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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 "Velpeau'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	▶ 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	▶ In vitro, in vivo or animal studies ▶ Studies not pertaining to HS ▶ Studies including less than 10 participants (to mitigate type II error)
Interventions	▶ Pharmacological treatment with any type of administered treatments for HS	▶ Studies regrading non-pharmacological, physical or surgical therapies ▶ Studies regarding imaging modalities (ie, ultrasound) ▶ Studies regarding disconnected node of treatments
Comparators	▶ Placebo, active comparator or standard of care	▶ Studies without control groups (single-arm studies)
Outcomes	▶ 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)	▶ 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	▶ An extensive search strategy from the inception of bibliographical databases forward to assure all published literature will be identified	▶ No restrictions were imposed on timing of start date or language
Setting	▶ Experimental study: RCTs (parallel or crossover trials) ▶ Non-randomised studies (open-label, multiple-armed clinical trial, comparative effectiveness observational studies)	▶ 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), intralesional 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 tau^2 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 approach[38] 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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Supplementary Online

Pharmacologic interventions for Hidradenitis Suppurativa: A Protocol for Systematic Review and Network Meta-Analysis of Randomised Trials and Non-Randomised Studies

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Supplementary Online Content

Table S1 Systematic review search strategy: Ovid MEDLINE(R) ALL 1946 to January 24, 2022

Search	Query	Items Found
#1	exp hidradenitis suppurativa/	2515
#2	hidradenitis suppurativ*.mp.	3566
#3	(hidradeniti* adj2 (suppurativ* or axillaris)).ti,ab,kw.	3354
#4	pyoderma adj2 (fistulans or significa)	481
#5	(hidradenitis suppurativ* or hidradeniti* or acne inversa or apocrine acne or apocrinitis or fox den disease or velpeau* disease or verneuil* disease).ti,ab,kw.	3804
#6	or/1-5	4411
#7	exp therapy, drug/	1448680
#8	exp biologic/	625004
#9	exp immunosuppressant/	331770
#10	(biologic* or biotherap* or anti-inflammator* or tumor necrosis factor alpha inhibitor* or TNF-alpha inhibitor* or interleukin receptor antagonist* or anti-TNF* or anti-interleukin or complement C5a receptor antagonist* or Janus kinases inhibitor* or JAK inhibitor* or immunosuppress* or immunomodula*).ti,ab,kw.	1363553
#11	(biologic* or anti-inflam* or TNF-alpha or TNF or interleukin or IL or C5a or Janus kinase* or JAK or immunosupp*) adj3 (inhibitor* or antagonist* or agent*).ti,ab,kw.	76782
#12	(adalimumab or infliximab or etanercept or anakinra or bermekimab or secukinumab or ixekizumab or brodalumab or bimekizumab or guselkumab or risankizumab or certolizumab or ustekinumab or spinosumab or lutikizumab or efalizumab or apremilast or IFX-1 or avacopan or upadacitinib or MABp1 or MEDI8968 or CJM112 or ABBV-066 or CFZ533 or LYS006 or LY3041658 or MAS825 or ABT-981 or INCB054707).ti,ab,kw,rn.	32695
#13	(retinoid* or hormonal agent* or antiandrogen* or gonadotropin-releasing hormone agonist* or GnRH analog* or GnRH receptor blocker* or antimicrobial agent* or antibiotic* or antibiotherap* or granulocyte-colony stimulating factor or G-CSF or platelet-derived growth factor or PDGF or antidiabetic*).ti,ab,kw.	503556
#14	(acitretin or alitretinoin or etretinate or isotretinoin or spironolactone or oral contraceptive pill or cyproterone acetate or ethinyloestradiol or finasteride or dutasteride or leuprolide acetate or flutamide or degarelix or ampicillin or ciprofloxacin or clindamycin or tetracycline or rifampicin or moxifloxacin or metronidazole or ceftriaxone or ertapenem or dapsone or cyclosporine or prednisone or methotrexate or hydroxychloroquine or chloroquine or corticosteroid* or metformin or glucagon-like peptide-1 receptor agonist* or GLP-1 analog* or resorcinol or chlorhexidine or peroxides or permanganate soak* or triamcinolone or zinc or benzoyl peroxide or botulinum toxin or intravenous immune globulin or IVIG).ti,ab,kw,rn.	702016
#15	or/7-14	4222825
#16	6 and 15	1565
#17	(news or newspaper article or comment or editorial or interview or letter or review or systematic review or case report or case series).pt.	5241969
#18	16 not 17	971
#19	limit 18 to human	746

Table S1 Systematic review search strategy: Embase via Elsevier 1966 to January 24, 2022

Search	Query	Items Found
#1	hidradenitis suppurativa/exp AND [embase]/lim	4785
#2	acne inversa/exp AND [embase]/lim	642
#3	velpeau disease/exp AND [embase]/lim	104
#4	verneuil disease/exp AND [embase]/lim	910
#5	(hidradeniti*:ti,ab,kw AND (suppurativ*:ti,ab,kw OR axillaris:ti,ab,kw)) AND [embase]/lim	4810
#6	(pyoderma:ti,ab,kw AND (fistulans:ti,ab,kw OR significa:ti,ab,kw)) AND [embase]/lim	12
#7	(‘hidradenitis suppurativ*’:ti,ab,kw OR hidradeniti*:ti,ab,kw OR ‘acne inversa’:ti,ab,kw OR ‘apocrine acne’:ti,ab,kw OR apocrinitis:ti,ab,kw OR ‘fox den disease’:ti,ab,kw OR ‘velpeau* disease’:ti,ab,kw OR ‘verneuil* disease’:ti,ab,kw) AND [embase]/lim	5294
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	6296
#9	therapy, drug/exp AND [embase]/lim	760698
#10	biologic/exp AND [embase]/lim	676511
#11	immunosuppressant/exp AND [embase]/lim	1120401
#12	(biologic*:ti,ab,kw OR biotherap*:ti,ab,kw OR ‘anti-inflammator*’:ti,ab,kw OR ‘tumor necrosis factor alpha inhibitor*’:ti,ab,kw OR ‘TNF-alpha inhibitor*’:ti,ab,kw OR ‘interleukin receptor antagonist*’:ti,ab,kw OR ‘anti-TNF*’:ti,ab,kw OR ‘anti-interleukin’:ti,ab,kw OR ‘complement C5a receptor antagonist*’:ti,ab,kw OR ‘Janus kinases inhibitor*’:ti,ab,kw OR ‘JAK inhibitor*’:ti,ab,kw OR immunosuppress*:ti,ab,kw OR immunomodula*:ti,ab,kw) AND [embase]/lim	1490904
#13	((biologic*:ti,ab,kw OR anti-inflam*:ti,ab,kw OR TNF-alpha:ti,ab,kw OR TNF:ti,ab,kw OR interleukin:ti,ab,kw OR IL:ti,ab,kw OR C5a:ti,ab,kw OR Janus kinase*:ti,ab,kw OR JAK:ti,ab,kw OR immunosupp*:ti,ab,kw) AND (inhibitor*:ti,ab,kw OR antagonist*:ti,ab,kw OR agent*:ti,ab,kw)) AND [embase]/lim	121407
#14	(adalimumab:ti,ab,kw,rn OR infliximab:ti,ab,kw,rn OR etanercept:ti,ab,kw,rn OR anakinra:ti,ab,kw,rn OR bermekimab:ti,ab,kw,rn OR secukinumab:ti,ab,kw,rn OR ixekizumab:ti,ab,kw,rn OR brodalumab:ti,ab,kw,rn OR bimekizumab:ti,ab,kw,rn OR guselkumab:ti,ab,kw,rn OR risankizumab:ti,ab,kw,rn OR certolizumab:ti,ab,kw,rn OR ustekinumab:ti,ab,kw,rn OR spinosumab:ti,ab,kw,rn OR lutikizumab:ti,ab,kw,rn OR efalizumab:ti,ab,kw,rn OR apremilast:ti,ab,kw,rn OR ‘IFX-1’:ti,ab,kw,rn OR avacopan:ti,ab,kw,rn OR upadacitinib:ti,ab,kw,rn OR MABp1:ti,ab,kw,rn OR MEDI8968:ti,ab,kw,rn OR CJM112:ti,ab,kw,rn OR ‘ABBV-066’:ti,ab,kw,rn OR CFZ533:ti,ab,kw,rn OR LYS006:ti,ab,kw,rn OR LY3041658:ti,ab,kw,rn OR MAS825:ti,ab,kw,rn OR ‘ABT-981’:ti,ab,kw,rn OR INCB054707:ti,ab,kw,rn) AND [embase]/lim	57748
#15	(retinoid*:ti,ab,kw OR ‘hormonal agent*’:ti,ab,kw OR antiandrogen*:ti,ab,kw OR ‘gonadotropin-releasing hormone agonist*’:ti,ab,kw OR ‘GnRH analog*’:ti,ab,kw OR ‘GnRH receptor blocker*’:ti,ab,kw OR ‘antimicrobial agent*’:ti,ab,kw OR antibiotic*:ti,ab,kw OR antibiotherap*:ti,ab,kw OR ‘granulocyte-colony stimulating factor’:ti,ab,kw OR ‘G-CSF’:ti,ab,kw OR ‘platelet-derived growth factor’:ti,ab,kw OR PDGF:ti,ab,kw OR antidiabetic*:ti,ab,kw) AND [embase]/lim	586593

#16	(acitretin:ti,ab,kw,rn OR alitretinoin:ti,ab,kw,rn OR etretinate:ti,ab,kw,rn OR isotretinoin:ti,ab,kw,rn OR spironolactone:ti,ab,kw,rn OR 'oral contraceptive pill':ti,ab,kw,rn OR 'cyproterone acetate':ti,ab,kw,rn OR ethinyloestradiol:ti,ab,kw,rn OR finasteride:ti,ab,kw,rn OR dutasteride:ti,ab,kw,rn OR 'leuprolide acetate':ti,ab,kw,rn OR flutamide:ti,ab,kw,rn OR degarelix:ti,ab,kw,rn OR ampicillin:ti,ab,kw,rn OR ciprofloxacin:ti,ab,kw,rn OR clindamycin:ti,ab,kw,rn OR tetracycline:ti,ab,kw,rn OR rifampicin:ti,ab,kw,rn OR moxifloxacin:ti,ab,kw,rn OR metronidazole:ti,ab,kw,rn OR ceftriaxone:ti,ab,kw,rn OR ertapenem:ti,ab,kw,rn OR dapsone:ti,ab,kw,rn OR cyclosporine:ti,ab,kw,rn OR prednisone:ti,ab,kw,rn OR methotrexate:ti,ab,kw,rn OR hydroxychloroquine:ti,ab,kw,rn OR chloroquine:ti,ab,kw,rn OR corticosteroid*:ti,ab,kw,rn OR metformin:ti,ab,kw,rn OR 'glucagon-like peptide-1 receptor agonist*':ti,ab,kw,rn OR 'GLP-1':ti,ab,kw OR resorcinol:ti,ab,kw,rn OR chlorhexidine:ti,ab,kw,rn OR peroxides:ti,ab,kw OR permanganate:ti,ab,kw OR triamcinolone:ti,ab,kw,rn OR zinc:ti,ab,kw,rn OR 'benzoyl peroxide':ti,ab,kw OR 'botulinum toxin':ti,ab,kw OR 'intravenous immune globulin':ti,ab,kw OR IVIG:ti,ab,kw) AND [embase]/lim	735288
#17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	4290466
#18	#8 AND #17	2547
#19	(news:it OR 'newspaper article':it OR comment:it OR editorial:it OR interview:it OR letter:it OR review:it OR 'systematic review':it OR 'case report':it OR 'case series':it) AND [embase]/lim	3601286
#20	#18 NOT #19	1950

Table S1 Systematic review search strategy: PubMed, From Inception to January 24, 2022

Search	Query	Items Found
#1	((hidradenitis suppurativa[MeSH Terms]) OR (acne inversa[MeSH Terms])) OR (hidradenitides[MeSH Terms])	2758
#2	(hidradeniti*[Title/Abstract]) AND (suppurativ*[Title/Abstract] OR axillaris[Title/Abstract])	3394
#3	(pyoderma[Title/Abstract]) AND (fistulan*[Title/Abstract] OR significa*[Title/Abstract])	493
#4	"hidradenitis suppurativ*"[Title/Abstract] OR hidradeniti*[Title/Abstract] OR "acne inversa"[Title/Abstract] OR "apocrine acne"[Title/Abstract] OR apocrinitis[Title/Abstract]	3776
#5	("fox den"[Title/Abstract] OR velpeau*[Title/Abstract] OR verneuil*[Title/Abstract]) AND (disease*[Title/Abstract])	87
#6	#1 OR #2 OR #3 OR #4 OR #5	4472
#7	((therapy, drug[MeSH Terms]) OR (biologics[MeSH Terms])) OR (agents, immunosuppressive[MeSH Terms])	2099177
#8	biologic*[Title/Abstract] OR biotherap*[Title/Abstract] OR "anti-inflammator*"[Title/Abstract] OR "tumor necrosis factor alpha inhibitor*"[Title/Abstract] OR "TNF-alpha inhibitor*"[Title/Abstract] OR "interleukin receptor antagonist*"[Title/Abstract] OR "anti-TNF*"[Title/Abstract] OR "anti-interleukin"[Title/Abstract] OR "complement C5a receptor antagonist*"[Title/Abstract] OR "Janus kinases inhibitor*"[Title/Abstract] OR "JAK inhibitor*"[Title/Abstract] OR immunosuppress*[Title/Abstract] OR immunomodula*[Title/Abstract]	1367810
#9	(biologic*[Title/Abstract] OR "anti-inflam*"[Title/Abstract] OR "TNF-alpha"[Title/Abstract] OR TNF[Title/Abstract] OR interleukin[Title/Abstract] OR IL[Title/Abstract] OR C5a[Title/Abstract] OR "Janus kinase*"[Title/Abstract] OR JAK[Title/Abstract] OR immunosupp*[Title/Abstract]) AND (inhibitor*[Title/Abstract] OR antagonist*[Title/Abstract] OR agent*[Title/Abstract])	352488
#10	adalimumab[Title/Abstract] OR infliximab[Title/Abstract] OR etanercept[Title/Abstract] OR anakinra[Title/Abstract] OR bermekimab[Title/Abstract] OR secukinumab[Title/Abstract] OR ixekizumab[Title/Abstract] OR brodalumab[Title/Abstract] OR bimekizumab[Title/Abstract] OR guselkumab[Title/Abstract] OR risankizumab[Title/Abstract] OR certolizumab[Title/Abstract] OR ustekinumab[Title/Abstract] OR spinosumab[Title/Abstract] OR lutikizumab[Title/Abstract] OR efalizumab[Title/Abstract] OR apremilast[Title/Abstract] OR "IFX-1"[Title/Abstract] OR avacopan[Title/Abstract] OR upadacitinib[Title/Abstract] OR MABp1[Title/Abstract] OR MEDI8968[Title/Abstract] OR CJM112[Title/Abstract] OR "ABBV-066"[Title/Abstract] OR CFZ533[Title/Abstract] OR LYS006[Title/Abstract] OR LY3041658[Title/Abstract] OR MAS825[Title/Abstract] OR "ABT-981"[Title/Abstract] OR INCB054707[Title/Abstract]	28420
#11	retinoid*[Title/Abstract] OR "hormonal agent*"[Title/Abstract] OR antiandrogen*[Title/Abstract] OR "gonadotropin-releasing hormone agonist*"[Title/Abstract] OR "GnRH analog*"[Title/Abstract] OR "GnRH receptor blocker*"[Title/Abstract] OR "antimicrobial agent*"[Title/Abstract] OR antibiotic*[Title/Abstract] OR antibiotherap*[Title/Abstract] OR "granulocyte-colony stimulating factor"[Title/Abstract] OR "G-	514776

	CSF"[Title/Abstract] OR "platelet-derived growth factor"[Title/Abstract] OR PDGF[Title/Abstract] OR antidiabetic*[Title/Abstract]	
#12	acitretin[Title/Abstract] OR alitretinoin[Title/Abstract] OR etretinate[Title/Abstract] OR isotretinoin[Title/Abstract] OR spironolactone[Title/Abstract] OR "oral contraceptive pill"[Title/Abstract] OR "cyproterone acetate"[Title/Abstract] OR ethinyloestradiol[Title/Abstract] OR finasteride[Title/Abstract] OR dutasteride[Title/Abstract] OR "leuprolide acetate"[Title/Abstract] OR flutamide[Title/Abstract] OR degarelix[Title/Abstract] OR ampicillin[Title/Abstract] OR ciprofloxacin[Title/Abstract] OR clindamycin[Title/Abstract] OR tetracycline[Title/Abstract] OR rifampicin[Title/Abstract] OR moxifloxacin[Title/Abstract] OR metronidazole[Title/Abstract] OR ceftriaxone[Title/Abstract] OR ertapenem[Title/Abstract] OR dapsone[Title/Abstract] OR cyclosporine[Title/Abstract] OR prednisone[Title/Abstract] OR methotrexate[Title/Abstract] OR hydroxychloroquine[Title/Abstract] OR chloroquine[Title/Abstract] OR corticosteroid*[Title/Abstract] OR metformin[Title/Abstract] OR "glucagon-like peptide-1 receptor agonist*"[Title/Abstract] OR "GLP-1"[Title/Abstract] OR resorcinol[Title/Abstract] OR chlorhexidine[Title/Abstract] OR peroxides[Title/Abstract] OR permanganate[Title/Abstract] OR triamcinolone[Title/Abstract] OR zinc[Title/Abstract] OR "benzoyl peroxide"[Title/Abstract] OR "botulinum toxin"[Title/Abstract] OR "intravenous immune globulin"[Title/Abstract] OR IVIG[Title/Abstract]	585845
#13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	4146308
#14	#6 AND #13	1527
#15	(((((((Case Reports[Publication Type]) OR Comment[Publication Type]) OR Editorial[Publication Type]) OR Guideline[Publication Type]) OR Letter[Publication Type]) OR News[Publication Type]) OR Newspaper Article[Publication Type]) OR Review[Publication Type]	7041469
#16	#14 NOT #15	640
#17	Filters applied: Humans.	460

Table S1 Systematic review search strategy: Cochrane Library (CENTRAL), From Inception to January 24, 2022

Search	Query	Items Found
#1	MeSH descriptor: [Hidradenitis Suppurativa] explode all trees	100
#2	(hidradeniti*):ti,ab,kw AND (suppurativ* OR axillaris):ti,ab,kw	274
#3	(pyoderma):ti,ab,kw AND (fistulan* OR significa*):ti,ab,kw	45
#4	(“fox den” OR velpeau* OR verneuil*):ti,ab,kw AND (disease*):ti,ab,kw	2
#5	(“hidradenitis suppurativ*” OR hidradeniti* OR “acne inversa” OR “apocrine acne” OR apocrinitis):ti,ab,kw	278
#6	#1 OR #2 OR #3 OR #4 OR #5	323
#7	MeSH descriptor: [Drug Therapy] explode all trees	146135
#8	MeSH descriptor: [Biology] in all MeSH products	1680
#9	MeSH descriptor: [Immunosuppressive Agents] explode all trees	5375
#10	(biologic* OR biotherap* OR “anti-inflammator*” OR “tumor necrosis factor alpha inhibitor*” OR “TNF-alpha inhibitor*” OR “interleukin receptor antagonist*” OR “anti-TNF*” OR “anti-interleukin” OR “complement C5a receptor antagonist*” OR “Janus kinases inhibitor*” OR “JAK inhibitor*” OR immunosuppress* OR immunomodula*):ti,ab,kw	57694
#11	(biologic* OR “anti-inflam*” OR “TNF-alpha” OR TNF OR interleukin OR IL OR C5a OR “Janus kinase*” OR JAK OR immunosupp*):ti,ab,kw AND (inhibitor* OR antagonist* OR agent*):ti,ab,kw	30638
#12	(adalimumab OR infliximab OR etanercept OR anakinra OR bermekimab OR secukinumab OR ixekizumab OR brodalumab OR bimekizumab OR guselkumab OR risankizumab OR certolizumab OR ustekinumab OR spinosumab OR lutikizumab OR efalizumab OR apremilast OR “IFX-1” OR avacopan OR upadacitinib OR MABp1 OR MEDI8968 OR CJM112 OR “ABBV-066” OR CFZ533 OR LYS006 OR LY3041658 OR MAS825 OR “ABT-981” OR INCB054707):ti,ab,kw	11192
#13	(retinoid* OR “hormonal agent*” OR antiandrogen* OR “gonadotropin-releasing hormone agonist*” OR “GnRH analog*” OR “GnRH receptor blocker*” OR “antimicrobial agent*” OR antibiotic* OR antibiotherap* OR “granulocyte-colony stimulating factor” OR “G-CSF” OR “platelet-derived growth factor” OR PDGF OR antidiabetic*):ti,ab,kw	41323
#14	(acitretin OR alitretinoin OR etretinate OR isotretinoin OR spironolactone OR “oral contraceptive pill” OR “cyproterone acetate” OR ethinyloestradiol OR finasteride OR dutasteride OR “leuprolide acetate” OR flutamide OR degarelix OR ampicillin OR ciprofloxacin OR clindamycin OR tetracycline OR rifampicin OR moxifloxacin OR metronidazole OR ceftriaxone OR ertapenem OR dapsone OR cyclosporine OR prednisone OR methotrexate OR hydroxychloroquine OR chloroquine OR corticosteroid* OR metformin OR “glucagon-like peptide-1 receptor agonist*” OR “GLP-1” OR resorcinol OR chlorhexidine OR peroxides OR permanganate OR triamcinolone OR zinc OR “benzoyl peroxide” OR “botulinum toxin” OR “intravenous immune globulin” OR IVIG):ti,ab,kw	104738
#15	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	307251
#16	#6 AND #15	241
#17	#6 AND #15 in Trials	228

Table S1 Systematic review search strategy: Web of Science, From Inception to January 24, 2022

Search	Query	Items Found
#1	TS=(hidradeniti* AND (suppurativ* OR axillaris))	4269
#2	TS=(pyoderma AND (fistulan* OR significa*))	479
#3	TS=((“fox den” OR velpeau* OR verneuil*) AND disease*)	45
#4	TS=(“hidradenitis suppurativ*” OR hidradeniti* OR “acne inversa” OR “apocrine acne” OR apocrinitis)	4596
#5	#1 OR #2 OR #3 OR #4	5047
#6	TS=(biologic* OR biotherap* OR “anti-inflammator*” OR “tumor necrosis factor alpha inhibitor*” OR “TNF-alpha inhibitor*” OR “interleukin receptor antagonist*” OR “anti-TNF*” OR “anti-interleukin” OR “complement C5a receptor antagonist*” OR “Janus kinases inhibitor*” OR “JAK inhibitor*” OR immunosuppress* OR immunomodula*)	1434545
#7	TS=((biologic* OR “anti-inflam*” OR “TNF-alpha” OR TNF OR interleukin OR IL OR C5a OR “Janus kinase*” OR JAK OR immunosupp*) AND (inhibitor* OR antagonist* OR agent*))	387434
#8	TS=(adalimumab OR infliximab OR etanercept OR anakinra OR bermekimab OR secukinumab OR ixekizumab OR brodalumab OR bimekizumab OR guselkumab OR risankizumab OR certolizumab OR ustekinumab OR spinosumab OR lutikizumab OR efalizumab OR apremilast OR “IFX-1” OR avacopan OR upadacitinib OR MABp1 OR MEDI8968 OR CJM112 OR “ABBV-066” OR CFZ533 OR LYS006 OR LY3041658 OR MAS825 OR “ABT-981” OR INCB054707)	50927
#9	TS=(retinoid* OR “hormonal agent*” OR antiandrogen* OR “gonadotropin-releasing hormone agonist*” OR “GnRH analog*” OR “GnRH receptor blocker*” OR “antimicrobial agent*” OR antibiotic* OR antibiotherap* OR “granulocyte-colony stimulating factor” OR “G-CSF” OR “platelet-derived growth factor” OR PDGF OR antidiabetic*)	406790
#10	TS=(acitretin OR alitretinoin OR etretinate OR isotretinoin OR spironolactone OR “oral contraceptive pill” OR “cyproterone acetate” OR ethinyloestradiol OR finasteride OR dutasteride OR “leuprolide acetate” OR flutamide OR degarelix OR ampicillin OR ciprofloxacin OR clindamycin OR tetracycline OR rifampicin OR moxifloxacin OR metronidazole OR ceftriaxone OR ertapenem OR dapsone OR cyclosporine OR prednisone OR methotrexate OR hydroxychloroquine OR chloroquine OR corticosteroid* OR metformin OR “glucagon-like peptide-1 receptor agonist*” OR “GLP-1” OR resorcinol OR chlorhexidine OR peroxides OR permanganate OR triamcinolone OR zinc OR “benzoyl peroxide” OR “botulinum toxin” OR “intravenous immune globulin” OR IVIG)	834322
#11	#6 OR #7 OR #8 OR #9 OR #10	2593460
#12	#5 AND #11	1683
#13	TS=(animal OR in vivo OR in vitro)	2660795
#14	#12 NOT #13	1592
#15	#12 NOT #13 and Review Articles or Letters or Editorial Materials or Corrections or News Items (Exclude – Document Types)	1058

Table S1 Systematic review search strategy: Scopus, From Inception to January 24, 2022

Search	Query	Items Found
#1	TITLE-ABS-KEY (hidradeniti* AND (suppurativ* OR axillaris))	4675
#2	TITLE-ABS-KEY (pyoderma AND (fistulan* OR significa*))	966
#3	TITLE-ABS-KEY ((“fox den” OR velpeau* OR verneuil*) AND disease*)	177
#4	TITLE-ABS-KEY (“hidradenitis suppurativ*” OR hidradeniti* OR “acne inversa” OR “apocrine acne” OR apocrinitis)	5355
#5	#1 OR #2 OR #3 OR #4	6329
#6	TITLE-ABS-KEY (biologic* OR biotherap* OR “anti-inflammator*” OR “tumor necrosis factor alpha inhibitor*” OR “TNF-alpha inhibitor*” OR “interleukin receptor antagonist*” OR “anti-TNF*” OR “anti-interleukin” OR “complement C5a receptor antagonist*” OR “Janus kinases inhibitor*” OR “JAK inhibitor*” OR immunosuppress* OR immunomodula*)	3642484
#7	TITLE-ABS-KEY ((biologic* OR “anti-inflam*” OR “TNF-alpha” OR TNF OR interleukin OR IL OR C5a OR “Janus kinase*” OR JAK OR immunosupp*) AND (inhibitor* OR antagonist* OR agent*))	1194425
#8	TITLE-ABS-KEY (adalimumab OR infliximab OR etanercept OR anakinra OR bermekimab OR secukinumab OR ixekizumab OR brodalumab OR bimekizumab OR guselkumab OR risankizumab OR certolizumab OR ustekinumab OR spinosumab OR lutikizumab OR efalizumab OR apremilast OR “IFX-1” OR avacopan OR upadacitinib OR MABp1 OR MEDI8968 OR CJM112 OR “ABBV-066” OR CFZ533 OR LYS006 OR LY3041658 OR MAS825 OR “ABT-981” OR INCB054707)	70319
#9	TITLE-ABS-KEY (retinoid* OR “hormonal agent*” OR antiandrogen* OR “gonadotropin-releasing hormone agonist*” OR “GnRH analog*” OR “GnRH receptor blocker*” OR “antimicrobial agent*” OR antibiotic* OR antibiotherap* OR “granulocyte-colony stimulating factor” OR “G-CSF” OR “platelet-derived growth factor” OR PDGF OR antidiabetic*)	1192370
#10	TITLE-ABS-KEY (acitretin OR alitretinoin OR etretinate OR isotretinoin OR spironolactone OR “oral contraceptive pill” OR “cyproterone acetate” OR ethinyloestradiol OR finasteride OR dutasteride OR “leuprolide acetate” OR flutamide OR degarelix OR ampicillin OR ciprofloxacin OR clindamycin OR tetracycline OR rifampicin OR moxifloxacin OR metronidazole OR ceftriaxone OR ertapenem OR dapsone OR cyclosporine OR prednisone OR methotrexate OR hydroxychloroquine OR chloroquine OR corticosteroid* OR metformin OR “glucagon-like peptide-1 receptor agonist*” OR “GLP-1” OR resorcinol OR chlorhexidine OR peroxides OR permanganate OR triamcinolone OR zinc OR “benzoyl peroxide” OR “botulinum toxin” OR “intravenous immune globulin” OR IVIG)	2210835
#11	#6 OR #7 OR #8 OR #9 OR #10	6455033
#12	#5 AND #11	3195
#13	TITLE-ABS-KEY (animal OR in vivo OR in vitro)	2392272
#14	#12 AND NOT #13	3140
#15	#14 AND NOT (TITLE-ABS-KEY (animal OR in AND vivo OR in AND vitro)) AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "er") OR EXCLUDE (DOCTYPE , "bk"))	1865

Table S1 Systematic review search strategy: CINAHL, From Inception to January 24, 2022

Search	Query	Items Found
#1	MJ (hidradenitis suppurativa OR acne inversa OR hidradenitis)	618
#2	AB (hidradeniti* AND (suppurativ* OR axillaris))	431
#3	AB (pyoderma AND (fistulan* OR significa*))	71
#4	AB (("fox den" OR velpeau* OR verneuil*) AND disease*)	2
#5	AB ("hidradenitis suppurativ*" OR hidradeniti* OR "acne inversa" OR "apocrine acne" OR apocrinitis)	451
#6	S1 OR S2 OR S3 OR S4 OR S5	814
#7	MJ (therapy, drug OR biologics OR immunosuppressant drugs)	415355
#8	AB (biologic* OR biotherap* OR "anti-inflammator*" OR "tumor necrosis factor alpha inhibitor*" OR "TNF-alpha inhibitor*" OR "interleukin receptor antagonist*" OR "anti-TNF*" OR "anti-interleukin" OR "complement C5a receptor antagonist*" OR "Janus kinases inhibitor*" OR "JAK inhibitor*" OR immunosuppress* OR immunomodula*)	115083
#9	AB ((biologic* OR "anti-inflam*" OR "TNF-alpha" OR TNF OR interleukin OR IL OR C5a OR "Janus kinase*" OR JAK OR immunosupp*) AND (inhibitor* OR antagonist* OR agent*))	26939
#10	AB (adalimumab OR infliximab OR etanercept OR anakinra OR bermekimab OR secukinumab OR ixekizumab OR brodalumab OR bimekizumab OR guselkumab OR risankizumab OR certolizumab OR ustekinumab OR spinosumab OR lutikizumab OR efalizumab OR apremilast OR "IFX-1" OR avacopan OR upadacitinib OR MABp1 OR MEDI8968 OR CJM112 OR "ABBV-066" OR CFZ533 OR LYS006 OR LY3041658 OR MAS825 OR "ABT-981" OR INCB054707)	5357
#11	AB (retinoid* OR "hormonal agent*" OR antiandrogen* OR "gonadotropin-releasing hormone agonist*" OR "GnRH analog*" OR "GnRH receptor blocker*" OR "antimicrobial agent*" OR antibiotic* OR antibiotherap* OR "granulocyte-colony stimulating factor" OR "G-CSF" OR "platelet-derived growth factor" OR PDGF OR antidiabetic*)	57652
#12	AB (acitretin OR alitretinoin OR etretinate OR isotretinoin OR spironolactone OR "oral contraceptive pill" OR "cyproterone acetate" OR ethinyloestradiol OR finasteride OR dutasteride OR "leuprolide acetate" OR flutamide OR degarelix OR ampicillin OR ciprofloxacin OR clindamycin OR tetracycline OR rifampicin OR moxifloxacin OR metronidazole OR ceftriaxone OR ertapenem OR dapsone OR cyclosporine OR prednisone OR methotrexate OR hydroxychloroquine OR chloroquine OR corticosteroid* OR metformin OR "glucagon-like peptide-1 receptor agonist*" OR "GLP-1" OR resorcinol OR chlorhexidine OR peroxides OR permanganate OR triamcinolone OR zinc OR "benzoyl peroxide" OR "botulinum toxin" OR "intravenous immune globulin" OR IVIG)	69031
#13	S7 OR S8 OR S9 OR S10 OR S11 OR S12	591838
#14	S6 AND S13	279
#15	MW (animal OR in vivo OR in vitro)	178869
#16	S14 NOT S15	278
#17	Expanders: Apply equivalent subjects Source Types: Academic Journals	255

Table S2 Grey literature search

Ongoing clinical trial register
• Australia and New Zealand's (ANZCTR) (http://www.anzctr.org.au) • Brazilian Clinical Trials Registry (ReBec) (http://www.ensaiosclinicos.gov.br) • Chinese Clinical Trial Registry (ChiCTR) (http://www.chictr.org.cn) • Clinical Research Information Service (CRiS), Republic of Korea (http://cris.cdc.go.kr) • Clinical Trials Registry - India (CTRI) (http://ctri.nic.in) • Cuban Public Registry of Clinical Trials(RPCEC) (http://registroclinico.sld.cu) • EU Clinical Trials Register (EU-CTR) (https://www.clinicaltrialsregister.eu) • German Clinical Trials Register (DRKS) (http://www.drks.de) • Iranian Registry of Clinical Trials (IRCT) (http://www.irct.ir) • Japan Primary Registries Network (https://rctportal.niph.go.jp) • The Netherlands Trial Register (http://www.trialregister.nl) • Pan African Clinical Trial Registry (PACTR) (http://www.pactr.org) • Peruvian Registry of Clinical Trials (http://www.ins.gob.pe/ensayosclinicos) • Philippine Health Research Registry (http://registry.healthresearch.ph) • Sri Lanka Clinical Trials Registry (SLCTR) (http://www.slctr.lk) • South African National Clinical Trials Register (http://www.sanctr.gov.za) • Swiss FOPH Human Research Projects (https://www.kofam.ch/en/swiss-clinical-trials-portal.html) • Tanzania Clinical Trial Registry (http://www.tzctr.or.tz) • Thai Clinical Trials Registry (http://www.clinicaltrials.in.th) • The United Kingdoms' ISRCTN registry (http://www.isrctn.com) • The US National Institutes of Health Ongoing Trials Registry (http://clinicaltrials.gov) • The World Health Organization International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/ictrp)
Preprint databases
• medRxiv (https://www.medrxiv.org) • bioRxiv (https://www.biorxiv.org)
Major dermatology scientific meetings
• American Academy of Dermatology (AAD) • British Association of Dermatologists (BAD) • Society for Investigative Dermatology (SID) • European Society for Dermatological Research (ESDR)

Table S3 Criteria of GRADE assessment by CINeMA[1,2]

Judgement	Criteria	Instruction for downgrading
Within-study bias	• Within-study bias was evaluated by majority of risk of bias assessment results within each comparison • We increased the concern to one level for comparisons with single study only	• Major concerns: downgrade the evidence one level • Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Reporting bias	• Reporting bias was evaluated by non-statistical consideration of likelihood of non-publication of evidence • We increased the concerns to one level for outcomes with evidence of small study effects in the network by comparison adjusted funnel plot	• Major concerns: downgrade the evidence one level • Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Indirectness	• Populations among studies were assessed by distributions of age, gender, and comorbidities • For continuous outcomes, outcomes assessment within each comparison was evaluated by the directness of validated measurement tools	• Major concerns: downgrade the evidence one level • Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Imprecision	• Imprecision was focused on width of CI based on a clinically important mean difference of 0.2 for continuous outcomes and odds ratio of 1.2 for binary outcomes • We increased the concern to one level if the width of CI is between 4 times and 10 times of lower limit • The concern level was increase two levels if the width of CI is above 10 times of lower limit	• Major concerns: downgrade the evidence one level • Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Heterogeneity	• Heterogeneity was evaluated according to the CINeMA documentation by variability of effects in relation to the clinically important size of effect and between-study variance for the network meta-analysis • We increased the concern to one level if there is no information regarding between-study heterogeneity for each direct comparison or I^2 index >50% in the direct comparison or inconsistency between 95% CI and 95% PrI	• Major concerns: downgrade the evidence one level • Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Incoherence	• Incoherence was evaluated by the design-by-treatment intervention model globally and the loop specific approach • We increased the concern to one level if there evidence of incoherence in the agreement between the main analysis and a set of sensitivity analyses	• Major concerns: downgrade the evidence one level • Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Quality of the evidence (GRADE): **High quality:** further research is very unlikely to change our confidence in the estimate of effect **Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low quality:** we are very uncertain about the estimate		

Abbreviations: CI, confidence interval; CINeMA, Confidence In Network Meta-Analysis; GRADE, Grading Recommendations Assessment, Development and Evaluation; PrI, prediction interval.

1. Nikolakopoulou A, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med. 2020;17(4):e1003082.
2. Puhan MA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.

Appendix I PRISMA-P 2015 checklist: recommended items to address in a systematic review protocol*

Section and Topic	Item No	Checklist Item	Reported on Page No.
ADMINISTRATION INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	17
Sponsor	5b	Provide name for the review funder and/or sponsor	17
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	17
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	6, 7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9, Table 1
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8 Table S2

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated.

Abbreviations: PRISMA-P, Preferred Reporting Items for Systematic review and Meta-Analysis Protocols.

Appendix I PRISMA-P 2015 checklist: recommended items to address in a systematic review protocol* (continued)

Section and Topic	Item No	Checklist Item	Reported on Page No.
METHODS			
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Table S1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8, 9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8, 9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Table 1
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12, 13, 14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	12, 13, 14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15, Table S3

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated.

Abbreviations: PRISMA-P, Preferred Reporting Items for Systematic review and Meta-Analysis Protocols.

Appendix II Replication of systematic review checklist

Checklist items	Response Options	Consideration regarding to this systematic review and network meta-analysis
Question 1. Has the priority for replication been assessed as high? For example, is it likely that a replication will remain relevant to policy and practice for a useful length of time? Is it likely for replication results to lead to implementation by practitioners and policy makers?	Yes / No	Yes
Question 2. Is it likely that direct replication by repetition or conceptual replication by broadening or narrowing of the scope will address uncertainties, controversies, or the need for additional evidence related to:		There are still many unexplored scope regarding to purely non-invasive pharmacologic options as the main treatment options especially regarding inclusions of many unaddressed non-randomised trials with potential beneficial outcomes.
2.1. The framing of the question in previous reviews?	Yes / No	Yes
2.2. The conduct and reporting of previous reviews?	Yes / No	Yes
2.3. Author influence or conflicts of interest in previous reviews?	Yes / No	No
2.4. Discordant findings in previous reviews?	Yes / No	Yes
Question 3. Would the implementation of the findings of a replication be likely to have a potentially important sizeable individual benefit or harm or affect a sizeable population?	Yes / No	Yes, replication with a specific scope focused on non-surgical pharmacologic treatment will create more accessibility to a definite treatment and decrease patient's economic burden regrading to treatment cost.
Question 4. Are resources (time, money) best spent on replication rather than on alternative systematic reviews (considering opportunity cost)?		The benefits of exploring the potential of non-invasive pharmacological treatment that shows a non-inferiority treatment outcome comparable to surgical intervention are justifiable.