endpoint was the percentage of patients achieving NRS30 (dichotomous variable) at week 12. The 12-week timeframe was chosen, as it is a sensible and widely used milestone regarding assessment of biologics’ efficacy both in research and clinical practice.

**Risk of Bias Assessment**

Two researchers (A.T. and E.S) independently used the Cochrane risk-of-bias tool [18] to assess the risk of bias for included randomized controlled clinical trials. Any disagreements were resolved through consensus. Seven items were rated as “high risk,” “low risk,” or “unclear risk” of bias: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other sources of bias. Non-randomized and/or uncontrolled studies were assessed through the Methodological Index for Non-randomized studies (MINORS) [19]. Studies were considered low risk if all items were reported and adequate. Observational studies were evaluated through the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies. Fourteen individual points were thus examined and an overall quality rating of good, fair, or poor was allocated to each study [20].

**Statistical analysis**

We performed all statistical analyses with Comprehensive Meta Analysis software (Comprehensive Meta-Analysis Version 3, Borenstein M, Hedges L, Higgins J, Rothstein H. Biostat). Confidence intervals, P values, standard deviations (SD) and other statistical measures were mentioned, if available. In the opposite case, authors were contacted and if they did not respond, results were described only narratively. The primary goal of this systematic review was to culminate in a meta-analysis – quantitative synthesis – of the main outcome measure. The principal summary measure used for the analysis of the primary endpoint was the mean difference in pain scores between baseline and week 12. A decrease in the mean of pain scores meant that adalimumab had a positive effect on pain. Associated 95% confidence intervals (CI) were estimated and differences were considered significant when P ≤ 0.05 (two-tailed). The secondary endpoint was analyzed through descriptive statistics (frequencies). The presence of heterogeneity across studies was examined through the I² statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). In case heterogeneity was substantial or considerable (≥30%), the random effects model was used. In the opposite case, the fixed effects model was used. A funnel plot was created to check for publication bias.
Results

Study Selection and Characteristics

Our search and screening process (Figure 1) culminated in 8 studies eligible for inclusion. Basic study characteristics are presented in Table 1. All studies were published in English. More than 1 publication was identified for 3 studies [14,21–23], in which case, one of those was chosen as the study identifier based on its relevance to this review’s primary endpoint. Four of the included studies were randomized controlled trials (RCTs) [14,23,24], 2 were prospective open-label uncontrolled trials [25,26], 1 was a retrospective cross-sectional study [27] and one was a post-marketing observational study [28,29]. A total of 863 participants with a mean age of 36.51 (SD = 11.59) years received either adalimumab subcutaneous injection (489 participants) or placebo (374 participants). The dosing of adalimumab was not consistent across all 8 studies or all study arms. Three studies [14,24,25] examined the efficacy of 40 mg of adalimumab administered every other week and 4 studies [14, 23, 26–28] evaluated the efficacy of 40 mg of adalimumab administered weekly. Alternate weekly dosing was also investigated in the second period of the 2 main phase III RCTs (PIONEER I and II), on which drug approval was based [23]. In the second period of a recent phase III study, alternate weekly administration of 80 mg of adalimumab was also assessed [26]. In most studies [14, 23,26–28] an introductory dosage of 160 mg at week 0, 80 mg at week 2, and 40 mg at week 4 was administered prior to maintenance treatment. A different introductory regimen was employed in 2 studies [24,25] (160 mg at week 0, 80 mg at week 1, 40 mg at week 4, and 80 mg at week 0 respectively). Baseline characteristics of participants are presented in Table 2.

Figure 1. Flow diagram of study selection based on the 2009 PRISMA statement format.
### Table 1. Study Characteristics

| Study identifier | Study design | Phase | Study sites | Inclusion criteria | Exclusion criteria |
|------------------|--------------|-------|-------------|--------------------|-------------------|
| [ClinicalTrials.gov](https://ClinicalTrials.gov) | *Clinical Trial* | *II* | 26 | Healthy adults, able to administer subcutaneous injections, negative chest X-ray and PPD test or completed anti-tuberculosis therapy | Prior anti-TNF treatment, unstable antibiotic therapy for HS, required medication washouts for other HS treatments, prior exposure to 1 year of adalimumab therapy, recent infection requiring hospitalization, recent injection requiring hospitalization, significant medical events or conditions, pregnancy or breastfeeding, normal laboratory values. |
| [ClinicalTrials.gov](https://ClinicalTrials.gov) | *Clinical Trial* | *I* | 1 | United States | Prior anti-TNF treatment, non-stable dose of antibiotics for HS within previous 28 days, oral opioid or non-stable dose of non-opioid analgesics for reasons unrelated with HS within past 14 days. |
| [ClinicalTrials.gov](https://ClinicalTrials.gov) | *Clinical Trial* | *II* | 48 | Australia, Canada, Czech Republic, Germany, Hungary, United States | Prior anti-TNF treatment, non-stable dose of antibiotics for HS within previous 28 days, oral opioid or non-stable dose of non-opioid analgesics for reasons unrelated with HS within past 14 days. |
| [ClinicalTrials.gov](https://ClinicalTrials.gov) | *Clinical Trial* | *III* | 101 | Denmark, Germany, Netherlands, United States | Prior anti-TNF treatment, non-stable dose of antibiotics for HS within previous 28 days, oral opioid or non-stable dose of non-opioid analgesics for reasons unrelated with HS within past 14 days. |

**Study period:**
- Scheinfeld et al 2016: April 2009 – November 2010
- Amano et al 2010: February 2007 – August 2008
- PIONEER I 2016: November 2011 – January 2014
- PIONEER II 2016: November 2011 – April 2014
| Study identifier   | Scheinfeld et al 2016 [14,21] | Amano et al 2010 [25] | PIONEER I 2016 [22, 23] | PIONEER II 2016 [22, 23] |
|-------------------|-------------------------------|----------------------|------------------------|------------------------|
| **Intervention**  | Adalimumab, subcutaneous injection, 160 mg at week 0, 80 mg at Week 2, and 40 mg weekly starting at Week 4 through Week 15. Or 80 mg at Week 0 and 40 mg every other week starting at Week 1 through Week 15. Period 2: 36 weeks, open label, adalimumab 40 mg every other week. | Adalimumab subcutaneous injection, 160 mg at Week 0, followed by 80 mg at Week 1, and 40 mg at alternate weeks until Week 12. | Period 1: Adalimumab, subcutaneous injection, 160 mg at Week 0, 80 mg at Week 2, 40 mg every week from Week 4 to Week 12. Period 2: prior placebo -> adalimumab 40 mg every week until week 35, prior adalimumab -> placebo every week, adalimumab 40mg every week or adalimumab 40mg every other week. | Period 1: Adalimumab, subcutaneous injection, 160 mg at Week 0, 80 mg at Week 2, 40 mg every week from Week 4 to Week 12. Period 2: prior placebo -> adalimumab 40 mg every week until week 35, prior adalimumab -> placebo every week, adalimumab 40mg every week or adalimumab 40mg every other week. |
| **Comparator**    | Placebo weekly starting at week 0 through week 15. | Not applicable. | Placebo. | Placebo. |
| **Follow-up duration** | 16 weeks. | 12 weeks. | 36 weeks. | 36 weeks. |
| **Primary endpoint(s)** | Proportion of patients achieving an HS-PGA score of clear, minimal, or mild with at least a 2-grade improvement relative to baseline at Week 16. | Proportion of patients achieving decrease of 50% from baseline in the HSSI score after 12 weeks of treatment. | Percentage of participants achieving HiSCR at Week 12. | Percentage of participants achieving HiSCR at Week 12. |
| **Secondary endpoints** | Proportion of patients achieving clinical response at Weeks 2, 4, 8, and 12 and all visits (period 2), HS-PGA score of clear, minimal, or mild, mean change in MSS, mean percentage of improvement in abscesses, draining fistulas, or inflammatory nodules, mean change in C-reactive protein levels, mean change in DLQI score, total work productivity impairment at Week 16. Post hoc analysis: proportion of patients achieving 30% or greater reduction and a 10-mm or greater absolute reduction in pain Visual Analogue scale score. | Difference from baseline at 12 weeks in pain measured by a Visual Analog Scale, DLQI, and PGA of disease severity, number of patients with a >30 and >50% disease activity at 12 weeks, adverse events. | Percentage of participants achieving AN count 0, 1 or 2, NRS30 – At worst at week 12, change of MSS at week 12. | Percentage of participants achieving AN count 0, 1 or 2, NRS30 – At worst at week 12, change of MSS at week 12. |

HS = hidradenitis suppurativa; ER = emergency room; AN count = abscess and inflammatory nodule count; NSAID = non-steroidal anti-inflammatory drug; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HS-PGA = Hidradenitis suppurativa – Physician’s Global Assessment; HSSI = Hidradenitis Suppurativa Severity Index; HiSCR = Hidradenitis Suppurativa Clinical Response; MSS: Modified Sartorius Score; DLQI = Dermatology Life Quality Index; NRS30 = at least 30% and 1 unit reduction in pain numeric rating scale score.
| Study title | ClinicalTrials.gov | Study design | Phase | Study sites | Countries included | Study period | Funding | Inclusion criteria | Exclusion criteria | Intervention | Comparator | Follow-up duration |
|-------------|-------------------|-------------|-------|------------|-------------------|-------------|---------|-------------------|-------------------|-------------|------------|-------------------|
| Morita et al. 2019 [26] | NCT02949992 | Clinical Trial | III | Japan | Japan | September 2016 – May 2019 | Abbott | 18–99 years, HS for at least 6 months & stable for at least 2 months, ≥2 anatomic areas, one at least Hurley Stage II or III, AN count ≥3 | Prior adalimumab or other anti-TNF treatment, other skin condition, antibiotic use during HS assessment, unstable dose of doxycycline or minocycline past 28 days, topical treatments or oral analgesics for HS within past 14 days, systemic treatment for HS within past 28 days | Adalimumab 160 mg subcutaneous injection Week 0, 80 mg Week 2, and 40 mg every other week starting Week 4. After Week 52, switch to 80 mg every other week after consent | Not applicable | Up to 12 weeks |
| HOPE 2019 [28] | NCT02739828 | Observational | Cross-sectional | Not applicable | Not applicable | Not reported | Not applicable | Not reported | Not reported | Not applicable | Not applicable | 108 weeks |
| Miller et al. 2011 [24] | NCT01239828 | Clinical Trial | Not applicable | Denmark | Not applicable | Not reported | Not applicable | Not reported | Not reported | Not applicable | Not applicable | Up to 24 weeks |
| Caposiena Caro et al. 2020 [27] | NCT02949992 | Clinical Trial | Not applicable | Sweden | Not applicable | Not reported | Not applicable | Not reported | Not reported | Not applicable | Not applicable | Up to 24 weeks |
| Study title | Morita et al. 2019 [26] | HOPE 2019 [28] | Miller et al. 2011 [24] | Caposiena Caro et al. 2020 [27] |
|-------------|-------------------------|----------------|-------------------------|-----------------------------|
| **Primary endpoint(s)** | Percentage of participants achieving HiSCR at Week 12 | Change in DLQI score from baseline at Week 12 | Change in Sartorius and Hurley scores at Weeks 12 and 24 | No outcome defined as primary |
| **Secondary endpoints** | Percentage of participants achieving AN count 0, 1 or 2 at Week 12, NRS30 – At Worst at Week 2, change of MSS at Weeks 2, 4, 8 & 12 | Change from baseline: of pain Numeric Rating Scale – at worst and on average at Weeks 4, 12 and 24, of DLQI at Weeks 4 and 24, of EQ-5D Questionnaire responses, EQ-5D VAS Score, HSIA Overall Score, WPAI-SHP score at Weeks 4, 12 & 24, achievement of HiSCR at Weeks 4, 12 & 24 | Change in VAS pain score at Weeks 12 and 24, self-reported days with lesions between visits, DLQI and evaluation of scarring [Manchester post-inflammatory scar scoring and Physician Global Assessment scar scoring], documentation of adverse events | Every 12 weeks: number of patients achieving HiSCR of ≥ 50% reduction in inflammatory lesion count, number of flares, mean time between flares, Hidradenitis Suppurativa IHS4, pain VAS and lesion count. Additionally, DLQI was assessed to measure quality of life (QoL) every 24 weeks. |

HS = hidradenitis suppurativa; AN count = abscess and inflammatory nodule count; HiSCR = Hidradenitis Suppurativa Clinical Response; DLQI = Dermatology Life Quality Index; NRS30 = at least 30% and 1 unit reduction in pain numeric rating scale score; MSS = Modified Sartorius Score; EQ-5D = instrument for evaluation of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; VAS = Visual Analogue Scale; HSIA = Hidradenitis Suppurativa Impact Assessment; WPAI-SHP = Work Productivity and Activity Impairment – Specific Health Problem; HiSCR: Hidradenitis Suppurativa Clinical Response; IHS4 = International Hidradenitis Suppurativa Severity Score System.
### Table 2. Baseline Characteristics of Participants

| Study identifier | Scheinfeld et al 2016 | Amano et al 2010 | PIONEER I 2016 | PIONEER II 2016 | Morita et al 2019 | HOPE 2019 | Miller et al.2011 | Caposiena-Caro et al.2020 |
|------------------|--------------------|----------------|---------------|----------------|----------------|--------|-------------------|-----------------------------|
| **Number of participants** | | | | | | | | |
| | 154 | 10 | 307 | 326 | 15 | 10 | 21 | 20 |
| **Adalimumab (Ada) (n, %)** | 103 (66.88) | 10 (100) | 153 (49.84) | 163 (50) | 15 (100) | 10 (100) | 15 (71.43) | 20 (100) |
| **Placebo (Pbo) (n, %)** | 51 (33.12) | 0 | 154 (50.16) | 163 (50) | 0 | 0 | 6 (28.57) | 0 |
| **Gender (%)** | | | | | | | | |
| **Adalimumab** | | | | | | | | |
| f: 74 (48.05) | f: 7 (70.0) | f: 91 (29.64) | f: 108 (33.13) | f: 2 (13.3) | f: 7 (70) | f: 12 (57.14) | f: 14 (70) |
| m: 29 (18.83) | m: 3 (30.0) | m: 62 (20.20) | m: 55 (16.87) | m: 13 (86.7) | m: 3 (30) | m: 3 (14.29) | m: 6 (30) |
| **Placebo** | | | | | | | | |
| f: 36 (23.38) | 0 | f: 105 (34.20) | f: 113 (34.67) | 0 | 0 | f: 5 (23.81) | 0 |
| m: 15 (9.74) | | m: 49 (15.96) | m: 50 (15.34) | m: 49 (15.96) | m: 50 (15.34) | m: 49 (15.96) | m: 50 (15.34) |
| **Age (years, mean, SD/95%CI)** | | | | | | | | |
| Ada: 35.6 (11.6) | Ada: 36.2 (10.83) | Ada: 34.9 (9.96) | 42.1 (6.94) | 42.7 (11.47) | Ada: 38.7 (30.9–46.4) | 35.1 (12) |
| Pbo: 37.8 (12.1) | Pbo: 37.8 (11.33) | Pbo: 36.1 (12.18) | | | | |
| **Race/ethnicity (n, %)** | | | | | | | | |
| **White** | Ada: 73 (47.4) | 5 (50) | Ada: 116 (37.79) | Ada: 143 (43.87) | 0 | NR | NR | NR |
| Pbo: 37 (24.03) | Pbo: 118 (38.44) | Pbo: 130 (39.88) | | | | | |
| **Black** | Ada: 21 (13.64) | 3 (30) | Ada: 33 (10.75) | Ada: 9 (2.76) | 0 | NR | NR | NR |
| Pbo: 8 (5.19) | Pbo: 29 (9.45) | Pbo: 20 (6.13) | | | | | |
| **Other** | NR | 2 (20) | Ada: 4 (1.3) | Ada: 11 (3.37) | 15 (100) | NR | NR | NR |
| | Pbo: 7 (2.28) | Pbo: 13 (3.98) | | | | | | |
| **Weight (kg, mean, SD)** | | | | | | | | |
| Ada: 97.62 (24.92) | NR | Ada: 97.1 (24.90) | Ada: 90.2 (21.74) | NR | NR | NR | NR |
| Pbo: 96.5 (24.8) | Pbo: 99.3 (25.13) | Pbo: 95.7 (25.87) | | | | | |
| **BMI (kg/m², n)** | | | | | | | | |
| <25 | Ada: 15 (9.74) | Ada: 24 (7.82) | Ada: 36 (11.04) | 7 (46.7) | 0 | Ada: 32 (25.7 – 38.4) | 28.4 (6) |
| Pbo: 9 (5.84) | Pbo: 13 (4.23) | Pbo: 26 (7.98) | | | | | | (continued)
| Study identifier        | Scheinfeld et al 2016 | Amano et al 2010 | PIONEER I 2016 | PIONEER II 2016 | Morita et al 2019 | HOPE 2019 | Miller et al 2011 | Caposiena-Caro et al 2020 |
|------------------------|-----------------------|------------------|----------------|----------------|-------------------|----------|-------------------|-------------------------|
| 25 to <30              | Ada: 23 (14.94)       | NR               | Ada: 31 (10.10)| Ada: 42 (12.88)| 4 (26.7)          | 2 (20)   | Pbo: 32.4 (24.7–40.2) |
|                        | Pbo: 6 (3.90)         |                  | Pbo: 38 (12.38)| Pbo: 36 (11.04)|                  |          |                   |                         |
| >30                    | Ada: 65 (42.21)       | NR               | Ada: 97 (31.60)| Ada: 85 (26.07)| 4 (26.7)          | 8 (80)   |                   |                         |
|                        | Pbo: 36 (23.38)       |                  | Pbo: 103 (33.55)| Pbo: 117 (35.89)|                  |          |                   |                         |
| Disease duration       | Ada: 11.1 (9.0)       | NR               | Ada: 8.8 [1.1, 40.4] | Ada: 9.0 [1.0, 43.5] | 14.1 (10.58) | NR       | NR                | 15.8 (10)               |
| (years, mean/median,   |                       |                  | Pbo: 9.4 [1.0, 43.0] | Pbo: 9.9 [1.2, 68.5] |                  |          |                   |                         |
| SD/range)              |                       |                  | Pbo: 13.4 (10.4) |                  |                  |          |                   |                         |
| Smoking                | Ada: 56 (36.36)       | NR               | Ada: 81 (52.60) | Ada: 105 (32.20)| 12 (80)          | 4 (40)   | Ada: 10 (47.62) | 12 (70)                 |
|                        | Pbo: 29 (18.83)       |                  | Pbo: 92 (59.74) | Pbo: 109 (33.44)|                  |          | Pbo: 5 (23.81) |                         |
| Hurley stage           |                       |                  |                |                | NR                |          |                   |                         |
| I or II                | Ada: 73 (47.40)       | NR               | Ada: 80 (51.95) | Ada: 86 (26.38) | 9 (60)           | 2 (20)   | NR                | 11 (55)                 |
|                        | Pbo: 36 (23.38)       |                  | Pbo: 81 (52.6)  | Pbo: 89 (27.30) |                  |          |                   |                         |
| III                    | Ada: 30 (19.48)       | NR               | Ada: 73 (47.40) | Ada: 77 (23.62) | 6 (40)           | 8 (80)   | NR                | 9 (45)                  |
|                        | Pbo: 15 (9.74)        |                  | Pbo: 73 (47.40) | Pbo: 74 (22.70) |                  |          |                   |                         |
| Baseline pain score    | Ada: 52.5 (25.36)     |                  | Ada: 5.1 (2.51) | Ada: 4.3 (2.62) | 4.6 (0.60)       | 5.9 (2.59)| Ada: 58 (40.63–75.37) | 4.8 (NR)               |
| (VAS or NRS, mean,     |                       |                  | Pbo: 57.8 (28.5) | Pbo: 4.8 (2.68) |                  |          |                   |                         |
| SD/95%CI)              |                       |                  | Pbo: 4.8 (2.73) |                  |                  |          |                   |                         |

N = number of participants; f = female; m = male; SD = standard deviation; 95% CI = 95% confidence interval; NR = not reported; VAS = visual analogue scale; NRS = pain numerical rating scale; BMI = body mass index.
Methodological Quality Assessment
The methodological quality of the 4 included RCTs [14,23,24] was assessed through the Cochrane Risk of Bias tool (Figure 2). The overall risk for these studies was found to be low. The 2 open-label uncontrolled studies were assessed through the MINORS tool (Table 3) and were found to be high risk. The observational studies were assessed through the Quality assessment tool for observational cohort and cross-sectional studies and their methodological quality was deemed fair (Table 4). According to the funnel plot no publication bias was detected (Figure 3).

Outcomes
Quantitative synthesis of the 4 controlled studies was possible for the primary outcome (data available for a total of 282 patients in the intervention group and 266 patients in the control group) (Figure 4). VAS values [14,24] were converted to PGA-NRS values through dividing by 10.
Table 3. Methodological Index for Non-randomized Studies (MINORS)

| Assessed items                                                                 | Amano et al 2010 | Morita et al 2019 |
|--------------------------------------------------------------------------------|-----------------|------------------|
| 1. A clearly stated aim                                                        | 2               | 2                |
| 2. Inclusion of consecutive patients                                           | 0               | 0                |
| 3. Prospective collection of data                                              | 2               | 2                |
| 4. Endpoints appropriate to the aim of the study                               | 2               | 2                |
| 5. Unbiased assessment of the study endpoint                                   | 0               | 0                |
| 6. Follow-up period appropriate to the aim of the study                        | 2               | 2                |
| 7. Loss to follow up less than 5%                                              | 1               | 1                |
| 8. Prospective calculation of the study size                                   | 0               | 2                |
| 9. An adequate control group                                                   | N/A             | N/A              |
| 10. Contemporary groups                                                         | N/A             | N/A              |
| 11. Baseline equivalence of groups                                             | N/A             | N/A              |
| 12. Adequate statistical analyses                                              | N/A             | N/A              |
| **Total score**                                                                | 9               | 11               |
| **Judgement**                                                                  | High risk       | High risk        |

Methodological Index for Non-randomized studies (MINORS) scale contains 8 assessment points for non-comparative studies and 4 extra points for comparative studies[19]. Each item receives 0, 1 or 2 points, if it is not reported, reported but inadequate or reported and adequate respectively, with an ideal overall score of 16 for non-comparative and 24 for comparative studies.

N/A = not applicable or not available? Please explain

Table 4. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

| Assessed Items                                                                 | HOPE 2019 | Caposiena Caro et al 2020 |
|--------------------------------------------------------------------------------|------------|---------------------------|
| 1. Was the research question or objective in this paper clearly stated?        | Yes        | Yes                       |
| 2. Was the study population clearly specified and defined?                     | Yes        | Yes                       |
| 3. Was the participation rate of eligible persons at least 50%?                | Yes        | Not reported              |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes        | Yes                       |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | No         | No                        |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | Yes        | Yes                       |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | Yes        | Yes                       |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)? | Not applicable | Not applicable |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes        | Yes                       |
| 10. Was the exposure(s) assessed more than once over time?                     | Yes        | Yes                       |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes        | Yes                       |
| 12. Were the outcome assessors blinded to the exposure status of participants? | No         | No                        |
| 13. Was loss to follow-up after baseline 20% or less?                          | No         | Yes                       |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | No         | No                        |
| **Overall rating (good, fair, poor)**                                         | Fair       | Fair                      |
Figure 3. Funnel plot for the assessment of publication bias, designed with Comprehensive Meta Analysis software.

The meta-analysis performed showed that adalimumab administered for 12 weeks significantly decreased pain compared to placebo (-0.418 reduction in mean pain score [95% CI –0.588, –0.248] and P = 0.000). There was very little heterogeneity across studies based on the I² statistic (2.985). Only the “adalimumab every week” arm of Scheinfeld et al [14] was included in the meta-analysis, as statistical data regarding the “adalimumab every other week” arm was missing. We contacted authors via email in an effort to acquire this data, but they did not respond.

No quantitative synthesis of controlled studies was possible for the secondary outcome, due to missing data (email communication with authors was fruitless). According to Scheinfeld et al [14], 63% (P < 0.001) and 43% of patients...
patients’ quality of life and the established under-treatment or difficult treatment of HS-related pain, the key finding of this study suggests that dermatologists should consider adalimumab when pain is a primary concern of a HS patient (in terms of severity, frequency and or perception).

The limitations of our study are the small number of studies included in the quantitative synthesis, which, however, reflects the actual paucity of evidence regarding the effect of adalimumab on HS-associated pain. What is more, the main body of evidence included in this review and analysis came from pre-drug-approval RCTs, which, though solid methodologically, may not accurately simulate real-life conditions eg strict inclusion and exclusion criteria, higher treatment compliance, more frequent doctor visits, etc. Another limitation of our study is that we did not check for confounding factors such as the impact of mood improvement on pain perception.

Pain is the principal determinant of life quality in HS patients [31]. A recent (2020) cross-sectional study included 1,795 HS patients, 83.6% of whom experienced pain [32]. Pain intensity correlated positively with female gender, smoking, multiple affected areas and more severe disease [32]. Commonly employed HS treatments offer inadequate pain relief and, on top of this, dermatologists tend to be insufficiently trained in clinical pain management [31]. As a result, patients frequently self-medicate and may expose themselves to the dangers of opioid or other substance misuse [31]. On another note, 82% of 110 HS patients tried to alleviate their pain through manually draining pus from their own lesions [33]. According to the European guidelines for the treatment of HS [34] a holistic approach is mandatory, when deciding how to manage HS patients. Aside from the principal pharmaceutical therapy, a plan should be made, among other things, for handling pain. There is, however,
only low-strength evidence (D) for the administration of common mild (nonsteroidal anti-inflammatory drugs) and strong (opioids) analgesics [34]. Therefore, well-studied drugs against HS with an established pain-reducing action, like adalimumab, are most precious weapons in the dermatologist’s arsenal.

Increased TNF-a levels in HS patients, and improvement of HS in patients with Crohn disease receiving adalimumab, led to adalimumab being tried as a primary treatment for moderate-to-severe HS [35]. Trials showed that the drug is both efficacious and easily tolerated, while positively affecting important secondary endpoints, like quality of life and pain [35]. Secukinumab reduced VAS pain score in a reported case of recalcitrant HS and its efficacy against HS is currently being examined in clinical trials [36]. Ustekinumab brought about significant reduction in VAS pain score in a phase II open-label trial of patients with moderate-to-severe HS [37]. Apremilast was also found to significantly reduce VAS pain score in a case-series of 9 patients (P = 0.026) [38].

It has been undoubtedly established, that pain should be brought into focus as far as HS-related research is concerned. Existing and potential new anti-HS drugs should be studied more rigorously in terms of their ability to mitigate acute and chronic HS pain, while standardized pain outcome measures, such as the newly introduced pain index, should be consistently used across such studies [39]. On the other hand, high-quality large-scale studies testing the efficacy and safety of various analgesics in HS patients should be designed and conducted soon. This evidence will act as the basis for the issuing of pain-specific treatment guidelines that will support dermatologists in their difficult role and improve the life-quality of HS patients.

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