

BMJ Open Pharmacological interventions for hidradenitis suppurativa: a protocol for systematic review and network meta-analysis of randomised trials and non-randomised studies

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ABSTRACT

Introduction Therapeutic recommendations for hidradenitis suppurativa (HS) have recently shifted towards non-invasive pharmacological options. Recent evidence has shown promising efficacy for specific treatments. However, data regarding the comparative efficacy of these treatments in patients with HS are still limited. Therefore, we plan to conduct a systematic review and network meta-analysis (NMA) to summarise the benefits and harms of different pharmacological interventions for treating people living with HS.

Methods and analysis We will search electronic databases, including Medline, Embase, PubMed, Web of Science, Scopus, CINAHL and Cochrane Library beginning from their inception dates with no language restrictions. A grey literature search will be performed to supplement the electronic databases. Both randomised trials and non-randomised studies using validated measurement tools that investigated the benefits and harms of pharmacological interventions among people living with HS will be included. The predefined primary outcomes will include treatment responses that reflect the patient's perspective and all-cause discontinuation. Screening, selection, extraction, assessment of the risk of bias and analysis of the strength of the evidence will be performed independently by a pair of reviewers. A two-step approach of traditional pairwise and NMA will be performed. Based on a random-effects model, standardised weighted mean differences and ORs with corresponding 95% CIs will be pooled as effect estimates for the continuous and categorical endpoints, respectively. Statistical and methodological heterogeneities will be assessed. Preplanned subgroup analyses and univariate meta-regression will be conducted to quantify the potential sources of heterogeneity. Evidence-based synthesis will be based on the magnitudes of effect size, evidence certainty and the surface under the cumulative ranking curve values.

Ethics and dissemination Ethical approval is not required because this study is based on existing published data. These findings will be disseminated through scientific meetings and publications in peer-reviewed journals.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A rigorous and comprehensive approach without language restrictions is anticipated to include all available evidence from the literature.
- ⇒ A contextualised approach will be employed to establish the network effect estimates based on the dimension of benefits and harms of pharmacological interventions for hidradenitis suppurativa.
- ⇒ Heterogeneity in study-specific estimates and differences in the definitions of exposure and outcomes across studies may affect the results.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic or relapsing inflammatory skin disorder characterised by the development of painful, inflamed nodules in areas containing apocrine follicles. Patients usually begin developing the disease between the onset of puberty and 40 years of age, and women are three times more likely to have HS than men.¹ The severity of HS can be classified using the Hurley clinical staging system. Patients with a mild form of HS can have recurrent episodes, but this is manageable by using only symptomatic treatments and lifestyle changes.² HS can become chronically debilitating in moderate and severe forms. Poorly controlled cases often experience complications, such as lymphoedema, infections, arthritis and long-term chronic inflammatory conditions (eg, anaemia, amyloidosis, hyperproteinaemia and other severe comorbidities).^{3–5} These events have a significant negative impact on the quality of life of the afflicted individual and might also cause depression, anxiety and increased suicidal risk.^{6–8}

Although surgical intervention is generally regarded as the most effective treatment for

HS,⁹ non-invasive pharmacological treatment is an alternative therapeutic option which might be more economically viable for many patients.¹⁰ According to the 2019 North American clinical management guidelines for HS, pharmacological therapies are classified into several modalities, such as topical and systemic antibiotics, biologics, retinoids and immunosuppressive agents.^{11 12} Topical clindamycin is widely used in practice as the first-line therapy in mild cases.¹³ In recalcitrant cases of HS that do not respond well to first-line therapy, arrays of systemic antibiotics and anti-androgenic drugs are recommended. However, the evidence underlying the efficacy of these drugs is limited.^{14–16} Biological immunomodulatory agents, such as tumour necrosis factor-alpha inhibitors and interleukin-17 antagonists, are the mainstay of treatment in moderate and severe cases.¹² These newer agents have shown promising efficacy with minimal adverse effects in various clinical trials.^{17–20} Other therapeutic options that are currently being explored include botulinum type B and retinoids, which have been shown to improve the median Dermatology Life Quality Index of patients with HS.²¹

Existing traditional meta-analysis and network meta-analysis (NMA) of pharmacological treatment have been published, but most have been focused on only randomised controlled trials (RCTs) or pharmacological monotherapy.^{16 22} Moreover, previous systematic reviews have also been conducted specifically to address the efficacy of non-pharmacological options, such as surgical procedures and light therapy.^{9 23} Over the past several years, evidence regarding the clinical efficacy of novel treatments has been accumulating, and guideline recommendations have shifted towards pharmacological interventions for patients with HS.^{12 24} Given the evidence gaps in the pharmacological treatments for HS, we aimed to summarise all available evidence to address some limitations of RCTs, generalisable of evidence, and expand the relevant outcomes of interest, such as the patient-reported outcomes (ie, health-related quality of life) to account for the patients' perspective. In light of these changes, this systematic review hopes to provide a comprehensive review of pharmacological treatments encompassing data from both RCTs and non-randomised studies.

METHODS

This systematic review and NMA will be performed in accordance with the recommendations of the Cochrane Collaboration Handbook for Systematic Reviews of Interventions V.6.2.²⁵ The prespecified protocol of this review has been submitted to the International Prospective Register of Systematic Reviews (CRD42022302795). The reporting of this protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement (online supplemental appendix I).²⁶ Based on the replication checklist by Tugwell and colleagues,²⁷ there is a need for the continuation of this NMA to summarise the benefits and harms of different

pharmacological interventions for treating people living with HS (online supplemental appendix II).

Patient and public involvement

Patients and the public had no role in this study.

Systematic searching

In collaboration with an experienced medical librarian, a systematic search of relevant evidence will be performed through electronic biomedical databases, including Medline, Embase, PubMed, Scopus, Web of Science, CINAHL and the Cochrane Central Register of Controlled Trials. The search strategy will be constructed using a combination of main keywords or medical subject headings terms regarding HS (ie, “hidradenitis suppurativa” OR “hidradenitis axillaris” OR “acne inversa” OR “apocrine acne” OR “fox den disease” OR “Velpheu's disease” OR “Verneuil's disease”). In addition to medical conditions, search terms related to pharmacological interventions will be incorporated based on treatments with individual pharmacological classes. The prespecified search strategy and the results of the preliminary searches for each database are provided in online supplemental table 1. The search will be conducted from the inception dates of each database to present with no language restrictions on eligible studies.

A grey literature search will also be performed, including Google Scholar, ongoing clinical trial registries and preprint databases (medRxiv and bioRxiv). Additionally, potentially relevant articles have been manually searched for from prior systematic reviews, reference lists of the included studies and major dermatology scientific meetings (online supplemental table 2). An updated search will be performed before formal analyses and dissemination.

Process of study selection

The selection process begins with de-duplication of the identified records selected from each database. Records will be then screened by two reviewers (NA and LL) independently using a web-based systematic review application, Rayyan.²⁸ Next, the full text of potentially relevant articles will be reviewed against the study selection criteria to obtain the final set of included studies. Potentially eligible articles published in languages other than English were translated before full-text review. For companion trials or post hoc analysis studies, we will assemble the relevant information regarding overlapping participants and/or study periods. Any inconsistency or ambiguity in the study selection at either stage will be resolved by consulting clinical experts (JS and MC) and methodologists (PP and SN). The final study selection process will be described using a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

Study selection criteria and predefined outcomes of interest

We will include both RCTs (ie, placebo-controlled trials, head-to-head trials, parallel trials or crossover trials) and non-randomised studies (ie, open-label, multiple-armed

Table 1 The PICOTS format: study inclusion/exclusion criteria

Study elements	Criteria for inclusion	Criteria for exclusion
Populations	<ul style="list-style-type: none"> ▶ Participants who were clinically diagnosed with HS with no restriction on age, sex, ethnicity or disease severity/Hurley stage, which addressed at least one of the outcomes of interest ▶ Other subgroups or secondary analyses will be also included if studies provide data to calculate the effect estimates of the outcomes of interest 	<ul style="list-style-type: none"> ▶ In vitro, in vivo or animal studies ▶ Studies not pertaining to HS ▶ Studies including less than 10 participants (to mitigate type II error)
Interventions	<ul style="list-style-type: none"> ▶ Pharmacological treatment with any type of administered treatments for HS 	<ul style="list-style-type: none"> ▶ Studies regarding non-pharmacological, physical or surgical therapies ▶ Studies regarding imaging modalities (ie, ultrasound) ▶ Studies regarding disconnected node of treatments
Comparators	<ul style="list-style-type: none"> ▶ Placebo, active comparator or standard of care 	<ul style="list-style-type: none"> ▶ Studies without control groups (single-arm studies)
Outcomes	<ul style="list-style-type: none"> ▶ Primary outcomes ▶ Treatment response: change in HS symptoms score from baseline using validated measurement tools (ie, HiSCR, IHS4, MSS, HS-PGA, SAHS, AISI, SASH, HASI/HASI-R) ▶ Treatment response: proportion of clinical responders (ie, ≥50% HiSCR or IHS4 reduction from baseline) ▶ Unacceptability of treatment (all-cause discontinuation) ▶ Secondary outcomes ▶ Change in total abscess and abscess and inflammatory nodule counts from baseline ▶ Percentage change in surface area of the HS surgical site from baseline ▶ Time to new HS exacerbation ▶ Proportion of participants who required no surgery as determined by the designed surgeon ▶ Change in high-sensitivity C reactive protein from baseline ▶ Occurrence of adverse event (participant with at least one reported adverse event) ▶ Occurrence of SAE (participant with at least one reported SAE) ▶ Patient-reported HRQOL, including general, dermatology-specific and HS-specific measures ▶ Additional outcomes ▶ Symptoms burden (ie, pain, fatigue, pruritus, malodour, sleep problems, sexual dysfunction) ▶ Work impairment (ie, absenteeism, presenteeism, work productivity and/or school performance) ▶ Psychosocial aspects (ie, depressive symptoms, anxiety, distress and well-being) ▶ Treatment satisfaction ▶ Healthcare utilisation (ie, emergency/unplanned visit during follow-up and costs of care) 	<ul style="list-style-type: none"> ▶ Studies not providing data to calculate the effect estimates of the outcome of interest ▶ Studies with a follow-up period of less than 2 weeks
Timing	<ul style="list-style-type: none"> ▶ An extensive search strategy from the inception of bibliographical databases forward to assure all published literature will be identified 	<ul style="list-style-type: none"> ▶ No restrictions were imposed on timing of start date or language
Setting	<ul style="list-style-type: none"> ▶ Experimental study: RCTs (parallel or crossover trials) ▶ Non-randomised studies (open-label, multiple-armed clinical trial, comparative effectiveness observational studies) 	<ul style="list-style-type: none"> ▶ Case-control, cross-sectional studies, N-of-one, case series/case reports and pharmacokinetic/pharmacodynamics studies ▶ Reports not involving primary data including narrative review, systematic review, meta-analysis, news items, consensus statement, guidelines and opinion/editorials

AISI, Acne Inversa Severity Index; HASI/HASI-R, Hidradenitis Suppurativa Area and Severity Index/Hidradenitis Suppurativa Area and Severity Index Revised; HiSCR, Hidradenitis Suppurativa Clinical Response; HRQOL, health-related quality of life; HS, hidradenitis suppurativa; HS-PGA, Hidradenitis Suppurativa-Physicians' Global Assessment; IHS4, International Hidradenitis Suppurativa Severity Score System; MSS, Modified Sartorius Score; PICOTS, populations, interventions, comparators, outcomes, timing, setting; RCTs, randomised controlled trials; SAE, serious adverse event; SAHS, Severity Assessment of Hidradenitis Suppurativa; SASH, Severity and Area Score for Hidradenitis.

clinical trials, comparative effectiveness observational studies) that investigated the benefits and harms of pharmacological treatment among participants who were clinically diagnosed with HS regardless of age, sex, ethnicity or disease severity. The key elements of the study design, eligibility criteria, and predefined outcomes based on the population, intervention, comparison, outcome, timing, and setting framework are described in [table 1](#).

The prespecified possible network intervention nodes included in this systematic review and NMA are: antibiotics (eg, clindamycin, tetracycline and dapsone), hormonal (eg, metformin, spironolactone and finasteride), topical antiseptics (eg, benzoyl peroxide and chlorhexidine), topical keratolytic (eg, resorcinol), intralésional corticosteroids (eg, triamcinolone), biologics (eg, adalimumab, secukinumab, etanercept and apremilast),

immunosuppressive agents (eg, systemic corticosteroids and ciclosporin), retinoids (eg, acitretin, isotretinoin and alitretinoin) and supplements (eg, zinc and vitamin D).

Data extraction

Independent data extraction by two reviewers (NA and LL) will be performed using a standardised approach and an electronic extraction form. The following data will be gathered from each study:

1. Characteristics of the study, including the names of the first and the corresponding authors, study year, study location, study setting, type of clinical trial (ie, single centre or multicentre), types of design (ie, parallel, crossover, head-to-head or placebo controlled), study population (ie, inclusion and exclusion criteria), study size of each treatment group and follow-up period.
2. Participant characteristics and potential effect modifiers, including the age of study participants (mean, median or prespecified age groups; paediatric, adult or elderly), age at symptom onset, proportion of male participants, race/ethnicity, body mass index, baseline disease severity and duration, history of psychiatric disorders or other systemic diseases, previous treatment, laboratory markers (eg, C reactive proteins and erythrocyte sedimentation rate) and other medications used.
3. Specific treatment intervention and comparison groups, including individual treatment comparisons, specific dosage of treatment, route of administration, and concomitant and rescue treatment medications.
4. Predefined outcomes of interest, both primary and additional, including detailed measurement methods.

The extracted data will then be reviewed by two methodologists (PP and SN) for cross-checking. Any discrepancies that appear during the extraction process will be resolved through group discussions. If there are any studies with missing data on an outcome of interest, we will contact the corresponding author via email and if no reply is given within 2 weeks, then a second attempt will be made. If no response is received after the second attempt, the data will be reported after a group discussion as missing or imputed depending on the quality of available information.

For numerical endpoints (ie, score changes from baseline), the mean and SD will be calculated. If SD values are missing and the corresponding author does not respond to our request or cannot provide the data, imputation of the SD will be conducted according to the methods recommended by the Cochrane Handbook for Systematic Reviews of Interventions.²⁵ For the binary endpoint, treatment arms with zero events will be replaced with 0.5 for continuity correction. For crossover trials, we will only include information from the period before the start of the crossover.

Risk of bias appraisal

Independent evaluation of the quality of selected RCTs will be performed using the Cochrane risk-of-bias version

2 assessment tool (RoB 2) by two reviewers (LL and PP).²⁹ The RoB 2 tool evaluates the presence of potential biases in RCTs of five domains: bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and bias in the selection of the reported result. With this assessment, each study will be categorised into low risk, high risk or with some concerns. For non-randomised studies, we will use the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool, which is comprised of seven domains, including bias due to confounding, selection of participants, classification of interventions, departures from intended interventions, missing data, measurement of outcomes and selection of reported results.³⁰ The ROBINS-I adjudications will be categorised as low risk, moderate risk, serious risk, critical risk or no information. During the rating process, any disagreements will be resolved by consulting with a third party (MC and SN).

Approach to evidence synthesis

Prior to the quantitative synthesis, a qualitative synthesis will be performed. Evidence synthesis will be conducted and reported according to the PRISMA extension statement for reporting of systematic reviews incorporating NMA of healthcare interventions.³¹

Because this NMA will use data from both RCTs and non-randomised studies, there are concerns of heterogeneity and inconsistency. To mitigate these factors, tabulation methods will be applied to examine the characteristics of all included studies and evaluate the heterogeneity (both clinical and methodological) of studies within each pairwise comparison. Moreover, transitivity assumption in terms of sufficiently similar between-treatment comparisons will be explored and look for the distribution of participant and study characteristics across all included studies.²⁵ Studies that do not meet our criteria will be excluded.

The quantitative data synthesis will be performed using a two-step approach for the traditional pairwise meta-analysis and NMA. First, a traditional pairwise meta-analysis will be undertaken for each pairwise treatment comparison regardless of heterogeneity using a random-effects model in order to create an initial pooled treatment effect estimates.^{32 33} Standardised weighted mean differences (SMDs) will be used to pool continuous endpoints. In contrast, the ORs will be used to pool the categorical endpoints. The 95% prediction intervals will be estimated to account for a predicted range of the true treatment effect. Statistical heterogeneity will be evaluated using the Cochran Q test, with a p value cut-off point of less than 0.10.

The degree of inconsistency will be evaluated using I^2 statistics and tau² statistics. Publication bias or the presence of potential small study effects will be visualised with funnel plots and statistically tested using Begg's and Egger's tests with a p value cut-off point of less than 0.10. Furthermore, potential small study effects will be analysed

using comparison-adjusted funnel plot symmetry. Publication bias evaluation will be conducted for pairwise comparisons that included 10 or more trials.³⁴

Second, NMA will be conducted to estimate the comparative efficacy for each outcome of interest among available pharmacological interventions using a frequentist approach with restricted maximum likelihood estimation. The following steps will be taken in conducting this NMA. A network plot will be created to evaluate the patterns of the connected nodes. Then, NMA multivariate modelling will be created using a consistency model. The test for inconsistency will be performed using the global test or Cochran's *Q* statistics, loop inconsistency and node-splitting approach. The results of both the consistency and inconsistency models will then be compared against one another. Because there is no clear consensus on the best method to address this inconsistency, additional sensitivity analyses will be performed. These methods include removing a network portion with inconsistency, splitting nodes in the network, and using study-level or individual-level covariates to explain the aetiology inconsistency.³⁵

Subsequently, the comparative treatment efficacy will be displayed using forest plots and league tables. The surface under the cumulative ranking curve (SUCRA) will be calculated and used to rank the pharmacological interventions within the connected network. Rankograms will then be used to visualise the predicted probability for comparative superiority between treatments. If more than half of the acceptability endpoints are available for the treatment pair analysis, a hierarchical cluster rank analysis will be performed to classify treatment options according to the SUCRA values of the efficacy and acceptability outcomes. Finally, comparison-adjusted funnel plots will be created to assess the publication bias.³⁶

Continuous endpoints of the pooled estimates will be expressed as SMDs or weighted mean differences and categorical endpoints will be expressed as ORs. The 95% prediction intervals for all pooled estimates will be calculated and presented concordantly.³⁷ For prespecified subgroup analyses, we will examine changes in the comparative treatment effects across different levels of the following effect modifiers:

1. Characteristics of the participants will include age (paediatric/adolescent, adults between 18 and 65 years old, or elderly aged 65 years or older), sex, race/ethnicity (white vs non-white), existing comorbidities, Hurley stage (stage I/II vs stage III) and the baseline severity of diseases (mild vs moderate to severe).
2. Characteristics of the studies will include sample size (less than 50 vs 50 or greater participants), duration of treatment follow-up (intermediate-term effects, which are less than 12 weeks, and long-term effects, which are 12 weeks or longer), study quality based on the risk of bias assessment (low, some concerns or high), study design (parallel vs crossover) and geographical regions.

In addition, several prespecified sensitivity analyses will be conducted to examine the robustness of the primary analysis under the following conditions: (1) removing a

single study one at a time (a leave-one-out sensitivity analysis); (2) removing studies with a high risk of bias; (3) removing studies with a small study size (less than the 25th percentile); (4) removing studies published before 2010; (5) performing separate analyses for head-to-head trials and placebo-controlled trials; and (6) adding data from unpublished literature (ie, conference abstracts, theses and ongoing proceedings).

All analyses will be performed using Stata V.17 software (StataCorp, College Station, Texas, USA). Analysis results with a two-tailed *p* value of less than 0.05 will be considered statistically significant.

Judging the strength of evidence and classification of pharmacological interventions

Independent grading of certainty and rating of evidence for each outcome will be performed by two reviewers (PP and SN) using the modified confidence in NMA approach³⁸ and the Grading of Recommended Assessment, Development and Evaluation approach (online supplemental table 3).³⁹ Upgrading or downgrading the quality of evidence will depend on the risk of bias, imprecision, inconsistency and indirectness of the findings. Each piece of evidence will be categorised into very low, low, moderate and high-quality evidence. A team discussion will resolve the disagreement regarding the certainty of the evidence grading.

Based on clinical and methodological points of view, we will employ a contextualised approach to establish the treatment network effect estimates with respect to the dimension of benefit (treatment responses) and harms (unacceptability of treatment or all-cause discontinuation).^{40 41} An evidence-based conclusion will be made using all the finalised data of treatment effect estimates by considering the magnitude of effect size, prediction intervals, SUCRA values and certainty of evidence. The estimated magnitude of the treatment effect will be interpreted as follows: very small effect (SMDs, less than 0.2; ORs, less than 1.68), small effect (SMDs, 0.2–0.4; ORs, 1.68–3.46), medium effect (SMDs, 0.5–0.7; ORs, 3.47–6.71) or large effect (SMDs, 0.8 or greater; ORs, 6.72 or greater).^{42 43} Taken together, pharmacological interventions will be classified as trivial (not different from placebo/standard treatment/usual care), small, moderate or large effects to inform clinical interpretation and rank the clinical evidence of the findings.^{40 41}

ETHICS AND DISSEMINATION

Due to the nature of this systematic review being an analysis of data that were published literature for synthesis and did not have direct involvement of human subjects, the Ethical Committee of the Faculty of Medicine, Chiang Mai University has granted an ethical exemption for this study (EXEMPTION 8805/2022, FAM-2565-08805). Findings from this systematic review and NMA will be reported in compliance with the PRISMA 2020 statement guideline,⁴⁴ and the PRISMA extension statement for reporting

of systematic reviews incorporating NMA of healthcare interventions.³¹ Our finalised findings will be published in peer-reviewed journals. Any further amendments to the review protocol will be included in the final report.

DISCUSSION AND CONCLUSION

With an increased understanding of the underlying pathogenesis of HS, new immunological targets that are responsive to drugs continue to be revealed.⁴⁵ Recent advances in genetic and pharmacological research have identified many new potential HS-associated genes, suggesting that more classes of drugs can be used in HS treatments.⁴⁶ Landmark trials, such as the PIONEER I and II—phase 3 trials, have solidified recommendations of pharmacological therapy, that is, the use of adalimumab as a mainstay treatment for refractory HS cases.^{12 17 47} Therefore, exploring pharmacological treatment in severe HS cases as a solution alternative to surgery seems worthy of consideration. However, there seems to be a paucity of NMAs that include broader types of studies with pharmacological options as their focus in their comparison. In addition, many existing traditional meta-analyses and NMAs have focused their objective on evaluating the efficacy of specific types of drugs or comparing them with surgical intervention.

In light of these circumstances, our NMA will gather available pharmacological studies of various designs. We aim to deliver a more comprehensive review that would show an overall comparative efficacy among the currently available pharmacological options. Finally, we hope that the findings from this study will reveal more positive correlations between remission and pharmacological treatment, which might encourage more studies to explore further the combinations of pharmacological therapy and ultimately benefit the overall well-being of patients with HS.

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Contributors NA, PP, MC and SN contributed to the study concept and design, and conducting the process evaluation. MC and SN designed the search strategy. LL and NJ support study management and coordination. JS, MC and SN provided a critical revision of the manuscript for important intellectual. NA and PP drafted the manuscript. MC and SN are the study chief investigators. All authors reviewed the final approval of the version to be published.

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Competing interests None declared.

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