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Efficacy and safety of adalimumab in hidradenitis suppurativa

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Adalimumab is used as a first-line biologic agent in the management of moderate-to-severe hidradenitis suppurativa (HS). The objective of the present study was to evaluate the efficacy and safety of adalimumab in patients with moderate-to-severe HS.

Methods: We performed a systematic review and meta-analysis according to Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines. Pooled estimates, namely standardized mean difference (SMD) and relative risk (RR), were calculated using random-effect model with trial sequential analysis. Small study effects were examined using the Doi plot. Certainty of evidence (CoE) was assessed using "The Grading of Recommendations Assessment, Development, and Evaluation" approach, and number-needed-to-treat (NNT) was calculated.

Results: Five randomized controlled trials, involving 1014 patients, were included. We performed subgroup analysis of adalimumab administered subcutaneously both weekly and every other week. Adalimumab administered weekly was associated with better clinical response achievement (RR 1.76, 95% confidence interval [95% CI] 1.35–2.29; trial sequential analysis TSA-adjusted CI 1.01–3.08; CoE: low; NNT = 5) and a significant improvement in modified Sartorius score (SMD = −0.45, 95% CI = −0.76 to −0.13; CoE: very low; NNT = 10) and dermatology life quality index (DLQI) (SMD −0.47, 95% CI −0.61 to −0.32; CoE: low; NNT = 10). Nevertheless, adalimumab administered every other week showed an improvement only in modified Sartorius score. The pooled RRs of adverse events in both groups revealed no statistical significance when compared with the placebo.

Conclusions: Adalimumab administered weekly resulted in not only better clinical responses than placebo but also significantly improved disease severity and quality of life of patients with moderate-to-severe HS. Our study provides supporting evidence to the current guidelines and aids decision-making in the application of adalimumab in HS management.

Abbreviations: 95% CI = 95% confidence interval, AE = adverse events, CoE = certainty of evidence, DLQI = dermatology life quality index, GRADE = the grading of recommendations assessment, development, and evaluation, HiSCR = hidradenitis suppurativa clinical response, HS = hidradenitis suppurativa, IS = information size, LFK index = Luis Furuya–Kanamori index, NNH = number-needed-to-harm, NNT = number-needed-to-treat, RCT = randomized controlled trials, RoB = risk of bias, RR = relative risk, SMD = standardized mean difference, TNF = tumor necrosis factor, TSA = trial sequential analysis.

Keywords: acne inversa, adalimumab, clinical response, hidradenitis suppurativa, meta-analysis, skin disease, trial sequential analysis

1. Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder that predominantly affects the skin in apocrine gland-bearing, intertriginous regions and results in recurrent, painful, and suppurating lesions.[1] The prevalence of HS varies from 0.05% to 4.00% depending on the population studied and the methodology used,[2] with not only medical burden but also socioeconomic burdens.[3] Despite several management strategies, such as topical, systemic, and surgical interventions, ineffective HS treatment remains a challenge for dermatologists.[4] With an improvement in the understanding of the pathophysiology of HS during recent years, biologic agents have been used to relieve HS symptoms and decrease the associated morbidity.[5]

Adalimumab, a fully human IgG1 monoclonal antibody specific for the membrane-bound tumor necrosis factor (TNF)-α, is currently approved for the treatment of moderate-to-severe HS based on the results of the PIONEER trials.[6,7] Several ongoing clinical trials are investigating the effectiveness and safety of adalimumab for HS.[8] In previous trials, clinical response rates have been reported using Hidradenitis Suppurativa Clinical Response (HiSCR) and Hidradenitis Suppurativa-Physician's Global Assessment (HS-PGA).[8] Previous systematic reviews and meta-analyses have concluded that adalimumab administered weekly is effective in treating HS and that it caused only tolerable adverse events (AEs).[9,10] However, the effects of adalimumab in patients achieving clinical responses have not been clarified, although the results of new trials have been published. Therefore, here, we performed a meta-analysis of randomized controlled trials (RCTs) with trial sequential analysis (TSA) to assess the efficacy and safety of adalimumab compared with those of a placebo for the treatment of HS. We aimed to update current evidence, by scoring the certainty of evidence (CoE) with "The Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) approach and calculating number-needed-to-treat (NNT). We applied a recently developed novel graphical approach, the Doi plot, instead of funnel plots and conventional quantitative approaches (such as Egger test), and the Luis Furuya–Kanamori (LFK) index, which is a quantitative measure, to improve the assessment of small study effects owing to a small number of studies.

2. Materials and methods

The present systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines [11] and the Cochrane Handbook for Systematic Reviews of Interventions.[12] We registered our protocol on the PROSPERO website (registration number: CRD42020193471). Two reviewers (JW Lu and YW Huang) independently searched articles, extracted data, and evaluated the quality of the included studies. Discrepancies and disagreement were resolved by discussion with the third author (TL Chen).

2.1. Information source and search strategy

We systemically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for studies published from inception until November 20, 2020. In brief, we searched for articles using the following query terms: "hidradenitis suppurativa" or "acne inversa"; and "adalimumab," "Humira," or "D2E7 Antibody." A detailed search strategy is described in Supplemental Digital Content Table S1, http://links.lww.com/MD/G165, and it was modified to satisfy the requirements of different databases. We also supplemented our search by filtering the reference lists or bibliographies of all included studies, and the identified studies were further screened. Current Controlled Trials, ClinicalTrials.gov, and www.centerwatch.com were searched for any unpublished or ongoing trials.

2.2. Study selection

Studies that compared the efficacy and safety of adalimumab with those of a placebo for the treatment of moderate-to-severe HS were considered eligible for inclusion. After the removal of duplicate studies, both authors screened the title and abstract of the remaining studies.

To avoid selection and confounding biases in non-RCTs, we enrolled only RCTs. Case reports, observational studies, letters to editors, quasi-experimental studies, and abstracts from conference proceedings were excluded. There was no language or age restriction. We also excluded animal studies or those conducted in laboratory settings.

2.3. Data extraction and quality assessment

We extracted the following data from the included studies: the first author; publication year; clinical trial identifier; study design; HS severity; sample size; patient age; intervention and control methods; outcome measures in terms of efficacy and safety; and potential confounders including dose, follow-up duration, and conflict of interest.

The revised Cochrane risk of bias (RoB 2.0) tool was used for methodological quality appraisal of the included RCTs.[13] This tool can be used to assess the following: allocation concealment, blinding of study participants, detection bias, attrition bias, and reporting bias. We used Risk-of-bias VISualization tool for creating "traffic light" plots of the domain-level judgments.[14]

2.4. Data synthesis and statistical analysis

We performed the meta-analysis using Stata Version 16 (StataCorp, College Station, TX). The efficacy outcomes included the following: patients achieving clinical response, change in the modified Sartorius score from baseline, and change in the dermatology life quality index (DLQI) from baseline. Safety outcomes included serious AEs, infectious AEs, headache, and nasopharyngitis. The estimated rate ratio or risk ratio (RR) was calculated with 95% confidence interval (CI) for dichotomous outcomes, whereas standardized mean difference (SMD) was calculated with 95% CI for continuous outcomes. If the data were not available for data synthesis, we contacted the corresponding authors to obtain relevant information.

Between-study heterogeneity was quantified using the I^2 statistic [15] with the DerSimonian and Laird random-effects model.[12] Heterogeneity was considered low, moderate, and high if the I^2 was <50%, 50% to 75%, and >75%, respectively. Results with a P value of less than .05 were considered significant.

To assess possible type I errors due to an increased risk of random error when limited data were analyzed and significance testing was repeated, we also applied TSA, using TSA Viewer, version 0.9.5.10 beta.[16,17] The required information size (IS; i.e., the lowest number of participants required for a statistically

significant result) was calculated. We adjusted all TSA for heterogeneity in accordance with an overall type I error of 5% and a power of 80%. We conducted a predefined subgroup analysis of adalimumab administered weekly and that administered every other week to differentiate the methods of administration. We also carried out a sensitivity analysis by omitting each study individually to identify the influence of each study on the overall pooled estimate.

Additionally, we calculated NNT and number-needed-to-harm (NNH) to determine the evidence-based efficacy and safety of adalimumab in the treatment of HS. NNT/NNH was calculated using the pooled RR in dichotomous outcomes.[18] NNT/NNH converted from SMD (presented in Cohen's d) was implemented in "*dmetar*" in R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) with a control event rate of 0.10,[19] using Furukawa's methodology.[20]

Small-study effects (e.g., publication bias) were examined using Doi plots, a recently developed graphical and quantitative method to visualize asymmetry.[21] The Luis Furuya–Kanamori index (LFK index) was utilized to quantify asymmetry of small study effects from the Doi plot.[21] The LFK indexes less than ± 1, greater than ± 1 but within ± 2, or greater than ± 2 represented no, minor, or major asymmetry, respectively. MetaXL software (version 5.3; EpiGear International Pty Ltd., Sunrise Beach, Queensland, Australia) was used to generate the Doi plot and LFK index.

2.5. Grading of certainty of evidence

We used the GRADE approach, which classifies evidence as high, moderate, low, or very low quality based on the risk of bias, consistency, directness, precision, and publication bias.[22]

3. Results

3.1. Search results

Our initial database search yielded 1010 articles, with 993 records identified in electronic databases and 17 records retrieved from ClinicalTrials.gov. After removing 292 duplicates, the titles and abstracts of 718 articles were screened. Among the 718 articles, 179 were identified to be potentially relevant, and their full text was accessed. One hundred seventy four studies were excluded because the contents were not relevant to our study or the study designs failed to meet our eligibility criteria. Ultimately, five RCTs were included in the meta-analysis. A summary of the selection process and detailed identification process are illustrated in Figure 1.

3.2. Characteristics of the included studies

Table 1 outlines the baseline characteristics of the 5 eligible RCTs.[7,19,23,24] Two trials were reported in 1 article by Kimball et al.[7] A total of 1,014 participants, investigated between 2011 and 2020, were evaluated. Most of the included publications came from the same research group. The tests used for determining the efficacy and safety of adalimumab in HS management compared with those of a matching placebo were summarized. Adalimumab was administered subcutaneously.

Among the 5 included studies, 4 studies were performed in 2 periods.[7,19,23] The first period was conducted in a randomized, placebo-controlled manner. In contrast, the second period was
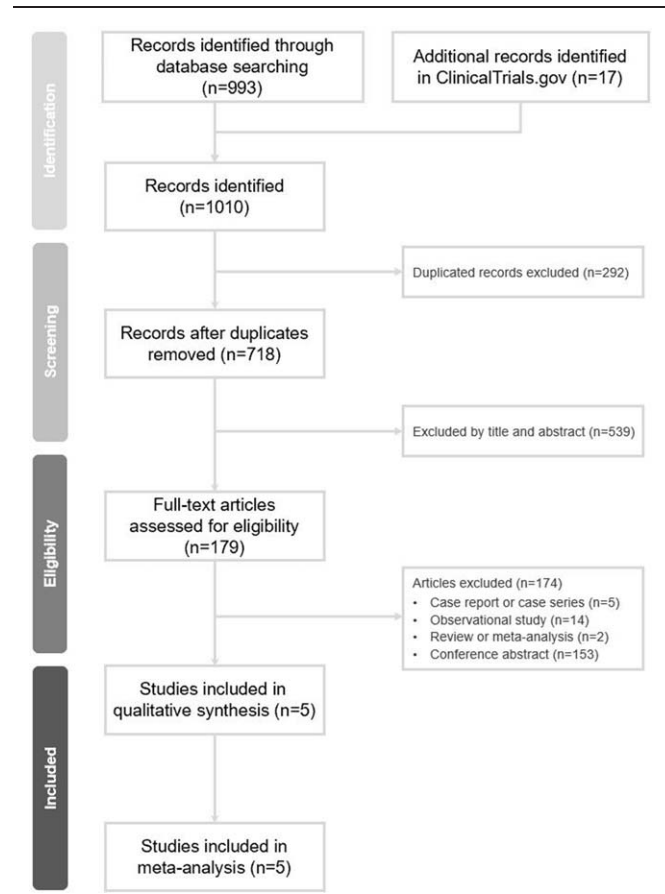
Figure 1. Flowchart of the study. Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) schematic of the search process.

carried out in either an observational, open-label, or a rerandomized controlled manner. To avoid the overall bias and period effect, we extracted data from only the first period, that is, the randomized controlled period.

3.3. Quality assessment of the included studies

We assessed the risk of bias (RoB) in the randomized controlled period. The RoB in each domain is illustrated in Figure 2. As for allocation bias, clinical trial NCT02808975 was classified under "some concern" because there was no information about allocation concealment, which might have caused prejudice in the randomization process. The other 4 studies were considered to have a "low" RoB.

3.4. Quantitative meta-analysis of efficacy

In terms of the pooled RR of patients achieving clinical response, patients who received adalimumab weekly showed better clinical responses than those who received the matching placebo (RR 1.76; 95% CI 1.35–2.29; TSA-adjusted CI 1.01–3.08; $I^2 =$ 44.6%; Fig. 3a). Adalimumab administered every other week did not significantly improve the clinical response (RR 3.43; 95% CI 0.75–15.75; Fig. 3a). Diversity-adjusted IS was calculated based on a clinical response rate of 46.4% in the adalimumab group and 25.9% in the placebo group ($\alpha = 5\%$ (two-sided) and $\beta =$

Table 1

Characteristics of the included studies.

| Study	Clinical Trial Identifier	Study design	Severity	Adalimumab group			Placebo group			Outcomes of Efficacy	Outcomes of Safety	Industrial COI
				No.	Age (years) mean ± SD	Methods	No.	Age (years) mean ± SD	Methods			
Miller 2011[23]	EudraCTnr: 2006-005297-48	Period 1: randomized, placebo-controlled period for 12 wks Period 2: observational period without treatment for 12 wks	moderate to severe	15	38.7±15.3	adalimumab 80 mg at baseline followed by 40 mg s.c. every other week for 12 weeks	6	40.2±17.9	1 injection at baseline followed by an injection every other week for 12 wks	- mean value and estimated mean change from baseline in Sartorius score, Hurley score, VAS, DLQI, percentage of days with lesions	- AEs during treatment, including symptoms and laboratory findings	Yes
Kimball 2012[19]	NCT00918255	Period 1: randomized, placebo-controlled period for 16 weeks Period 2: open-label period for 36 wks	moderate to severe	51	35.1±10.7	adalimumab 160 mg at baseline, 80mg at week 2, followed by 40 mg weekly from week 4 to wk 15	51	37.8±12.1	4 injections at wk 0, 2 injections at wk 2, 1 injection weekly from wk 3 to wk 15, and 2 injections at wk 16	- proportion of patients achieving clinical response (defined as HS-PGA score), estimated mean change form baseline in C-reactive protein levels - estimated mean percentage of improvement from baseline in inflammatory nodules, abscesses, draining fistulas - estimated mean change from baseline in modified Sartorius score, DLQI, TWPI, PHQ-9	- AEs during treatment, including serious and infectious AEs	Yes
Kimball 2016 (PIONEER I)[7]	NCT01468207	Period 1: randomized, placebo-controlled period for 12 wks Period 2: re-randomized, placebo-controlled period for 24 wks*	moderate to severe	52	36.1±12.5	adalimumab 80 mg at baseline followed by 40 mg every other wk for 15 wks						
				153	36.2±10.8	adalimumab 40 mg weekly for 12 wks	154	37.8±11.3	matching placebo injection for 12 wks	- proportion of patients achieving clinical response (defined as HiSCR) - rank-ordered end points: total abscess and inflammatory-nodule count of 0,1,2, ≥30% reduction and ≥1-unit reduction in pain score, mean value and estimated mean change from baseline in modified Sartorius score - nonranked end points: estimated mean change from baseline in DLQI, etc.[†]	- AEs during treatment, including serious and infectious AEs	Yes

Table 1 (continued).

Study information of the randomized controlled period

Study	Clinical Trial Identifier	Severity	Adalimumab group			Placebo group			Outcomes of Efficacy	Outcomes of Safety	Industrial COI
			No.	Age (years) mean ± SD	Methods	No.	Age (years) mean ± SD	Methods			
Kimball 2016 (PIONEER II) [7]	NCT01468233	moderate to severe	163	34.9±10.0	adalimumab 40 mg weekly for 12 weeks	163	36.1±12.2	matching placebo injection for 12 wks	- proportion of patients achieving clinical response (defined as HiSCR) - rank-ordered end points: total abscess and inflammatory-nodule count of 0,1,2, ≥30% reduction and ≥1-unit reduction in pain score, mean value and estimated mean change from baseline in modified Sartorius score - nonranked end points: estimated mean change from baseline in DLQI, etc.[†]	- AEs during treatment, including serious and infectious AEs	Yes
NCT02808975 2020 (SHARPS) [24]	NCT02808975	moderate to severe	103	38.5±11.7	adalimumab 160 mg at baseline, 80mg at wk 2, followed by 40 mg wkly from wk 4 to wk 23	103	36.8±10.8	matching placebo injection for 24 wks	- proportion of patients achieving clinical response (defined as HiSCR, with and without the HS surgical site) - proportion of patients achieving clinical response (defined as HiSCR), percent change in the surface area of the HS surgical site from baseline, percentage of patients that require a less extensive surgery than the surgical plan or no surgery	- treatment-related AEs f/u 70 days after the last dose, including vital signs, symptoms and laboratory findings	Yes

Study design:
- Kimball 2016 (PIONEER II): Period 1: randomized, placebo-controlled period for 12 wks; Period 2: re-randomized, placebo-controlled period for 24 wks[‡]
- NCT02808975 2020 (SHARPS): randomized, placebo-controlled period for 24 wks

AE = adverse event, COI = conflict of interest, DLQI = Dermatology Life Quality Index, HiSCR = Hidradenitis Suppurativa Clinical Response, HS-PGA = Hidradenitis Suppurativa Physician's Global Assessment, No. = participant number, PHQ-9 = Patient Health Questionnaire-9, SD = standard deviation, TWPI = Total Work Productivity Index, VAS = Visual Analogue Scale.

* All patients who received adalimumab in period 1 and continued to period 2 underwent a second randomization at week 12; patients who received placebo in period 1 were reassigned to adalimumab 40 mg weekly in a blinded fashion for 24 weeks. To avoid bias, we only extracted data from period 1; therefore, only the study information of period 1 was displayed.[7]

[†] Full information about nonranked end points were displayed in Kimball et al. for PIONEER I and II.[7]

[‡] All patients who received adalimumab in period 1 and continued to period 2 underwent a second randomization at week 12; patients who received placebo in period 1 were reassigned to receive placebo in a blinded fashion for 24 weeks. To avoid bias, we only extracted data from period 1; therefore, only the study information of period 1 was displayed.
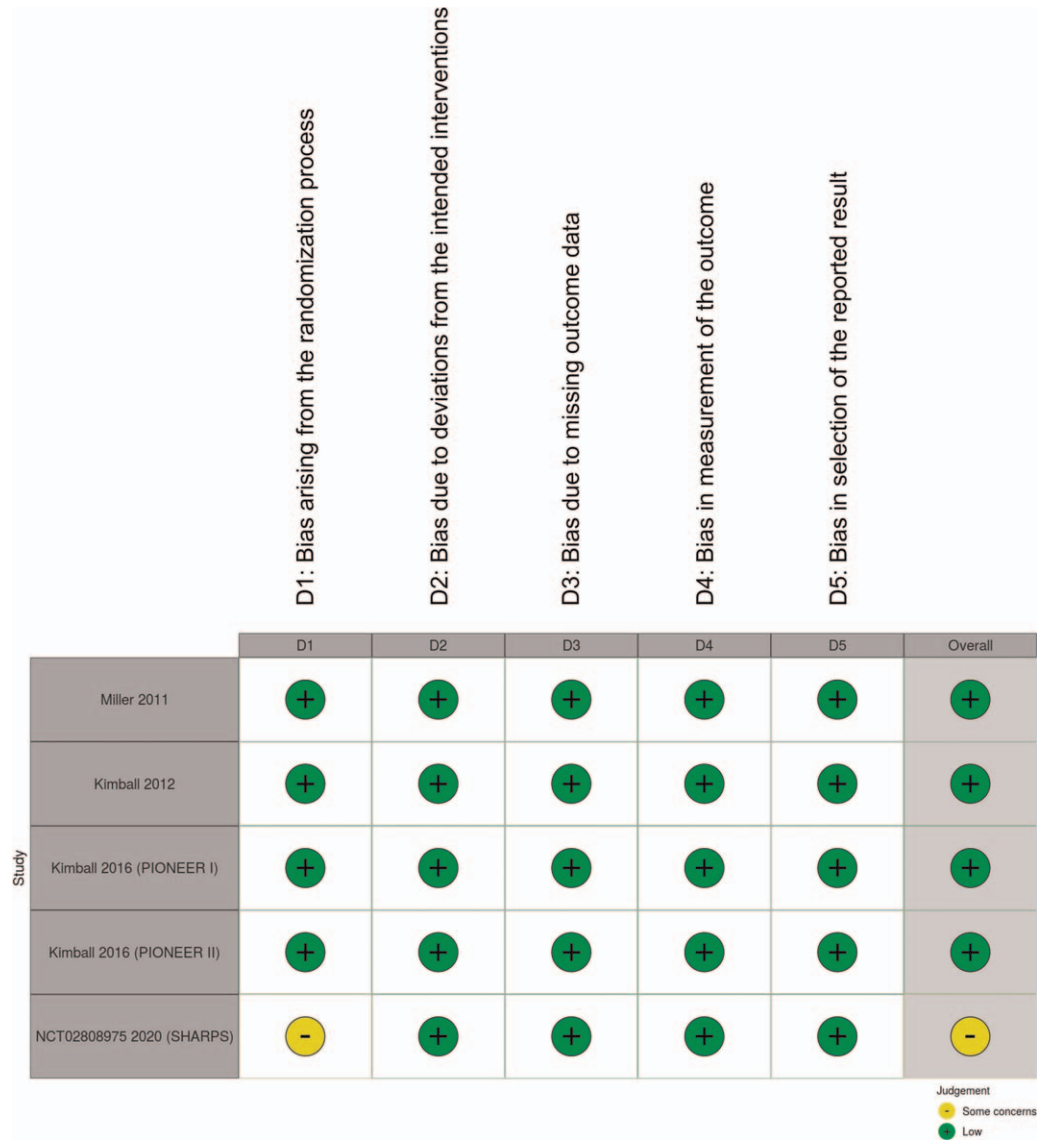
Figure 2. Risk of bias table for the included studies. Green circles represent a low risk of bias, yellow circles depict some concern of bias, and red circles indicate a high risk of bias.

20%). The cumulative Z-curve crossed the trial sequential monitoring boundary and reached the required IS of 506, making the present meta-analysis findings conclusive (Fig. 3b). In addition, as illustrated in Figure 3c, a major asymmetry across studies in patients achieving clinical response suggests small study effects, and this was supported by the LFK index of 3.43.

Patients who received adalimumab weekly or every other week showed a significant reduction in the modified Sartorius score from baseline (Fig. 4a). The SMD presented in Cohen's d was -0.45 (95% CI -0.76 to -0.13; $I^2 = 75.4\%$) and -0.74 (95% CI -1.11 to -0.37; $I^2 = 0\%$) for patients who received adalimumab weekly or every other week, respectively. Furthermore, the patients who received weekly injections exhibit significant changes in the DLQI from baseline (SMD in Cohen's d -0.47; 95% CI -0.61 to -0.32; $I^2 = 0\%$; Fig. 4b). The patients who received injections every other week showed no improvements in the DLQI (SMD in Cohen's d -0.21; 95% CI -0.57 to 0.14; $I^2 = 0\%$; Fig. 4b). The results pertaining to efficacy remained similar after sensitivity analyses of

each outcome (see Supplemental Digital Content Table S2 for details, http://links.lww.com/MD/G166).

3.5. Quantitative meta-analysis of safety

Patients receiving adalimumab for HS treatment did not show a significantly higher risk of developing AEs than patients receiving the placebo. As illustrated in Figure 5a–d, the pooled RRs of serious AEs, infectious AEs, headache, and nasopharyngitis were comparable between the weekly and every-other-week adalimumab groups. The sensitivity analysis performed by omitting 1 study at a time yielded similar results (see Supplemental Digital Content Table S3 for details, http://links.lww.com/MD/G167).

3.6. Small-study effects across studies

As mentioned above, a major asymmetry across studies in patients achieving clinical response suggests small study effects
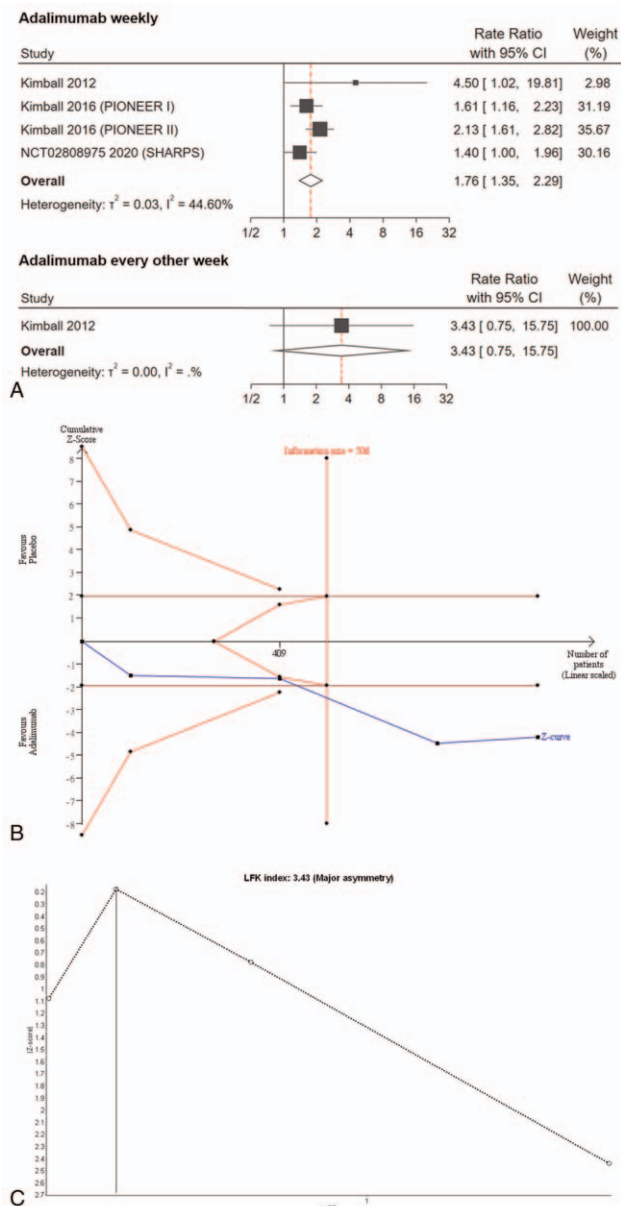
Figure 3. Forest plots of patients who achieved clinical response (a), trial sequential analysis (TSA) of clinical response (b), and Doi plot of clinical response (c). LFK index, Luis Furuya–Kanamori index; RR = risk ratio.

(the LFK index of 3.43; Fig. 3c). Based on the asymmetry of the Doi plots and LFK index, minor (LFK index, −1.16) and major asymmetries (LFK index, −2.09) were observed with regard to the modified Sartorius score and DLQI outcomes.

Small study effects were not detected in the pooled RR of nasopharyngitis (LFK index, −0.77); whereas, a minor asymmetry was observed in the groups of serious AEs (LFK index, −1.68) and infectious AEs (LFK index, 1.37). However, a major asymmetry (LFK index, 2.78) was observed in the group of patients with headache.

3.7. GRADE approach for CoE

The effects of administering adalimumab weekly and every other week are summarized in Tables 2 and 3, respectively, using the

GRADE proGDT platform. An explanation for downgrading in each domain of outcomes is also listed. The NNT for the effectiveness of adalimumab in HS management is presented in the far-right column.

As shown in Table 2, the levels of inconsistency in the modified Sartorius scores were downgraded by 2 levels because the I^2 was >75%. The levels of publication bias were downgraded by 1 or 2 level(s) owing to the minor or major asymmetry in the Doi plot, respectively. In summary, the CoE of clinical response, modified Sartorius score, and DLQI for the efficacy of adalimumab in HS management, as well as serious AEs, infectious AEs, headache, and nasopharyngitis were classified as low, very low, low, moderate, moderate, low, and high, respectively.

As the Doi plot was not applicable when there were only 2 studies in the group of patients administered adalimumab every other week, small-study effects were not detected using the approach. Alternatively, per the guidance of the Cochrane handbook,[12] the levels of publication bias were further downgraded owing to potential conflict of interests (Table 3). The overall CoE of each outcome was judged as "moderate."

4. Discussion

In this review, we demonstrate that subcutaneous adalimumab is an effective treatment for moderate-to-severe HS with tolerable adverse effects. The efficacy of adalimumab was indicated by clinical response and the changes in the modified Sartorius score and DLQI from baseline. Additionally, TSA provided conclusive evidence for clinical response. The safety issues of adalimumab were not significant compared with those of the placebo. The sensitivity analysis yielded similar results, making the pooled effect estimates robust. Nevertheless, limited CoE with small study effects must be taken into consideration when the findings are clinically applied by dermatologists.

Several inflammatory modulators have been proposed in the pathophysiological mechanism of HS, including TNF-α, interleukin (IL)-1β, IL-10, and IL-17.[25,26] In fact, it has been reported that the TNF-α concentration was significantly higher in the skin and serum of patients with HS than in those of healthy controls.[27,28] The use of TNF-α inhibitors in HS management stemmed from the recognition that patients with inflammatory bowel diseases treated with these medications showed a concurrent improvement in their HS symptoms.[29,30] Previous case reports and case series have elucidated the potential of TNF-α inhibitors in the treatment of HS and other chronic diseases such as psoriasis.[31,32] In real-life observational research, treatment with adalimumab was associated with both clinical remission of HS and an improvement in the quality of life of patients.[33] Both modified Sartorius score and DLQI significantly decreased during evaluation (Friedman test; P < .001).

Our results of quantitative meta-analysis supported the findings of a previous review conducted by Tchero et al.[10] Furthermore, we assumed that the true effect of adalimumab in treating moderate-to-severe HS varies from 1 study to another, owing to the different loading doses and pharmacological effects between individuals. Therefore, we considered the random-effect model is more suitable for pooled effect size estimation. Moreover, after our evidence-based appraisal, efficacy outcomes regarding adalimumab administered weekly yielded low and very low CoE because of likely and very likely publication biases. Interestingly, adalimumab administered every other week influenced the modified Sartorius score with moderate CoE from
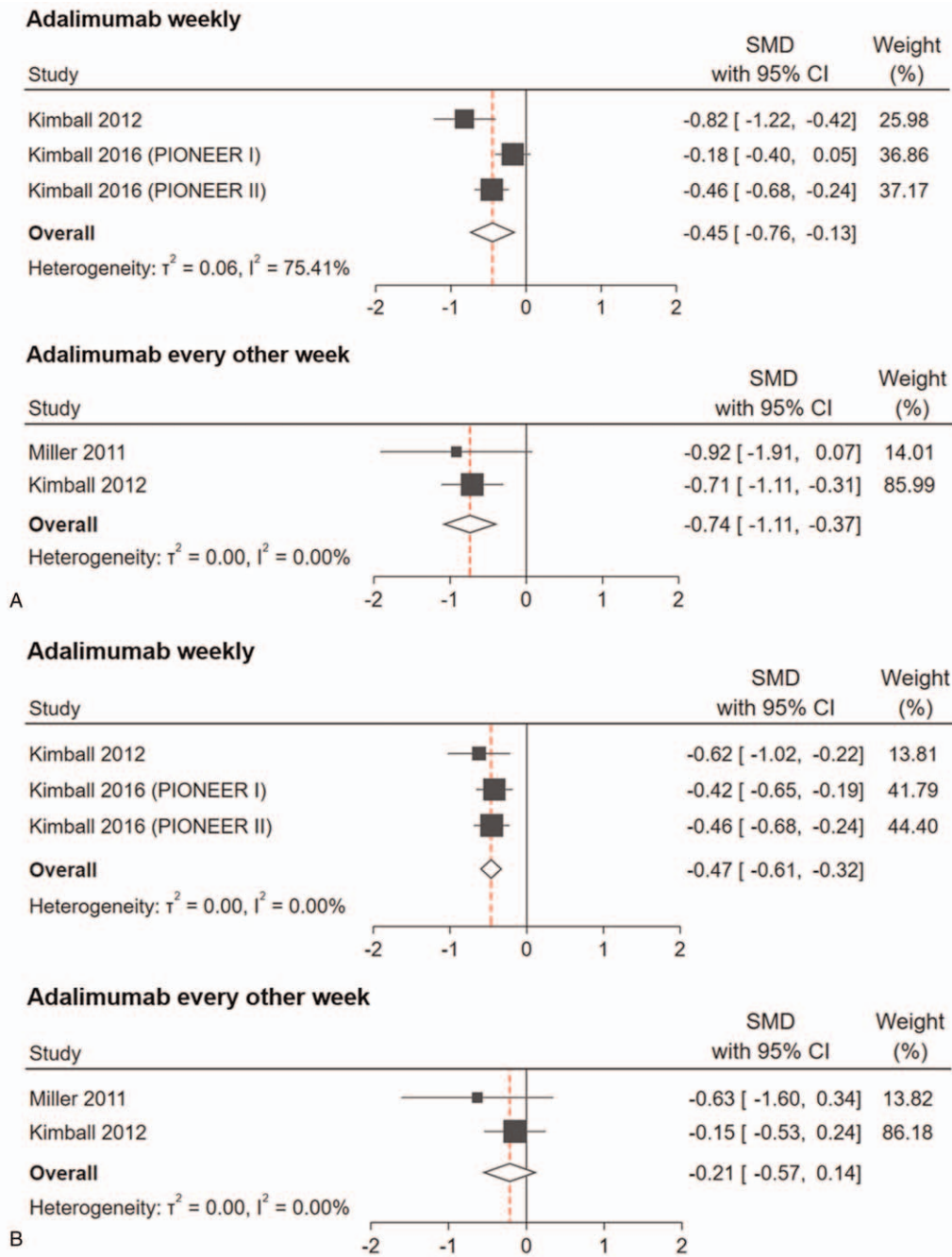
Figure 4. Forest plots of the (a) changes in the modified Sartorius score from baseline and (b) changes in the dermatology life quality index from baseline. SMD = standardized mean difference.

baseline. This result was different from that of a previous GRADE systematic review [9] in 2016, probably because we included more recent studies. Considering the prevalence, disease burden, and high cost of biologic agents, more studies on the cost-effectiveness of adalimumab in clinical practice are warranted.

Among the RCTs in patients with HS, 90% of the outcomes lacked validated measurement to support their clinical applicability.[34] HiSCR is a validated outcome measure, which is supported by good-quality evidence and is recommended for the assessment of treatment effectiveness in controlling inflammatory manifestations in patients with HS (evidence level 2, grade of

recommendation B).[16,35] There were 3 studies that applied HiSCR to report the proportion of patients achieving clinical response. Other novel treatment outcome measures that correlate with HS severity have been introduced for implication.[36] To the best of our knowledge, this is the first meta-analysis to assess the pooled RR of clinical response of adalimumab in treating HS.

The NNT is widely recommended as a quantitative measure of effectiveness to overcome the lack of intuitiveness of traditional measures of risk from clinical trials.[37] While the acceptable value of NNT depends on the "threshold NNT" in different circumstances,[38] single-digit NNTs have been often considered
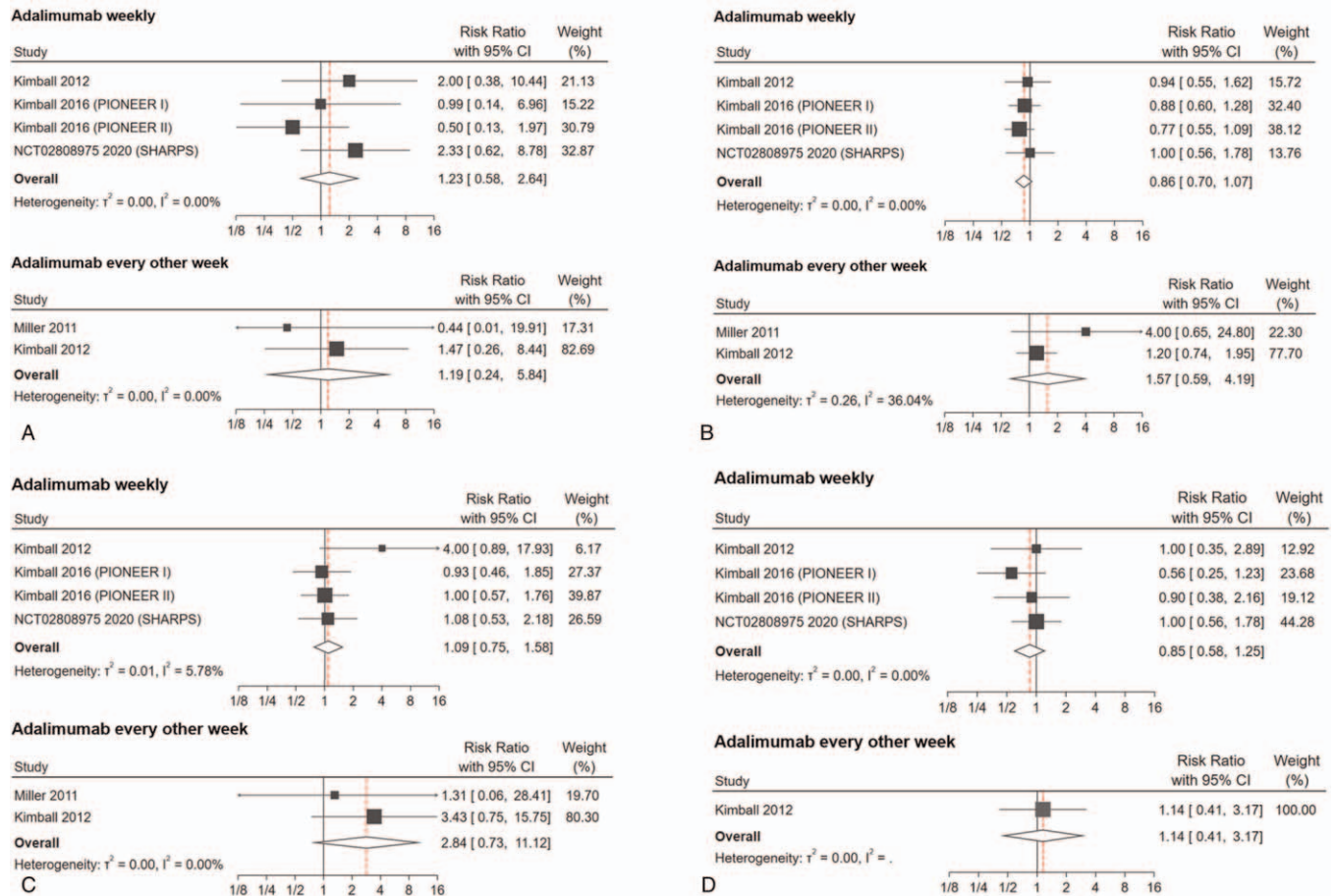
Figure 5. Forest plots of (a) serious adverse events, (b) infectious adverse event, (c) headache, and (d) nasopharyngitis.

Table 2

Certainty of evidence by GRADE (adalimumab weekly).

of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall CoE	NNTs / NNHs Mean (95% CI)
Clinical response							
941 (4 RCTs)	not serious	not serious	not serious	not serious	very likely[†]	⊕⊕◯◯ LOW	NNT = 5 (3–11)
Modified Sartorius score							
839 (3 RCTs)	not serious	very serious[*]	not serious	not serious	likely[‡]	⊕◯◯◯ VERY LOW	NNT = 10 (5–41)
Dermatology Life Quality Index							
839 (3 RCTs)	not serious	not serious	not serious	not serious	very likely[†]	⊕⊕◯◯ LOW	NNT = 10 (7–15)
Serious adverse events							
939 (4 RCTs)	not serious	not serious	not serious	not serious	likely[‡]	⊕⊕⊕◯ MODERATE	NR
Infectious adverse events							
939 (4 RCTs)	not serious	not serious	not serious	not serious	likely[‡]	⊕⊕⊕◯ MODERATE	NR
Headache							
939 (4 RCTs)	not serious	not serious	not serious	not serious	very likely[†]	⊕⊕◯◯ LOW	NR
Nasopharyngitis							
939 (4 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	NR

CI = confidence interval, CoE = certainty of evidence, NNT/NNH = number-needed-to-treat/number-needed-to-harm, NR = not reasonable (no statistical significance in meta-analysis), RCT = randomized controlled trial.

[*] $I^2 > 75\%$.

[†] Doi plot indicated major asymmetry.

[‡] Doi plot indicated minor asymmetry.

Table 3

Certainty of evidence by GRADE (adalimumab every other week).

of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall CoE	NNTs / NNHs Mean (95% CI)
Clinical response							
103 (1 RCT)	not serious	not serious	not serious	not serious	likely*	⊕⊕⊕◯ MODERATE	NR
Sartorius score							
124 (2 RCT)	not serious	not serious	not serious	not serious	likely*	⊕⊕⊕◯ MODERATE	NNT = 6 (4–13)
Dermatology Life Quality Index							
124 (2 RCT)	not serious	not serious	not serious	not serious	likely*	⊕⊕⊕◯ MODERATE	NR
Serious adverse events							
124 (2 RCT)	not serious	not serious	not serious	not serious	likely*	⊕⊕⊕◯ MODERATE	NR
Infectious adverse events							
124 (2 RCT)	not serious	not serious	not serious	not serious	likely*	⊕⊕⊕◯ MODERATE	NR
Headache							
124 (2 RCT)	not serious	not serious	not serious	not serious	likely*	⊕⊕⊕◯ MODERATE	NR
Nasopharyngitis							
103 (1 RCT)	not serious	not serious	not serious	not serious	likely*	⊕⊕⊕◯ MODERATE	NR

CI = confidence interval, CoE = certainty of evidence, NNT/NNH = number-needed-to-treat/number-needed-to-harm, NR = not reasonable (no statistical significance in meta-analysis), RCT = randomized controlled trial.

* Potential conflict of interest was indicated.

as "clinically desirable" for drug application.[39] In our study, the NNTs were low for the efficacy outcomes, and this indicated an acceptable effect in clinical practice. Consequently, the results of our evidence-based approach may be informative to both patients and physicians in clinical dermatology.

Based on the available evidence, there is a high risk of infection after the initiation of TNF-α inhibitor therapy.[40] Despite the risk of developing malignancies and tuberculosis, mild upper respiratory tract infection is the most common AE.[41,42] The safety issues of adalimumab in our analysis were comparable and consistent with the expected adalimumab AE profile.[43] We demonstrated that the pooled estimates of developing headaches and nasopharyngitis account for over 10% in each of the study arms in the PIONEER trials. Although the CoE of safety issues have been influenced by potential small study effects, the pooled results did not indicate significant risks of serious or infectious AEs following the administration of adalimumab either weekly or every other week. On the contrary, a recent data analysis of PIONEER I and II revealed minimal differences in the incidence of respiratory infections between patients with HS on adalimumab and those on placebo.[44] Both patients and physicians should cautiously consider infections when making treatment decisions for patients with HS, especially during the unfolding COVID-19 pandemic.

The I^2 was less than 50% in nearly all our desired outcomes, except for the modified Sartorius score in the weekly adalimumab-administered group. Owing to the small number of the included studies, meta-regression for addressing heterogeneity was not accessible. Thus, we failed to explore the substantial heterogeneity in the modified Sartorius score of the weekly adalimumab-administered group.

The occurrence of small study effects such as publication bias suggests an overestimation of treatment benefits.[45,46] In their meta-analysis, Tchero et al[10] did not use funnel plot or quantitative approach, such as Egger test, because the number of studies was less than 10.[12] Additionally, there have been concerns about Egger asymmetry test and its power to detect asymmetry, especially when the number of studies is small;[47] this a common feature in meta-analysis.[48] Recently, the Doi plot and LFK index have been shown to outperform Egger P test for potential small study effects, even when the number of studies is

small. A comparison using Egger P test revealed that the LFK index had superior areas under the receiver operating characteristic curve (0.74–0.88 vs 0.58–0.75) and higher sensitivity (71.3%–72.1% vs 18.5%–43.0%).[21] However, the specificity was higher for Egger P test (87.6%–90.0% vs 64.7%–87.1%).[20] We used the Doi plot and LFK index to detect major and minor asymmetries in several outcomes of our interest, which may be ignored by the inapplicability of funnel plot and quantitative approaches such as Egger P test.

A major strength of this study was the application of Cochrane methodology. We conducted an up-to-date literature search and included recent trials in the analysis. RoB 2.0 was assessed for eligible RCTs, and the GRADE approach was used for essential outcomes to emphasize the certainty of our meta-analysis results. The TSA was performed to explore the risk of random error because of sparse data and repetitive testing to increase the robustness of our meta-analysis. Furthermore, this is the first meta-analysis to assess the pooled RR of clinical response in moderate-to-severe HS treatment with adalimumab. We believed that the RR of clinical response might be more comprehensive and practical to both physicians and patients in clinical practice than the actual value of mean difference. Finally, we evaluated small study effects using methods with high sensitivity, such as the Doi plot and the LFK index.

There were some limitations to our study. First, we only included five studies in our analysis and therefore, the sample size was small. The TSA was conducted to calculate IS and possible type I error adjustment. However, because of the inherent limitation of TSA software, we were unable to perform TSA considering the SMD effect size. Second, the between-study heterogeneity was unclear. Most of the included publications came from the same research team and the sample size of individual studies is generally small. Finally, while the LFK index has been shown to discriminate asymmetry better and have higher sensitivity, its specificity is lower than that of the Egger P value.

5. Conclusions

In our systematic review and meta-analysis, adalimumab administered weekly was found to be an effective biologic agent

for achieving clinical response and improving symptoms in and quality of life of patients with HS. The risk of developing adverse reactions was comparable between the intervention and control groups. Given the limited CoE, future large-scale RCTs are necessary to obtain more robust evidence for the application of adalimumab in the treatment of moderate-to-severe HS.

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References

[1] Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: epidemiology, clinical presentation, and pathogenesis. J Am Acad Dermatol 2020;82:1045–58.

[2] Jemec GB, Kimball AB. Hidradenitis suppurativa: epidemiology and scope of the problem. J Am Acad Dermatol 2015;73:S4–7.

[3] Tzellos T, Yang H, Mu F, Calimlim B, Signorovitch J. Impact of hidradenitis suppurativa on work loss, indirect costs and income. Br J Dermatol 2019;181:147–54.

[4] Saunte DML, Jemec GBE. Hidradenitis suppurativa: advances in diagnosis and treatment. JAMA 2017;318:2019–32.

[5] Folkes AS, Hawatmeh FZ, Wong A, Kerdel FA. Emerging drugs for the treatment of hidradenitis suppurativa. Expert Opin Emerg Drugs 2020;25:201–11.

[6] Haslund P, Lee RA, Jemec GB. Treatment of hidradenitis suppurativa with tumour necrosis factor-alpha inhibitors. Acta Derm Venereol 2009;89:595–600.

[7] Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. N Engl J Med 2016;375:422–34.

[8] Maarouf M, Clark AK, Lee DE, Shi VY. Targeted treatments for hidradenitis suppurativa: a review of the current literature and ongoing clinical trials. J Dermatolog Treat 2018;29:441–9.

[9] Ingram JR, Woo PN, Chua SL, et al. Interventions for hidradenitis suppurativa: a Cochrane systematic review incorporating GRADE assessment of evidence quality. Br J Dermatol 2016;174:970–8.

[10] Tchero H, Herlin C, Bekara F, Fluieraru S, Teot L. Hidradenitis suppurativa: a systematic review and meta-analysis of therapeutic interventions. Indian J Dermatol Venereol Leprol 2019;85:248–57.

[11] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

[12] Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

[13] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

[14] McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth 2021;12:55–61.

[15] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[16] Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol 2008;61:763–9.

[17] Shah A, Smith AF. Trial sequential analysis: adding a new dimension to meta-analysis. Anaesthesia 2020;75:15–20.

[18] Furukawa TA, Guyatt GH, Griffith LE. Can we individualize the 'number needed to treat'? An empirical study of summary effect measures in meta-analyses. Int J Epidemiol 2002;31:72–6.

[19] Kimball AB, Kerdel F, Adams D, et al. Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. Ann Intern Med 2012;157:846–55.

[20] Furukawa TA, Leucht S. How to obtain NNT from Cohen's d: comparison of two methods. PLoS One 2011;6:e19070.

[21] Furuya-Kanamori L, Barendregt JJ, Doi SAR. A new improved graphical and quantitative method for detecting bias in meta-analysis. Int J Evid Based Healthc 2018;16:195–203.

[22] Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. Lancet 2017;390:415–23.

[23] Miller I, Lynggaard CD, Lophaven S, et al. A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. Br J Dermatol 2011;165:391–8.

[24] US National Library of Medicine. Safety and Efficacy of Humira (Adalimumab) for Hidradenitis Suppurativa (HS) Peri-Surgically (SHARPS Study) (SHARPS); 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02808975. Accessed July 31, 2020.

[25] Tricarico PM, Boniotto M, Genovese G, et al. An integrated approach to unravel hidradenitis suppurativa etiopathogenesis. Front Immunol 2019;10:892.

[26] Kelly G, Hughes R, McGarry T, et al. Dysregulated cytokine expression in lesional and nonlesional skin in hidradenitis suppurativa. Br J Dermatol 2015;173:1431–9.

[27] van der Zee HH, de Ruiter L, van den Broecke DG, et al. Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. Br J Dermatol 2011;164:1292–8.

[28] Matusiak L, Bieniek A, Szepietowski JC. Increased serum tumour necrosis factor-alpha in hidradenitis suppurativa patients: is there a basis for treatment with anti-tumour necrosis factor-alpha agents? Acta Derm Venereol 2009;89:601–3.

[29] Koelink PJ, Bloemendaal FM, Li B, et al. Anti-TNF therapy in IBD exerts its therapeutic effect through macrophage IL-10 signalling. Gut 2020;69:1053–63.

[30] Ringerike T, Elvsaas IKØ, Coll P, et al. TNFα-Inhibitors in Inflammatory Bowel Disease [Internet]. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2008. Report from Norwegian Knowledge Centre for the Health Services (NOKC) No. 32-2008.

[31] Fougerousse AC, Reguiai Z, Roussel A, et al. Hidradenitis suppurativa management using tumor necrosis factor inhibitors in patients younger than 18 years: a series of 12 cases. J Am Acad Dermatol 2020;83:199–201.

[32] Yen CF, Huang YH, Chi CC. Concomitant psoriasis and hidradenitis suppurativa responsive to adalimumab therapy: A case series. Indian J Dermatol Venereol Leprol 2021;87:223–6.

[33] Kyriakou A, Trigoni A, Galanis N, Sotiriadis D, Patsatsi A. Efficacy of adalimumab in moderate to severe hidradenitis suppurativa: real life data. Dermatol Reports 2018;10:7859.

[34] Zouboulis CC, Bechara FG, Dickinson-Blok JL, et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization - systematic review and recommendations from the HS ALLIANCE working group. J Eur Acad Dermatol Venereol 2019;33:19–31.

[35] Kimball AB, Jemec GB, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa

Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br J Dermatol 2014;171:1434–42.

[36] Hessam S, Scholl L, Sand M, et al. A novel severity assessment scoring system for hidradenitis suppurativa. JAMA Dermatol 2018;154:330–5.

[37] Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: an appraisal. BMC Med 2017;15:112.

[38] Sinclair JC, Cook RJ, Guyatt GH, Pauker SG, Cook DJ. When should an effective treatment be used? Derivation of the threshold number needed to treat and the minimum event rate for treatment. J Clin Epidemiol 2001;54:253–62.

[39] Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract 2013;67:407–11.

[40] Crawford M, Curtis JR. Tumor necrosis factor inhibitors and infection complications. Curr Rheumatol Rep 2008;10:383–9.

[41] Nagy A, Mátrai P, Hegyi P, et al. The effects of TNF-alpha inhibitor therapy on the incidence of infection in JIA children: a meta-analysis. Pediatr Rheumatol Online J 2019;17:4.

[42] Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis

of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275–85.

[43] Ryan C, Sobell JM, Leonardi CL, et al. Safety of adalimumab dosed every week and every other week: Focus on patients with hidradenitis suppurativa or psoriasis. Am J Clin Dermatol 2018;19:437–47.

[44] Blaszczak A, Trinidad JCL, Cartron AM. Adalimumab for treatment of hidradenitis suppurativa during the COVID-19 pandemic: safety considerations. J Am Acad Dermatol 2020;83:e31.

[45] Atakpo P, Vassar M. Publication bias in dermatology systematic reviews and meta-analyses. J Dermatol Sci 2016;82:69–74.

[46] Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

[47] Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53:1119–29.

[48] Davey J, Turner RM, Clarke MJ, Higgins JP. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. BMC Med Res Methodol 2011;11:160.