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[Intervention Protocol]

Treatments for alopecia areata: a network meta-analysis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the comparative effectiveness and safety of interventions used in the management of alopecia areata (AA), including patchy alopecia (PA), alopecia totalis (AT) and alopecia universalis (AU).

To establish rankings of the available treatments for AA, based on their effectiveness and safety (primary outcomes), through a network meta-analysis.

BACKGROUND

A glossary of terms is provided in Table 1.

Description of the condition

Alopecia areata (AA) is a common, inflammatory, nonscarring type of hair loss, characterized by small patches of hair loss on the scalp or around the body, as well as periods of relapse or remission, affecting the quality of life of both patients and their caregivers (Hunt 2005; Villasante 2015). AA primarily affects the scalp; however, it also can affect nails, eyelashes, eyebrows, and other hair follicles in the patient's body (Strazzulla 2018b).

Involvement of the nails occurs in 10% to 66% of all cases of AA and is present in 15.4% of AA universalis cases; it is more frequent in severe forms of AA. Deterioration of the nails can be observed before hair loss and can persist after treatment and hair regrowth; it may indicate severity of AA and disease that does not get better with treatment (refractory disease) (Ferreira 2016). The clinical signs are nail dystrophy (change in nail shape), brittleness, fragility, pitting and trachyonychia (damaged or broken nails).

There are three types of alopecia areata, defined according to the affected area: a) patchy alopecia (PA), as seen in 90% of clinical diagnoses; b) alopecia totalis (AT), that affects all scalp hairs; and c) alopecia universalis (AU), involving all scalp and body hairs (Islam 2015). The cause of AA is still being researched, but currently genetics and immune function seem to be the most relevant contributors to disease. Recently, some studies have suggested that the destruction of the hair follicle generated by an immune disorder could play a role in the appearance of AA (Juarez-Rendon 2017; Paus 2018; Pratt 2017; Strazzulla 2018b).

The lifetime incidence reported for the US population ranges between 1.7% and 2.1%, and the prevalence varies between populations and studies, ranging from 0.1% to 0.2% in the general population (Mirzoyev 2014; Safavi 1992; Safavi 1995). The pooled prevalence estimates are 0.08% for AT and 0.03% for AU, and the overall incidence proportion is 3.37% for AT and 0.02% for AU (Lee 2019). There are no clear differences by race or gender, however almost 20% of patients have a family history of AA. Of all cases with AA, 20% occur in childhood. The prevalence of AA in children and adolescents is 1.83%, and between 10% and 51.6% of those with AA have a family history of the condition. 40.2% present their first episode of AA at 20 years old (Lee 2019; Korta 2018; Pratt 2017). The extent of hair loss is considered the most important prognostic factor; those with greater hair loss respond less to treatment, and have a greater likelihood of progressing to chronic disease. Other factors related to less favourable prognosis are early age, atopic dermatitis, autoimmune diseases, and nail changes (Lee 2017).

There is a strong association between AA and other autoimmune diseases; thyroid disorders are the most common accompanying conditions, with a prevalence of 19% (Islam 2015). Other diseases commonly associated with AA include: lupus erythematous, atopic dermatitis, and psychiatric diseases (Conic 2017; Lee 2019).

The psychological and social effects of AA impact substantially on patients' health-related quality of life. Compared with the general population, people with AA have increased risk in three out of the four mental health domains of the SF-36 physical and mental health summary scales ("role-emotional, mental health, vitality") (Rencz 2016). Psychiatric disorders can trigger the onset of AA and the role of psychological stress in people with AA may be related to psychiatric comorbidities including anxiety, depression, social phobia, and personality disorders. Young male patients are at greater risk for psychological distress and suicide, and require careful monitoring (Rencz 2016).

The diagnosis of AA is based on typical clinical presentation (acute alopecia in well-circumscribed patches of normal-appearing skin) (Gilhar 2012). The 'pull test' (pulling different sections of the hair to assess the severity of hair loss) is useful to evaluate the activity of the disease. Trichoscopy (a method of magnification to assess the hair and scalp) may be useful to confirm the diagnosis and for uncertain cases. The main trichoscopic features of AA are: 'exclamation mark' hairs, yellow dots, black dots, broken hairs and coudability hairs (Strazzulla 2018b). Biopsy should be performed in unclear cases. Acute AA has the following histopathological features: peribulbar lymphocytic infiltrate (known as 'swarm of bees'), dilated follicular infundibula (known as 'swiss cheese pattern'), and increased percentage of telogen hairs (a resting phase where hair is shed) (Gordon 2011). In patients with chronic disease, this pattern may be absent (Gilhar 2012; Strazzulla 2018b).

In the natural history of the disease, hair regrowth occurs in 34% to 50% of patients within one year, and 15% to 25% will progress to AT. The long-term prognosis is directly associated with the severity of AA (Bernardis 2018; Hammerschmidt 2014). It has been a challenge for researchers and clinicians to quantify AA in real time. The Severity of Alopecia Tool Scoring (SALT) is a quantitative, reproducible, standardized and simple system that allows a clinical assessment of the amount of terminal hair loss in four views, and can be used to track treatment response (Olsen 2004; Strazzulla 2018b).

Description of the intervention

Most cases of AA remit spontaneously, and it may be appropriate not to medically treat if this is consistent with the patient's wishes; however, remission is not common in severe AA. A considerable number of patients require medical management to improve the growth of their hair; such management is mainly focused on stopping the local immune response against the hair follicle. There are different types of interventions currently in use, including local and systemic corticosteroids, contact immunotherapy, topical immune suppressants, biological agents, laser treatment, psychological support, and cosmetic strategies (Lee 2017; Murad 2018; Pratt 2017).

Immunosuppressant therapy

Normally in the paediatric population, the treatment used as the first option is topical corticosteroids of class I and II, since they have minimal adverse effects and are easily applied in their different presentations (lotion, foam, or shampoo). Adverse events that may occur due to chronic use must be taken into account (Peloquin 2017). Intralesional corticosteroids are among the first-line alternatives in patients older than 12 years old with patchy AA (Lee 2017; Pratt 2017). Usually, triamcinolone acetonide is administered by injection with a fine needle into the superior subcutaneous tissue, with the aim of stimulating hair growth at the site of injection (Kassim 2014). Most patients need multiple injections (Pratt 2017). Oral corticosteroids (e.g. oral prednisolone, prednisone, and dexamethasone) have been

used successfully for extensive and rapidly progressive AA (e.g. an extension larger than 50% of the scalp). As some patients would need a prolonged treatment to maintain hair growth, the benefits of this management should be balanced against the adverse effects (e.g. cutaneous atrophy, Cushing's syndrome) (Pratt 2017).

Systemic cyclosporine, methotrexate and azathioprine could be used as an isolated treatment or as an adjuvant therapy to reduce the use of systemic corticosteroids. They have potential adverse effects (e.g. hepatotoxicity, renal failure, higher risk of infections), so a careful study of benefit-risk balance should be performed in each case (Pratt 2017).

There are other therapeutic options considered to be immunosuppressant, mostly used in combination with first-line agents: topical calcineurin inhibitors (Price 2005), and phototherapy with psoralens-(PUVA) (Whitmont 2003).

Anti-TNF biological agents

TNF alpha is an inflammatory cytokine that has been implicated in AA, and anti-TNF biologic agents (etanercept, adalimumab, infliximab, among others) are drugs that inhibit the physiological response to this pro-inflammatory cytokine and help stop inflammation. These drugs are not the first choice for the treatment of AA, as there is scarce evidence of their efficacy (Alsantali 2011).

Other biological agents

Other new biological agents (e.g. alefacept, tofacitinib, ruxolitinib, baracitinib), have been recently proposed as potentially useful for severe forms of AA. Among them, the most promising alternative are the Janus kinases (JAK) inhibitors (Hosking 2018; Kostovic 2017; Liu 2018; Strazzulla 2018a).

Topical immunotherapy (contact immunotherapy)

Contact immunotherapy is the first line of management for patients with more than 50% of hair loss of the scalp (Perera 2015; Sutherland 2015; Yoshimasu 2016). This intervention starts with an induced contact dermatitis through topical administration of a chemical sensitizer (e.g. dinitrochlorobenzene-DNCB, diphencyprone-DPCP, squaric acid dibutyl ester-SADBE, or anthralin-dithranol) (Jang 2017). The local contact dermatitis induces a change in the lymphocytes as well as a Th2 response (the effect is due to irritancy not allergy). Related adverse events include local (e.g. pruritus, blistering, exudate) and distant reactions (e.g. disseminated eczema, urticaria). Contact immunotherapy is free of systemic adverse effects and it can be maintained over a long-term period.

Hair growth stimulants

Minoxidil has been evaluated in several studies of AA in both adults and children, and its efficacy is related to a sustained hair growth effect. In general, it is used in combination with other treatments (i.e. topical or intralesional steroids) (Fiedler-Weiss 1987; Maitland 1984; Price 1987).

Other therapies

Additional therapeutic options (mostly used in combination with first-line agents) include laser therapy, cryotherapy, and vitamins (Gupta 2017; Strazzulla 2018a).

How the intervention might work

Pathogenesis of AA is related to several factors, including autoimmunity in combination to a genetic contribution (Spano 2015). In selected cases with limited patchy hair loss, spontaneous resolution occurs within the first year in 34% to 50% of cases. However, extensive areas of AA have a poor prognosis (Tosti 2006). Currently, there is no cure for AA, although there are many possible treatments focusing on the degree of hair loss and the patient's preferences.

Immunosuppressant therapy

The mechanism of action of corticosteroids involves the reduction of CD3+ T cells, CD8+ T cells, CD11c+ dendritic cells and CD1a + Langerhans cells. In addition, it has been reported that corticosteroid treatment causes a downregulation effect over genes that encode several interleukins and chemokines (proteins and molecular messengers) (IL12B, CC-chemokine ligand 18, and IL32), as well as upregulation of genes encoding several keratins (KRT35, KRT75, and KRT86) (Fuentes-Duculan 2016; Kurosawa 2006).

Although the mechanism of action of methotrexate in the management of AA is not completely known, the evidence suggests that it produces an inhibition of the enzyme dihydrofolate reductase, then causing an increase in adenosine and release into the extracellular space, which inhibits the accumulation of white blood cells, as well as a variety of activities of monocytes, macrophages and T cells, but it also leads to a reduction in synthesis of TNF-α and interferon gamma (Hammerschmidt 2014).

Cyclosporine has an immunosuppressive effect (suspends the immune response), which allows it to block gene transcription in activated T cells that codify for different cytokines. It also regulates nuclear translocation and activation of NFAT (nuclear factor of activated T-cells) due to the inhibition of the phosphatase activity of calcineurin (Matsuda 2000).

Azathioprine inhibits the synthesis of DNA and decreases the proliferation of T and B lymphocytes. In addition, it decreases the number of Langerhans cells and other antigen-presenting cells of the skin (Farshi 2010).

Anti-TNF biological agents

Recent studies on AA development suggest the involvement of the tumour necrosis factor-alpha (TNF-alpha); hence, some biological drugs such as adalimumab, infliximab and etanercept, among others, could have benefits in the management of this condition by blocking this factor (Alsantali 2011).

Other biological agents

Patients with AA present with hair follicle dystrophy and acceleration of hair follicles into the catagen phase, due to an over-expression of a variety of proinflammatory cytokines in the hair follicle, along with a tissue upregulation of several γ-chain cytokines (such as interleukin 2, 7, 15, and 21) and IFN-γ elements, which are signalled through JAK1 and JAK2. The JAK-inhibitors are able to block JAK signals, and suppress the T-cell-mediated inflammatory responses, which promotes hair growth by stimulating the activation and proliferation of hair follicle stem cells and other related mechanisms (Schwartz 2017).

Topical immunotherapy (contact immunotherapy)

The mechanism of action of contact immunotherapy is not fully understood. Some studies suggest that the induced allergic contact dermatitis attracts CD4+ T away from the perifollicular region, changing the milieu of immune cells surrounding hair follicles. Other potential mechanisms include the non-specific stimulation of T suppressor cells in the skin, the increase of local expression of transforming growth factor beta, and the activation of myeloid suppressor cells contributing to auto-reactive T cell silencing (Pratt 2017).

Hair growth stimulants

Minoxidil is a vasodilator that causes hypertrichosis (excessive hair growth anywhere on the body) as a secondary effect, and some authors have proposed a role for it as a topical treatment for AA. This effect could be the result of vasodilation, which facilitates the supply of oxygen and nutrients to the hair follicles, which in turn induces formation of new vessels (Choi 2018). On the other hand, it is important to mention that vascular endothelial growth factor, produced by endothelial cells and expressed in hair follicles, is associated with vasodilation processes and seems to be involved in hair growth (Wu 2018).

Other therapies

There are other treatments for which mechanisms of action are not fully understood. Laser therapy has been used in children with patchy AA, with variable results. The most common wavelengths used are 308 nanometer (nm) (excimer laser), 904 nm (diode laser), and 1540 nm (Er:glass laser) (Al-Mutairi 2007; Waiz 2006; Yoo 2010).

Cryotherapy has also been used in patches of alopecia areata, however its mechanism of action is not clear. It could be related to the effect produced by exposure for a short period to liquid nitrogen, which increases blood flow and improves microcirculation through reactive vasodilatation (Jun 2017).

Why it is important to do this review

In 2017, Cochrane Skin undertook a large-scale exercise with stakeholders for prioritization of systematic reviews to be developed in the next two years. Specifically, one of the target conditions prioritized was AA, which is a common autoimmune disease affecting all types of people around the world, with reports of cumulative life incidence up to 2% (Mirzoyev 2014). As mentioned above, AA affects the quality of life of patients and caregivers, and interferes especially with their daily activities. In addition, AA is an important cause of absence from both school and work, and it generates consequences in the global economy and excess of burden for the healthcare system.

In addition, it is important to highlight the contribution of Macbeth and colleagues, who presented the top 10 research priorities for AA in the UK, which include at least three issues related to the objectives of this review, as follows (Macbeth 2017).

- Are immunosuppressant therapies better than placebo in the treatment of AA?
- In AA, are biological therapies (including JAK inhibitors and anti-cytokine therapies) more effective than placebo in causing hair regrowth?
- Do any treatments have a long-term therapeutic benefit in AA?

Cochrane Skin published a systematic review of AA in 2008 (Delamere 2008); however, new evidence about the effectiveness and safety of potential treatments has been published in the last decade. The update of this systematic review is essential. In addition, due to the numerous interventions proposed for the management of AA, the methodology of a systematic review with network meta-analysis will be an important tool to assess the different alternatives and to guide clinical practice through a complete comparison of proposed treatments for AA.

Finally, this updated systematic review will identify the existing gaps in the evidence related to the management of this condition, and can be used to inform new lines of AA research.

OBJECTIVES

To assess the comparative effectiveness and safety of interventions used in the management of alopecia areata (AA), including patchy alopecia (PA), alopecia totalis (AT) and alopecia universalis (AU).

To establish rankings of the available treatments for AA, based on their effectiveness and safety (primary outcomes), through a network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) that evaluate effectiveness and safety, or both. We will consider RCTs with parallel groups, cluster-randomized trials, cross-over trials, experiments with repeated measures on participants, multiple intervention groups, half-head studies, and multiple body parts.

Types of participants

We will consider individuals who have been diagnosed by a medical practitioner with AA, AT or AU, including both paediatric and adult populations. We will only include studies in which there is a subset of relevant participants if it is possible to obtain specific and separate information. We will pose no restrictions on age, sex, or ethnicity of the participants. This absence of restrictions may threaten transitivity and introduce heterogeneity, as several of the characteristics of the participants act as potential treatment effect and safety modifiers (see 'Assessment of transitivity in the network meta-analysis', below). This issue will be addressed by performing subgroup analyses and network meta-regression (see Subgroup analysis and investigation of heterogeneity). Diagnosis of AA can be achieved by clinical examination, trichoscopy/dermoscopy, or biopsy. We will exclude trials with participants suffering from androgenetic alopecia and cicatricial alopecia.

Types of interventions

Decision Set

Studies should include one or more of the following interventions, delivered at any dose, duration, and follow-up time.

Immunosuppressant therapy

- Topical corticosteroids
- Topical calcineurin inhibitors
- Intralesional corticosteroids

- Systemic corticosteroids (e.g. prednisolone)
- Systemic cyclosporine
- Methotrexate
- Azathioprine
- Hydroxychloroquine
- Sulfasalazine
- Psoralens taken by mouth + exposure to ultraviolet light A (PUVA)

Anti-TNF biological agents

- Etanercept
- Adalimumab
- Infliximab

Other biological agents

- Abatecept
- Alefacept
- Apremilast
- Dupilumab
- Ustekinumab
- Tofacitinib
- Ruxolitinib
- Baractinib

Topical immunotherapy (contact immunotherapy)

- Dinitrochlorobenzene (DNCB)
- Diphencyprone (DPCP)
- Squaric acid dibutyl ester (SADBE)
- Anthralin (dithranol)

Hair growth stimulants

- Oral minoxidil
- Topical minoxidil
- Topical bimatoprost

Other therapies

- Cryotherapy
- Laser
- Vitamins supplementation
- Aromatherapy
- Mesotherapy (zinc, selenium, biotin, platelet-rich plasma)

Interventions can be administered either as single therapy or in combination.

Reference set

The comparators will be placebo, no treatment, vehicle only, or another active compound.

Types of outcome measures

We consider for this section the recommendations of the consensus of Olsen and colleagues to obtain objective outcome measures on AA. We will use the Severity of Alopecia Tool (SALT), which evaluates the percentage scalp involvement, in preference to other reported measures (Olsen 2018).

Primary outcomes

1. The proportion of participants with clinically significant hair regrowth, as rated by the participant or medical practitioner (where both types of rating are available, we will use medical assessment). We deem ≥ 75% regrowth of the affected area to constitute significant hair regrowth.

2. Incidence of serious adverse events: including mortality, hospitalization, surgical intervention, temporary or permanent sequelae, and serious infections. We will consider the number of participants with at least one serious adverse event.

Secondary outcomes

1. Health-related quality of life, measured with validated instruments such as the Alopecia Areata Quality of Life Index (AA-QLI) (Fabbrocini 2013), Dermatology Life Quality Index (DLQI) (Finlay 1994), and Skindex (versions 29 and 16) (Chren 2012).

2. The proportion of patients with long-term sustainability of hair regrowth (greater than 26 weeks).

Studies which do not report outcomes of interest will not be excluded. In this case, the outcomes will be described as presented by the study authors. In case of studies with extremely vague outcomes, or if the outcome is not clearly described but seems most likely to map to one of our predefined outcomes, then we will describe the outcome narratively and take into consideration narrative information when interpreting the results of the meta-analyses.

Timing of outcomes

Regarding time points and follow-up, Olsen and colleagues recommend that at least a 12-week observation period should be measured (Olsen 2018). Therefore, we will describe the results obtained in the longest follow-up time reported by adequate numbers of trials for meaningful and representative meta-analysis. We will classify outcomes as short-term (between 12 and 26 weeks) and long-term (greater than 26 weeks). In case of multiple time points of measurements, we will use the result closest to 12 weeks for short-term outcomes and closest to one year for long-term outcomes. We will assess whether the time point assessment reported is biologically reasonable, and we will also consider the quantity and quality of data available for each time-point that might be pooled in meta-analysis. We will take these considerations into account when assessing the quality of the study. We will perform analyses of studies with outcome data at similar time points.

The duration of the treatment may threaten transitivity as it is a potential safety modifier (see 'Assessment of transitivity in the network meta-analysis', below). This issue will be addressed by comparing adverse events at similar timings (long-term).

Search methods for identification of studies

We aim to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist will search the following databases for relevant trials, with no restriction by date.

- The Cochrane Skin Specialised Register
- The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE via Ovid (from 1946 onwards)
- Embase via Ovid (from 1974 onwards)

The Information Specialist has devised a draft search strategy for RCTs for MEDLINE (Ovid), which is displayed in Appendix 1. This will be used as the basis for search strategies for the other databases listed.

Trial registers

We (MGUR, DSC) will search the following trial registers using the key words “alopecia areata” or “patchy alopecia areata” or “alopecia universalis” or “alopecia areata universalis” or “alopecia totalis” or “alopecia areata totalis”.

- ClinicalTrials.gov (www.clinicaltrials.gov)
- The World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch)

Searching other resources

Searching reference lists

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials, including the reference lists of the previous Cochrane Review of AA (Delamere 2008).

Correspondence with trialists/experts/organizations

We will contact original authors for clarification and further data if trial reports are unclear, specifically to obtain non-reported data or missing results that are relevant for the estimation of the outcomes of interest.

Adverse effects

We will not perform a separate search for adverse effects of interventions used for the treatment of AA. We will consider adverse effects described in included studies only.

Data collection and analysis

The results of the literature search will be collected in an EndNote library, where duplicate studies will be removed. The file will then be exported to Covidence for the screening process (Covidence 2019).

Selection of studies

Two review authors from a panel of four (MN, GSV, MGUR, DSC) will independently select studies for eligibility. We will review titles and abstracts of all identified studies to determine whether they fulfil the inclusion criteria. We will assess the full texts of selected studies to confirm their relevance for inclusion. We will be selecting RCTs based on the comparison within the trials. We will resolve any disagreements by consulting a third author (SVG). We will not be blinded to the study authors’ names and institutions, journal of publication, or study results at any stage of the review. We will record the reasons for exclusion of potential studies in the 'Characteristics of excluded studies' tables.

Data extraction and management

Two review authors from a panel of four (SVG, MGUR, LGM, DSC) will independently use The Skin Group's data extraction form, tailored for this systematic review, to extract information on the description of interventions, participants, outcome measures, methods, and methodological quality. This data extraction form will be piloted with a set of included trials.

Regarding outcomes, we will extract the number of participants allocated to each intervention group and the proportion of patients that reached more than 75% hair regrowth. We will extract the proportion or incidence of participants in each group with at least one serious adverse event (mortality, hospitalization, surgical intervention, temporary or permanent sequelae, and serious infections). We will extract from each trial the event rates and descriptions of serious adverse effects. We will also extract the results related to our secondary outcomes: health-related quality of life and incidence of disease relapse. We will extract means and standard deviations per study arm if outcomes are reported as continuous outcomes rather than binary outcomes.

We will resolve any disagreement by discussion with a third review author (GSV). We will enter extracted data into Review Manager 5.4 (RevMan 2020) or RevMan Web (RevMan Web 2019), or both; and we will use Stata Statistical Software (release 15) for further analyses (Higgins 2019a; Stata 2017).

Assessment of risk of bias in included studies

We will use version 2 of the Cochrane 'Risk of bias' tool (RoB2) for RCTs (Sterne 2019) to evaluate the risk of bias of each included trial. This will be done independently by two review authors from a panel of four (IAR, GSV, MN and SVG), following the recommendations in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b). Disagreements will be resolved by discussion with a third author (JZ). The interest of our review will be assessing the effect of assignment to the interventions at baseline. As the *Handbook* recommends, we will evaluate each outcome using the RoB2 tool. The domains of this tool for RCTs include the following.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

Each domain has a group of signalling questions to retrieve relevant information for an assessment of risk of bias. The options are: yes, probably yes, probably no, no, no information. According to the answers, the 'Risk of bias' judgement for each domain would be either: low risk of bias, some concerns, or high risk of bias.

The overall judgement about risk of bias depends on the result of each domain, as presented below.

- Low risk of bias: the study is judged to be at low risk of bias for all domains for this result.
- Some concerns: the study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.

- High risk of bias: the study is judged to be at high risk of bias in at least one domain for this result, or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

The 'Risk of bias' assessments will inform our GRADE evaluations of the certainty of evidence for those outcomes presented in the 'Summary of findings' tables, and will also be used to inform the sensitivity analysis for studies at low risk of bias for the primary outcomes (see Sensitivity analysis).

For each bias judgement we will use the Excel template, which is available at https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2. Each file will be stored on a scientific data website, available to readers.

Risk of bias in cluster-randomized controlled trials

In case of cluster-RCTs, we will start with RoB2 as it is, but we will also include the domain: 'bias derived from the moment of identification and recruitment of participants', using the signalling questions from Domain 1b. We will also follow the description included in Section 23.1.2 in the *Cochrane Handbook* and in Table 23.1, to assess bias in this type of study (Higgins 2019c).

Risk of bias in cross-over randomized controlled trials

For this type of study we will start with RoB2 as it is, and for Domain 2 ('bias due to deviations from the intended interventions') and Domain 3 ('bias due to missing outcome data'), we will use the respective signalling questions from the RoB2 tool guidance for cross-over RCTs (Higgins 2019c).

Measures of treatment effect

Relative treatment effects

For each dichotomous outcome, we will estimate the relative treatment effects using risk ratios (RRs), with 95% confidence intervals (CIs). In case of a continuous outcome (i.e. quality-of-life scores), we will analyze data using mean differences (MDs) or standardized mean differences (SMDs), with their respective 95% CI. We will make the SMD easier to understand by back-transforming to a known scale.

Relative treatment ranking

We will present treatment hierarchies using rankograms, cumulative probability plots and clustered ranking graphs (Chaimani 2013). We will use SUCRA and mean rank, along with corresponding CIs, to indicate the uncertainty of rankings (Salanti 2011). We will not determine rankings using probabilities. If we identify too much uncertainty, we will not rank treatments.

Unit of analysis issues

Following the guidance from the *Handbook* (Higgins 2019d), we will consider the potential impact of different designs on the analysis, including special considerations for cluster-randomized trials, cross-over trials, experiments with repeated measures on participants, multiple intervention groups, and multiple body parts.

Cluster-randomized trials

In case of cluster-randomized trials, we will perform the analysis at the same level as the allocation, using a summary measurement from each cluster, following the recommendations in the *Handbook* (Higgins 2019c). If a cluster-randomized trial provides results unadjusted for its cluster design, we will reduce the effective sample size accounting for the design effect using the reported intracluster correlation coefficient (ICC), or in case the study does not report the ICC, we will use an ICC obtained from a similar trial from the literature. We will assess the effect of the unit of randomization in a sensitivity analysis.

Cross-over trials

Clinical research in dermatology often uses cross-over designs, by the assignment of patients to a sequence of interventions (AB or BA). We will check the appropriateness of a cross-over design (i.e. check for the presence of a carry-over effect of intervention, or period effect or irreversibility of outcome). In accordance with the guidance in the *Handbook* (Higgins 2019c), we will follow the conservative option of including data from the first trial period only if the cross-over design is deemed inappropriate.

Repeated measures on participants

Where there are repeated measures of the outcome of interest within a study (for instance, at three, six, nine, and 12 months), we will analyze the longest follow-up time reported, and classify it as short-term (less than 12 weeks) or long-term (greater than 12 weeks) (see 'Timing of outcomes', above). During the analysis we will group trials that report similar timings, to make comparisons between studies.

Multiple intervention groups

If we include trials which have relevant comparisons between more than two groups in a pair-wise meta-analysis, we will split participants in the control group into two or more groups; this is to avoid double-counting participants. In the network meta-analysis, multi-arm trials are split into separate nodes of the network, so double-counting of patients is not a concern as long as within-trial correlation is adequately considered in the analysis (Franchini 2012).

Multiple body parts

In the context of AA, different parts of the body could be randomized to different interventions (i.e. split-head designs). If outcomes are evaluated at the level of body parts despite being randomized at participant level, and the data were not correctly analyzed, we will assess whether it is possible to approximate the correct analysis following guidance provided in the *Handbook* (Higgins 2019c). If studies do not provide sufficient information to approximate the correct analysis, we will exclude the data from the analysis.

Dealing with missing data

In studies with missing data, we will contact trial authors or sponsors and we will make requests for missing data. We will create a table with information about the authors contacted and the information requested and received.

Assessment of heterogeneity

We will explore the variability between studies, analyzing the different sources of clinical and methodological heterogeneity. We will describe trial population characteristics across included trials and will assess the presence of clinical or methodological heterogeneity by comparing their characteristics. For our pair-

wise analyses, we will use the statistical test included in Review Manager 5.4 or RevMan Web (RevMan 2020; RevMan Web 2019). The Chi^2 test performs an evaluation of the chance to explain the variability, with heterogeneity occurring if a P value is less than 0.1. In addition, we will use the I^2 to quantify the heterogeneity, through a description of the variability in effect estimates that is due to heterogeneity. We will explore sources of heterogeneity by performing subgroup analysis and meta-regressions (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity in the network meta-analysis

The transitivity assumption concerns the validity of making indirect comparisons. This assumption relies on whether the effect of an intervention estimated using indirect comparisons is similar to the effect estimated using a direct comparison. We will tabulate direct, indirect and mixed evidence for each comparison to facilitate the assessment of transitivity. We will explore trial characteristics to identify between-study differences in the distribution of potential treatment effect modifiers across each of the comparisons in the network (Jansen 2013). We will consider the following clinical and methodological factors to be potential treatment effect modifiers: for efficacy outcomes, we will consider age, early onset of the disease, clinical form, severity of the disease, extension of hair loss, and coexisting nail changes. Regarding safety, we will consider age, treatment duration, comorbidities and poly-medication (see Subgroup analysis and investigation of heterogeneity).

Assessment of statistical incoherence in the network meta-analysis

If there are differences across studies that involve different interventions of the network, the transitivity assumption may not be met and it may generate statistical incoherence (Higgins 2012).

We will check for local incoherence using the node-splitting approach, which requires a closed loop with at least three treatments compared to each other (Dias 2010). This technique will be applied to all comparisons in the network to estimate the difference between direct and indirect comparisons, jointly with 95% CIs. To determine global consistency of the network, we will use the “design by treatment” interaction model (Higgins 2012), using multivariate meta-analysis. The model will estimate a global Chi^2 test for network incoherence. We will consider as incoherence a P value of less than 0.05. We will explore the following variables as a possible source of incoherence: severity of disease, adult or paediatric population, risk of bias, and duration of follow-up, among others.

Assessment of reporting biases

We will use funnel plots for the primary outcomes to provide a visual assessment of reporting bias, if at least 10 trials are available (Higgins 2019a; Sterne 2011). We will assess reporting bias for pairwise comparisons using contour-enhanced funnel plots. We will also use two tests to assess asymmetry in the corresponding funnel plots: the regression asymmetry test (Egger 1997) and the adjusted rank correlation test (Begg 1994). Assessment of reporting bias will be performed in pairwise meta-analysis. We will use comparison-adjusted funnel plots to assess reporting biases and small-study effects for the network meta-analysis (Chaimani 2012; Chaimani 2013).

Data synthesis

Methods for direct treatment comparisons

We will perform pairwise meta-analysis for each direct comparison, using the random-effects model (DerSimonian and Laird method). This allows us to summarize the findings while accounting for between-study heterogeneity. If the available number of studies is insufficient to estimate between-study variance (e.g. only two studies), we will perform a fixed-effect meta-analysis instead. As treatment effect measures, dichotomous outcomes will be reported as RRs with 95% CIs. Where results are estimated for individual studies with low numbers of events (less than 10 in total), or where the total sample size is less than 30 participants and a RR is used, we will report the proportion of events in each group together with a P value from a Fisher’s Exact test. Where outcomes are expressed as continuous data (i.e. quality-of-life scores), the analysis will use MD, or SMD if the same outcome is measured with different measurement tools, including 95% CIs (Higgins 2019a). We will use the software Review Manager 5.4 or RevMan Web (RevMan 2020; RevMan Web 2019).

Methods for network meta-analysis

Firstly, we will build a graphical description of the evidence network to assess its geometry (Chaimani 2013). We plan to represent graphically the network structure with nodes and edges, including a short-term efficacy network, a long-term efficacy network, and a long-term security network, with all the individual treatments that meet the requisites. Secondly, we will assess whether the transitivity assumption holds comparing populations and settings among studies. Finally, we will assess consistency formally in the network using methods described above, then we will perform the network meta-analysis within a frequentist framework using multivariate meta-analysis. We will use random-effects models to estimate the relative treatment effects using RRs and SMDs, with 95% CIs for each intervention compared to the anchor treatment. We will estimate rankings of the relative effect of all interventions on AA and on safety, using the probability to be the best treatment and the surface under the cumulative ranking curve (SUCRA) (Chaimani 2013; Salanti 2011; Shim 2017). The analyses will be performed using Stata Statistical Software, release 15 (Stata 2017), using the 'network' suite of commands designed for this purpose (White 2015). If the assumptions that preserve the validity of the NMA are not met, only direct comparisons and a narrative description of the findings will be made.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses and network meta-regression if we identify a sufficient number of available studies, especially for the factors that could explain the differences between the treatments. The subgroup analysis will be performed for the pairwise meta-analysis and the network meta-analysis. Subgroups of main interest will be:

- age group (less than 12 years versus 12 years or more)
- the extent of hair loss (less than 75% versus 75% or more)
- the three types of alopecia according to the affected area: a) patchy alopecia (PA); b) alopecia totalis (AT); and c) alopecia universalis (AU).

We will also investigate other clinical or methodological factors identified during the review process that may threaten transitivity, as sources of incoherence or heterogeneity.

To compare the estimations of the subgroups, we will add the subgroup factor into the random-effects model. To test its statistical significance, we will use a P value of less than 0.05 as a threshold to consider a significant difference.

Sensitivity analysis

We will perform a sensitivity analysis, using the risk of bias as a variable to explore the robustness of the findings. We will verify the behaviour of our estimators, including and excluding studies with a high risk of bias overall (see Assessment of risk of bias in included studies).

Summary of findings and assessment of the certainty of the evidence

We will create 'Summary of findings' tables for the primary outcomes (see Primary outcomes). Each treatment will be compared to placebo (reference) and ranked in order of effectiveness and safety in the 'Summary of findings' tables. We will use the GRADE approach to assess the certainty of evidence for each outcome listed above for our main comparisons (Schünemann 2013). In the 'Summary of findings' tables we will include: PICO information, the network meta-analysis graphic, data presentation, certainty of evidence, ranking of treatments, and interpretation of findings. The assessment of the certainty of evidence is based on a methodological framework which considers six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. To perform this assessment we will use the CINeMA approach (Salanti 2014), and the CINeMA web application (Nikolakopoulou 2019).

Two review authors from a panel of four (GSV, IAR, MN, SVG) will independently appraise the certainty of evidence. Disagreements between authors will be resolved through discussion or by consultation with a third review author from a panel of three (DSC, MGUR, JZ), where necessary.

We will use the approach proposed by Yepes-Nuñez and Schünemann (Yepes-Nuñez 2018) to create our 'Summary of findings' tables and undertake our GRADE assessments (Appendix 2).

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ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Adjuvant therapy	Additional treatment given to the primary or initial therapy to maximize its effectiveness
Alopecia areata (AA)	A common, inflammatory, nonscarring type of hair loss, characterized by small patches of baldness on the scalp or around the body, as well as periods of relapse or remission
Alopecia totalis (AT)	Alopecia that affects all scalp hairs
Alopecia universalis (AU)	Alopecia that involves all scalp and body hairs
Antigen	A substance that invokes an immune response
Biologic agents	Compounds produced by living cells using recombinant DNA technology
Blistering	Circumscribed elevations of the epidermis, fluid-filled due to separation of two layers of tissue and the leakage of plasma into the space
Catagen phase	A phase of 2 to 3 weeks of duration when growth stops and the follicle shrinks
Chemokines	Molecular messengers through which epithelial cells communicate with key cells in the immune system
Coudability hairs	Normal-looking hairs tapered at the proximal end (i.e. the hair root)
Cryotherapy	Tissue destruction techniques produced by the application of cold on the skin
Cutaneous atrophy	Skin thinning
Dendritic Cells	The major antigen-presenting cells; these cells capture, process, and present antigens to T cells in order to induce adaptive immunity or tolerance to self-antigens
Downregulation	The process by which a cell reduces or suppresses the quantity of a cellular component
Exclamation mark hairs	Short hairs, 3 mm long, with irregular thickening and terminal dilation
Exudate	A fluid rich in protein and cellular elements that results from a continuous inflammatory response
First choice	Treatment regimen accepted for the primary or initial therapy
Hair follicle	A small cavity in the epidermis, from which a hair develops
Hepatotoxicity	The result of chemical-driven liver damage
Immune privilege	Multiple mechanisms that prevent autologous attack by immune cells in certain locations, such as the hair follicle
Immunosuppressant therapy	Treatment that reduces the activity of the body's immune system
Incidence	The rate of new (or newly diagnosed) cases of the disease
Interleukins	Potent cytokines (proteins) produced by some leukocytes (white blood cells), which function as mediators of cell growth, inflammation, immunity, differentiation and repair
Keratins	A fibrous protein that occurs in the outer layer of the skin and in the hair and nails

Table 1. Glossary of terms *(Continued)*

Langerhans cells	Dendritic cells (which regulate the cellular immune response) present in all layers of the epidermis as a dense network of immune system indicators
Laser therapy	A medical treatment where a light source is used; radiant energy in the form of photons and waves is capable of producing special biological effects
Lymphocytes	Leukocyte whose main function is the regulation of the adaptive immune response
Macrophages	Cells derived from monocytes residing in various tissues; their function is to present the antigens to the lymphocytes to initiate the immune response and destroy, by phagocytosis (the process by which a cell binds to and engulfs something), the antigens and the cells that transport them
Monocytes	Circulating blood cells whose main function is phagocytosis
Patchy alopecia (PA)	Round or oval patches of alopecia located on the head or in different regions of the body
Phototherapy	Therapeutic use of ultraviolet radiation
Prevalence	Proportion of individuals from a population that present with the event in a given period of time
Pruritus	Feeling that leads to scratching
Psoralens	Photoactive medication
PUVA	Administration of a psoralen and subsequent exposure to ultraviolet radiation A
Regrowth	Reappearance or return
T cells	Cells that are programmed to recognize, respond to, and remember antigens
Tumour Necrosis Factor alpha (TNF alpha)	An inflammatory cytokine produced by macrophages/monocytes responsible for different signalling events within cells, leading to necrosis (cell death) or apoptosis (programmed cell death)
Upregulation	The process by which a cell increases the quantity of a cellular component
Vehicle	A treatment without active ingredients

APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1. exp Alopecia Areata/
2. nonscarring hair loss$.ti,ab.
3. non-scarring hair loss$.ti,ab.
4. ophiasi$.ti,ab.
5. sisaipho.ti,ab.
6. atrichia$.ti,ab.
7. pseudopelade$.ti,ab.
8. porrigo decalvans.ti,ab.
9. ((spot$ or patch$) and baldness).ti,ab.
10. autoimmune hair loss$.ti,ab.
11. (alopecia adj3 (spot$ or nonscarring or non-scarring or areat$ or barbae or patch$ or semiuniversalis or autoimmune or totalis or circumscripta or liminaris or universalis or circumscribed or diffuse or Jonston$ or marginal or snake-shaped)).ti,ab.
12. or/1-11
13. randomized controlled trial.pt.

14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp animals/ not humans.sh.
22. 20 not 21
23. 12 and 22

Appendix 2. NMA-SoF Table

GRADE-NMA.
Estimates of the effects, confidence intervals and certainty of the evidence: treatments in patients with alopecia areata

Patient or population:					**Geometry of the network**		
Interventions:							
Comparator (reference):							
Outcome:							
Setting:							
Total studies: n. **Total participants**: n	**Relative effect [a] (CI 95%)**	**Anticipated absolute effect (CI 95%) [b]**			**Certainty of evidence**	**Ranking (CI 95%) [c]**	**Interpretation of findings**
		Without intervention	**With intervention**	**Difference**			
Intervention. Number of studies. Number of participants	RR (CI 95%)				Very low, low, moderate, high		

NMA-SoF table definitions

[a] **Estimator of effect, with confidence interval in frequentist approach or credible interval in Bayesian analysis.**

[b] **Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the risks of the control group.**

[c] **Surface under the cumulative ranking (SUCRA), with confidence interval in frequentist approach or credible interval in Bayesian analysis. Probability to be the best, the second, the third, and so on until the least effective treatment.**

Explanatory footnotes of certainty of evidence

HISTORY

Protocol first published: Issue 9, 2020

CONTRIBUTIONS OF AUTHORS

GSV was the contact person with the editorial base.
GSV co-ordinated the contributions from the co-authors and wrote the final draft of the protocol.
GSV, IAR, AT, and JZ worked on the methods sections.
MN, SVG, DSC, LGM, and MGUR drafted the clinical sections of the background and responded to the clinical comments of the referees.
GSV, IAR, AT, and JZ responded to the methodological and statistical comments of the referees.
GSV, MN, IAR, SVG, AT, DSC, JZ, MGUR, LGM, and JT contributed to writing the protocol.
JT was the consumer co-author and checked the protocol for readability and clarity. They also ensured that the outcomes are relevant to consumers.
GSV is the guarantor of the final review.

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DECLARATIONS OF INTEREST

Monica Novoa: none known.
Guillermo Sánchez Vanegas: none known.
Ingrid Arevalo-Rodriguez: none known.
Sergio Vaño-Galván: I have received payment from Cantabria Labs, ISDIN, Pfizer and Almirall for my role as scientific advisor. My institution has received a research grant from Novartis, as well as payment from Cantabria Labs for my role as scientific advisor. I have also received payment from Cantabria Labs, Ducray and Almirall for speaking.
Mayra Gizeth Urueña Rodriguez: none known.
Lucia Giraldo: none known.
David Saceda Corralo: I received payment from ISDIN for lectures given to dermatologists.
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