Efficacy and safety of topical and intralesional therapies on suppurative hidradenitis patients. A systematic review of literature

Materials and methods

1. Study design

This systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Collaboration's tool for assessing risk of bias in randomised trials. The research question was: what does the available scientific evidence say regarding the effectiveness and safety of topic treatments for Hidradenitis suppurativa management? Following the PICO(T) principle, participants (P), intervention (I), comparator (C), outcomes (O) and type of studies (T) were defined.

1.1 Study participants

Patients of any gender, age and ethnicity were included in the study. Both, individuals diagnosed from Hidradenitis Suppurativa via clinical anamnesis or according to the diagnostic criteria established at the 2nd International Conference of *Hidradenitis Suppurativa* at San Francisco, CA, USA on March the 5th of 2009, were accepted. From the late ones, the three criteria had to be present: 1) presence of typical lesions (nodules, fistula, scars and pseudocomedones), 2) lesions have to appear on typical areas (armpits, groins or buttock region).

1.2 Intervention

The present review aimed to evaluate topic and intralesional treatments for *Hidradenitis Suppurativa,* thus, any pharmacological or physical intervention was included. On the one hand, topic treatment was understood as any externally and locally used medicine that is to be applied on the affected skin area with independence of its pharmaceutical form (powder, ointment, lotion, cream or paste). On the other, intralesional treatment were those medicines that were subcutaneously administered in the affected area to maximize its local effect and, hereby, avoiding systemic effects. From all the physical therapies, it is important to highlight

the photodynamic therapy which consists of topical or intralesional administration of a drug that needs to be externally activated by a determined length wave electromagnetic radiation.

Therefore, any study conducted involving diverse interventions, from antibiotics, antiseptics, anti-inflammatory drugs to keratolytic substances or photodynamic therapy were included.

Essentially destructive and reconstructive therapies (laser, surgery) were excluded. Studies evaluating a combination of topic and systemic interventions were also discarded.

1.3 Comparator

Studies comparing any of the interventions previously detailed with placebo, absence of intervention or any other medical intervention (topical or systemic) were included. Studies comparing different topic or intralesional treatments were also included.

1.4 Outcomes

Two primary outcomes, one regarding efficacy and other regarding safety were defined, following Cochrane recommendations. The outcome selection was fundamented on the International *Dermatology Outcome Measures* (IDEOM) consensus document for developing *Hidradenitis Suppurativa* results measurements.

1.4.1 Primary outcomes

1. Self-perceived life quality. Generic validated questionnaires were accepted (SF36 or EQ-5D), dermatology-focused scales, such as Dermatology Life Quality Index (DLQI), Skindex 29, and Hidradenitis suppurativa specific tests (Hidradenitis Suppurativa Quality of Life 24, HSQoL-24) were also included.
2. Any adverse event derived from the different interventions evaluated were measured as relative frequency.

1.4.2 Secondary outcomes

1. Global subjective evaluation of the patient's disease status. This outcome combines patients' perception regarding diverse aspects of their disease course: number of outbreaks, outbreak's duration, number of lesions, affected body surface,

therapeutic failures, symptom's severity, psychological impairment, life quality, among others.

2. Pain intensity due to *Hidradenitis Suppurativa* lesions was assessed by a visual analogue scale (VAS) or other methods. Results were reported as change in pain measured or patients with an improvement superior to 30%.

3. *Pruritus* induced by *Hidradenitis Suppurativa* lesions evaluated by VAS or any other scale.
4. Disease activity, measured by any scale commonly used to assess *Hidradenitis Suppurativa,* namely: Hurley's stages (I-III), the International Hidradenitis Suppurativa Severity Scoring System (IHS4), the Hidradenitis Suppurativa Clinical Response (HiSCR), Hidradenitis Suppurativa Area and Severity Index (HS-LASI), Sartorius' scoring system, reduction in size, lesions count, etc.
5. Global subjective clinical evaluation, assessed by unspecific tests, VAS or Likert, or validated scales, such as *Hidradenitis Suppurativa Physician Global Assessment* (HS-PGA).
6. Treatment perception or satisfaction, evaluated by the *Consumer Reports Effectiveness Scale* (CRES-4).
7. Treatment failures due to adverse events.

1.4.3 Outcomes temporal evaluation

Two temporal periods were considered: short-term (<3 months) and long-term (>3 months). Any data available regarding temporal course was extracted and, if feasible, combined. When temporal data were not available or missing, the time course was automatically considered short-term.

1.4.5 Adverse events' evaluation

The following adverse events were classified as mild: pain, pruritus, pigment changes, local inflammation, non-disfiguring scars, no movement limiting scars, 1st or 2nd degree burns, systemic signs or symptoms that did not require hospital care. Contrarily, adverse events were

interpreted as severe when they resulted in hospital admission, prolongation of hospital stay or death.

Adverse events were also divided into early onset if they occurred before 3 months since the beginning of the treatment; otherwise, they were considered late onset.

1.5 Study types

Both experimental and observational studies were included. The minimum sample size required to be included in the present systematic review was of 5 participants. Narrative reviews and studies with less than 5 patients were excluded.

1.6 Additional exclusion criteria

Studies unavailable as complete publications (for example, congress communications or papers pending for publication) were excluded. Only fully published studies in English, Spanish or French were taken into consideration for the present work.

2. Search strategy

2.1 Key papers

Prior to the bibliography search, 6 publications were defined as 'key papers' to be included in the present systematic review: Álvarez 2020 , Boer 2010 , Clemensen 1983, Fajgenbaum 2019 , Jemec 1998 and Pascual 2017

2.2 Search strategy

A search of the literature included in the three main scientific databases (Cochrane Library, MEDLINE and EMBASE) was performed in February 2022. Due to the difficulty to properly define the intervention with accuracy, search was only restricted by the study population (patients with *Hidadenitis Suppurativa*). To do so, a combination of standardised terms (MeSH) and free terms was employed. Details of the search are shown in **tables 1—3**.

Table 1: Search strategy in MEDLINE via Pubmed	
1	hidradenitis suppurativa [MeSH Terms]
2	invers* acne[Title/Abstract]
3	acne invers*[Title/Abstract]
4	hidradeniti* suppurativ*[Title/Abstract]
5	suppurativ* hidradeniti*[Title/Abstract]
6	velpeau disease[Title/Abstract]
7	verneuil* disease[Title/Abstract]
8	1 OR 2 OR 3 OR 4 OR 5 OR 7

Table 2: Search strategy in EMBASE	
1	'suppurative hidradenitis'/exp
2	'invers* acne':ab,ti
3	'acne invers*':ab,ti
4	'hidradeniti* suppurativ*':ab,ti
5	'suppurativ* hidradeniti*':ab,ti
6	'velpeau disease':ab,ti
7	'verneuil* disease':ab,ti.
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7

Table 3: Search strategy in Cochrane	
1	(acne invers*):ti,ab,kw
2	(Verneuil*):ti,ab,kw
3	(velpeau*):ti,ab,kw
4	(hidradeniti* suppurativ*):ti,ab,kw)
5	MeSH descriptor: [Hidradenitis Suppurativa] explode all trees

6	1 OR 2 OR 3 OR 4 OR 5

2.3 Other sources

References from the obtained articles were checked to identify potential papers with relevant information. A search in *ClinicalTrials.gov* was performed with the terms *'Hidradenitis Suppurativa'* and the filter 'complete'. No additional search through the main American and European congresses' communications was performed. After performing a 'pilot' search, the works obtained from the main databases in Spanish, LILACS and Scielo, were discarded.

3. Data analysis

The review of all the abstracts obtained via the search of the databases was carried out by two of the authors (RHQ and JPR). The decision on which studies to be included or excluded from the final analysis was done after a review of the full-text articles. Disagreements between the authors were resolved with the intervention of a third author (FSM). Results obtained from the bibliography search were incorporated to citation manager EndNote® X7.

Data screening and extraction was independently performed by RHQ and JPR by an *ad hoc* designed formulary, based on the 'Checklist of items to consider in data collection or data extraction' available in 'Cochrane Handbook for Systematic Reviews of Interventions'. An individual data extraction sheet was filled for each study. Finally, to facilitate the results comprehension, data obtained were grouped by intervention: intralesional photodynamic therapy, topical photodynamic therapy, intralesional steroids, resorcinol, topical antibiotics, and other interventions.

3.1 Bias risk assessment

After data screening, the risk of bias and methodologic quality of the studies included were evaluated by RHQ and JPR independently. Due to the studies heterogeneity (from case series

to clinical essays), different tools for proper assessment were stablished, following *Cochrane's 'Risk of bias' tool (RoB1) for clinical essays.*

3.2 Intervention outcome measurement

Statistical analyses were performed with *IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.* Intervention's outcome was expressed as relative frequency for dichotomous variables. For continuous variables, the outcome was expressed as mean and standard deviation. For dichotomic studies, in which a comparator was used, intervention measurements were expressed as proportion and 95% confidence interval (95% CI).

3.3 Heterogeneity analyses and data synthesis

For those interventions with two or more scientific publications which were comparable among themselves, data were combined in a meta-analysis. For heterogeneity analyses, the I^2 test was used. Fixed effects model was selected for $I^2 < 40\%$ values and random effects model if $40\% < I^2 < 75\%$. Meta-analysis was avoided when $I^2 > 75\%$.