INTERVENTIONS FOR ALOPECIA AREATA

Delamere Finola M, Sladden Michael J, Dobbins Helen M, Leonardi-Bee Jo

Delamere Finola M, Sladden Michael J, Dobbins Helen M, Leonardi-Bee Jo

Cochrane Database of Systematic Reviews, Issue 7, 2015 (Status in this issue: EDITED (NO CHANGE TO CONCLUSIONS))

DOI: 10.1002/14651858.CD004413.pub2

This review should be cited as: Delamere Finola M, Sladden Michael J, Dobbins Helen M, Leonardi-Bee Jo. Interventions for alopecia areata. Cochrane Database of Systematic Reviews. In: *The Cochrane Library,* Issue 7, Art. No. CD004413. DOI: 10.1002/14651858.CD004413.pub2

A B S T R A C T

Background

Alopecia areata is a disorder in which there is loss of hair causing patches of baldness but with no scarring of the affected area. It can affect the entire scalp (alopecia totalis) or cause loss of all body hair (alopecia universalis). It is a relatively common condition affecting 0.15% of the population. Although in many cases it can be a self-limiting condition, nevertheless hair loss can often have a severe social and emotional impact.

Objective

To assess the effects of interventions used in the management of alopecia areata, alopecia totalis and alopecia universalis.

REVIEW_ABS_OTHER

We searched the Cochrane Skin Group Specialised Register in February 2006, the Cochrane Central Register of Controlled Clinical Trials (The Cochrane Library Issue 1, 2006), MEDLINE (from 2003 to February 2006), EMBASE (from 2005 to February 2006), PsycINFO (from 1806 to February 2006), AMED (Allied and Complementary Medicine, from 1985 to February 2006), LILACS (Latin American and Caribbean Health Science Information database, from 1982 to February 2006), and reference lists of articles. We also searched online trials registries for ongoing trials.

Selection criteria

Randomised controlled trials that evaluated the effectiveness of both topical and systemic interventions for alopecia areata, alopecia totalis, and alopecia universalis.

Data collection and analysis

Two authors assessed trial quality and extracted the data. We contacted trial authors for more information. We collected adverse effects information from the included trials.

Main results

Seventeen trials were included with a total of 540 participants. Each trial included from 6 to 85 participants and they assessed a range of interventions that included topical and oral corticosteroids, topical ciclosporin, photodynamic therapy and topical minoxidil. Overall, none of the interventions showed significant treatment benefit in terms of hair growth when compared with placebo. We did not find any studies where the participants self-assessed their hair growth or quality of life.

Authors' conclusions

Few treatments for alopecia areata have been well evaluated in randomised trials. We found no RCTs on the use of diphencyprone, dinitrochlorobenzene, intralesional corticosteroids or dithranol although they are commonly used for the treatment of alopecia areata. Similarly although topical steroids and minoxidil are widely prescribed and appear to be safe, there is no convincing evidence that they are beneficial in the long-term. Most trials have been reported poorly and are so small that any important clinical benefits are inconclusive. There is a desperate need for large well conducted studies that evaluate long-term effects of therapies on quality of life.

PLAIN LANGUAGE SUMMARY

There is no good trial evidence that any treatments provide long-term benefit to patients with alopecia areata, alopecia totalis and alopecia universalis.

Alopecia areata is a condition that causes patchy hair loss. The size and number of patches and progress of the disease can vary between people. It can affect the entire scalp (alopecia totalis) or cause loss of all body hair (alopecia universalis). Sometimes the condition will get better on its own, but in some cases it can get worse.

Treatments include a variety of different creams or lotions applied to the scalp such as topical or oral corticosteroids, minoxidil and some light-based therapies. Some of the skin treatments can have unpleasant side effects such as itching or hair growth in areas of the body away from where the cream was applied. Oral steroids may cause serious side effects. Also, there is no guarantee that any hair regrown during treatment will persist once the treatment is finished.

We found 17 randomised controlled trials involving 540 participants. Only one study which compared two topical corticosteroids showed significant short-term benefits. No studies showed long-term beneficial hair growth. None of the included studies asked participants to report their opinion of hair growth or whether their quality of life had improved with the treatment.

WHAT'S NEW

What's new
Last assessed as up-to-date: 4 December 2007.

Date	Event	Description
25 April 2008	Amended	Converted to new review format.

BACKGROUND

Background

Description of the condition

Alopecia areata is a disorder where there is a loss of hair with no scarring to the affected area (see). The cause of alopecia areata is not yet fully understood (Green 2000). It can start at any age, although the majority (60%) of individuals develop alopecia areata before 20 years of age (Madani 2000). Both sexes are affected equally and there is no known race preponderance.

The severity and pattern of hair loss can vary considerably between individuals. Alopecia areata is typically multi-focal, occurring on the scalp or any other hair-bearing region of skin (Sinclair 1999). The bald areas are commonly oval or circular in shape and smooth to the touch. Hair shaped like an exclamation mark can be present around the margins of the patch. The condition can affect the entire scalp (alopecia totalis) or can cause loss of all body and scalp hair (alopecia universalis) (Price 1999). The number of people with alopecia areata who progress to develop alopecia totalis or universalis is not known, but estimates range from 7 to 30% (Muller 1963). Vitiligo and autoimmune thyroid disorders are sometimes associated with alopecia areata (Madani 2000).

Epidemiology

Alopecia areata is a relatively common condition which occurs all over the world (Madani 2000). It accounts for approximately 2% of new cases attending dermatology outpatient clinics in the UK and USA (Madani 2000). A population-based study in Minnesota, USA, found an overall incidence of alopecia areata was 20.2 per 100,000 person-years (Safavi 1995). The lifetime risk has been estimated at 1.7% (Safavi 1995). The majority of people affected experience only the occasional bald area, which spontaneously resolves within a year, but most will suffer a relapse at some stage in their life. The prognostic factors for a less favourable outcome include: a family history of alopecia areata; childhood onset of alopecia areata; severe hair loss, as in alopecia totalis or universalis; a history of atopic diseases such as eczema, asthma or hay fever; other autoimmune conditions, particularly thyroid disease (Madani 2000).

Causes

Alopecia areata is an autoimmune disease which affects genetically susceptible individuals (Colombe 1999). The autoimmune response may be triggered by the interaction of genetic and other factors, such as physical stress, trauma or a major life crisis (Madani 2000), but often a specific trigger cannot be identified (Sinclair 1999).

Impact

Alopecia areata can cause significant psychosocial problems. In an image orientated society, hair loss can be psychologically devastating for people affected and their families. Hair defines individuality and appearance; therefore, alopecia may result

in reduced self-esteem and may negatively affect the quality of life (McMichael 1998). The unpredictable nature of the disease and the possibility of long-term, potentially unpleasant, therapy all add to the anxiety experienced when living with this condition.

Description of the intervention

In alopecia areata the hair follicle is not destroyed and maintains the potential to re-grow hair should the disease go into remission (Price 1999). There is, however, no cure for alopecia areata and no universally proven therapy to induce hair re-growth and sustain remission (Sinclair 1999). It is unclear if any treatment alters the long-term course of the disease (Price 1999). It can be difficult to assess the efficacy of interventions in the absence of a control group because spontaneous recovery can occur, particularly in mild forms of the disease. A range of therapies are available that may promote acceptable hair re-growth, however, clinical outcomes are variable. It is particularly frustrating for the person affected if the therapy induces only temporary hair re-growth, or if new bald areas occur as those being treated improve. Treatment choice depends on two main factors: the extent of hair loss, and the age of the person (Price 1999 ; Madani 2000). However, treatment decisions may also be influenced by drug availability, anecdote and the personal preference of the individual with hair loss.

Current treatments include: topical corticosteroids; corticosteroids injected directly into the bald patch (not usually used for young children); systemic immunosuppression, e.g. psoralens taken by mouth plus exposure to ultraviolet light A (PUVA); corticosteroids (taken orally or by injection); oral ciclosporin; topical immunotherapy, e.g. diphencyprone (DPCP); anthralin; minoxidil therapy (also used in combination with corticosteroids).

All of the above therapies have documented side effects, some of which can be unpleasant or potentially serious. Treatments such as topical immunotherapy can be very time consuming. Individuals may consider the adverse effects of treatment and the unpredictable outcome unacceptable. When hair loss is extensive, a wig or hairpiece may be worn during treatment, or be a long-term option if the alopecia persists.

Why it is important to do this review

There is some evidence in the literature to support the use of the above therapies. However, many of the trials include people with different degrees of alopecia or with poorly defined disease. Adverse effects may be an important factor to consider for some of the therapies, such as the systemic agents. Topical immunotherapy is widely used, yet not licensed for such use. This systematic review will help determine the most effective therapies, when and for whom they should be used, the duration of treatment, possible risks and side effects and the level of acceptability for the person affected. It will also enable an assessment of the level and quality of the evidence that is currently available, and will identify areas of uncertainty or gaps in knowledge that require further research.

OBJECTIVES

To assess the effects of interventions used in the management of alopecia areata, alopecia totalis and alopecia universalis.

METHODS OF THE REVIEW

Methods

Criteria for considering studies for this review

Types of studies

All randomised controlled trials that evaluate the effectiveness of both topical and systemic interventions for alopecia areata, alopecia totalis, and alopecia universalis were considered.

Types of participants

Any individual who has been diagnosed by a medical practitioner with alopecia areata, alopecia totalis or alopecia universalis.

Types of interventions

Immunosuppressant therapy

topical corticosteroids

topical tacrolimus

intralesional corticosteroids

systemic corticosteroids e.g. prednisolone

systemic ciclosporin

psoralens taken by mouth plus exposure to ultraviolet light A (PUVA)

Topical immunotherapy

dinitrochlorobenzene (DNCB)

diphencyprone (DPCP)

squaric acid dibutyl ester (SADBE)

anthralin (dithranol)

Hair growth stimulants

topical minoxidil

Other therapies

cryotherapy

aromatherapy

anti-depressants

anti-virals

The interventions can be either single therapy, or combination therapy. The comparators will be either no treatment, vehicle only, or another active compound.

Types of outcome measures

Primary outcomes

The proportion of participants with clinically significant hair regrowth, as rated by the participant or medical practitioner. We have taken >50% re-growth of the affected area as the measure of moderate hair growth and thus as a clinically significant improvement.

Improvement in quality of life questionnaires.

Secondary outcomes

Serious adverse events, i.e. serious enough to require withdrawal of the treatment.

Minor participant reported adverse events not requiring withdrawal of the treatment.

Long-term sustainability of hair regrowth (greater than six months).

Pattern of hair regrowth.

The quality of the hair regrown.

Tertiary outcome measure

Duration of remission and or prevention of subsequent episodes of hair loss.

Search methods for identification of studies

Electronic searches

We searched The Cochrane Skin Group Specialised Register in February 2006 using the following terms:
(alopecia and areata) or (alopecia and totalis) or (alopecia and universalis) or (alopecia and celsi) or (nonscarring and hair and loss) or ophia*

We searched The Cochrane Central Register of Controlled Clinical Trials (The Cochrane Library Issue1,2006) using the search strategy in Appendix 1 :

We searched MEDLINE (OVID) (from 2003 to February 2006) using the strategy in Appendix 2 which included the search strategy to locate RCTs with the search terms 1-29 as given in the Cochrane Handbook (Higgins 2005), Appendix 5b.2.

We searched EMBASE (from 2005 to February 2006) using the strategy in Appendix 3 .

We searched PsycINFO (from 1806 to February 2006) using the strategy in Appendix 4 .

We searched AMED (Allied and Complementary Medicine,1985 to February 2006) using the strategy in Appendix 5 .

We searched LILACS (Latin American and Caribbean Health Science Information database, from 1982 to February 2006) using the strategy in Appendix 6 .

Searching other resources

References from published studies

The bibliographies of included and excluded RCTs were checked for possible references to further RCTs.

Unpublished literature

Trial authors of papers and abstracts were contacted where possible to ask for more information about their studies.

The following ongoing trials registries were searched in February 2006: www.nottingham.ac.uk/ongoingskintrials and www.clinicaltrials.gov using the term 'alopecia areata' and www.controlled-trials.com using the terms areata, totalis and universalis. Identified studies have been placed in the 'Studies Awaiting Assessment' section

Conference proceedings

The abstracts from the International Research Workshops 1999 and 2003 on alopecia areata were scanned for RCTs.

Adverse effects

All the adverse events detailed in the included studies were extracted and are summarised in the body of the review.

Searches were made of the websites of the Regulatory Agencies in October 2006: www.emea.eu; http://medicines.mhra.gov.uk; www.fda.gov/medwatch and www.tga.gov.au for reports of adverse events associated with minoxidil, 5-ALA, desoximetasone cream, prednisolone cream, betamethasone, ciclosporin A, SADBE, interferon, DPCP, DNCB, latanoprost, PUVA, thymopentin, clobetasol propionate, inosiplex and croton oil. These searches did not yield any additional data

Language

No language restrictions were imposed and translations were sought for several papers.

Data collection and analysis

Selection of studies

Two authors (HD,FD) identified and checked the titles and abstracts from the searches. Where it was clear that the study did not refer to a randomised controlled trial on alopecia areata, it was excluded. Two authors (FD,HD) independently assessed each study to determine whether it met the pre-defined selection criteria, any differences were resolved through discussion.

Data extraction and management

Two authors (HD,FD) developed and piloted a data extraction form in order to summarise the trials. Two authors (FD,MS) independently performed data extraction and differences were resolved by e-mail discussion. Data was checked and entered by one reviewer (FD).

Assessment of risk of bias in included studies

The quality assessment includes an evaluation of the following components for each included study, since there is some evidence that these are associated with biased estimates of treatment effect (Juni 2001):

the method of generation of the randomisation sequence;

the method of allocation concealment - this has been considered 'adequate' if the assignment could not be foreseen;

who was blinded / not blinded (participants, clinicians, outcome assessors);

how many participants were lost to follow up in each arm (split into post-randomisation exclusions and later losses if possible), and whether participants were analysed in the groups to which they were originally randomised (intention to treat).

In addition the quality assessment also included:

degree of certainty that the participants have alopecia areata, totalis or universalis;

baseline assessment of the participants for age, sex, duration and severity of alopecia;

aims, interventions (including drug doses and duration of treatment) and outcome measures clearly defined;

use and appropriateness of statistical analyses.

In assessing the quality of the trials for our review our methods differed slightly from the plans in our protocol above. This is explained below.

Measures of treatment effect

After data extraction, our analyses differed slightly from the plan in our protocol:
There were only two studies with a similar type of intervention where a meta-analysis was performed to calculate a weighted treatment effect using a random effects model. The results have been expressed as risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes which were deemed to be more suitable for pharmaceutical interventions than expressing the results as odds ratios which was the original plan. Where it was not possible to perform a meta-analysis, the data has been summarised for each trial. We did not find any paper with continuous outcomes.

Only two of the trials explicitly stated intention-to-treat (ITT) analysis, where this was not stated we used the numbers originally randomized to the groups even though there were dropouts in most of the trials.

Unit of analysis issues

There was one cross-over trial by White 1985: only the data from the first phase of the trial was analysed. However, there were no usable data to combine with the results from other parallel group studies.

For the within-patient studies, we extracted the data and results of statistical tests from the original papers. We did not combine data from parallel and within-patient studies as there is some evidence that there can be systemic effects away from the site of topical application (Bissonnette 2000)

We originally stated we would list non-randomised controlled studies, but this was not feasible because the searches found a large number of such studies. We have referred only to those studies that initially appeared to be RCTs but upon further examination were excluded; we have not listed all the controlled clinical trials.

Dealing with missing data

Where there was uncertainty or missing data, we contacted trial authors for clarification. One author was a consumer who ensured the readability of the final review.

Assessment of heterogeneity

We planned to assess heterogeneity using I2 and if substantial heterogeneity (I2 > 50%) existed we would have explored the possible reasons for this, such as disease severity, dosage and duration of treatment. However, because there were so few studies there was not much heterogeneity. The studies were clinically heterogenous for variables such as disease duration and duration of treatment.

Data synthesis

Our primary outcome measure was 'the proportion of participants with clinically significant hair regrowth, as rated by the participant or medical practitioner'. However as the participant rated assessment was not reported in any of the included trials, we used the clinician rating instead, and highlight the lack of participant-reported outcomes in our conclusion.

We have taken an outcome measure of >50% re-growth of the affected area as the measure of moderate hair growth and thus as a clinically significant improvement. Our reason for deviating from the protocol was because once we started data extraction we became aware that many of the studies did not report on 'clinically significant hair growth' and we thought that this measure would be a pragmatic means to indicate treatment benefit with those with this hair loss condition.

We considered data that have been recorded for less than six months as reflecting short-term benefit. We analysed this data separately from data that had been recorded for greater than six months, which we considered to reflect a minimum time period to capture any longer term benefit.

Subgroup analysis and investigation of heterogeneity

We had planned to do subgroup analysis if adequate information was given about the categories of alopecia areata, alopecia totalis, alopecia universalis and age of participants as described by the trial authors, however insufficient information was provided to do this.

Sensitivity analysis

Sensitivity analyses were not carried out as there were too few trials.

Adverse effects

Studies with adverse effects data were described qualitatively, except in one study where it was possible to determine a quantitative measure.

RESULTS

Results

Description of studies

See: Characteristics of included studies ; Characteristics of excluded studies ; Characteristics of ongoing studies .

Results of the search

We identified 37 studies from our searches, of which we included 17 (a total of 540 participants). We excluded five studies which are presented in the Characteristics of Excluded Studies table. We found 4 studies that are ongoing trials and we are awaiting replies about a further 11 studies which are listed in Studies awaiting classification. We hope to include these studies in future revisions of this review.

There were five publications describing two RCTs (Shapiro 1993 , Khoury 1992); these are grouped together in the included studies references and the primary paper indicated.

We did not find a single study where participant self-assessment was evaluated and reported, nor were there any quality of life measures. We found only clinician rated evaluations.

As alopecia areata is a chronic relapsing condition, we expected to find studies addressing the long-term sustainability of hair growth and the quality of hair re-grown.

There were several studies of six months duration or longer which we classed as the 'long-term' studies, these were: Perini 1994 (six months), Pipoli 1995 (outcome data reported at six months after finishing therapy), Rongioletti 1992 (six months), and Tosti 1991 (nine months) and Galbraith 1987 (10 months). In the Kar 2005 study, the intervention continued for three months and the outcomes were reported at three and six months. However, it was not possible to interpret Kar's six month data with clarity, so we have used only the three month outcome data.

We found 11 parallel studies (Charuwichitratana 2000; Kar 2005 ; Khoury 1992 ; Mancuso 2003 ; Nelson 1994 ; Perini 1994 ; Pipoli 1995 ; Price 1987a ; Price 1987b ; Rongioletti 1992 ; Tosti 1991)

We found four within-patient studies (where both the intervention and the comparison are applied to different sites on the same individual). In two studies (Shapiro 1993 , Tosti 2005) one half of the scalp received the intervention and the other half the placebo. In the study by Bissonnette 2000 the intervention doses and vehicle (the medium alone without the drug) were applied to circular sites on the scalp and in the study by Ross 2005 , one eyebrow was assigned to the intervention and the other was the control.

We found two cross-over studies (Galbraith 1987 , White 1985).

Included studies

The 17 included studies (of which 14 were placebo/vehicle-controlled and 3 had active controls) are detailed in the Characteristics of included studies table. The range of years of publication of these studies is from 1985 to 2005. They comprise eight studies of immunosuppressant therapies (with a total of 342 participants), one study of a topical immunotherapy (with a total of 30 participants), five studies of hair growth stimulants (with a total of 110 participants), one study of a systemic immunomodulator (with 34 participants) and two other studies which used interventions not usually employed for the treatment of alopecia areata (with a total of 24 participants).

The outcome measures were clinically significant hair re-growth which was defined in a variety of ways by measurements of scalp coverage.

Immunosuppressant Therapies

Six of these randomised controlled trials were parallel group studies (Charuwichitratana 2000; Kar 2005 ; Mancuso 2003 ; Nelson 1994 ; Rongioletti 1992 ; Tosti 1991) and two were within-patient studies (Bissonnette 2000 ; Tosti 2005)

Topical corticosteroids

There were two trials (Charuwichitratana 2000; Mancuso 2003) of topical steroids on participants with moderate alopecia areata and one on participants with moderate to severe alopecia areata (Tosti 2005). In the Charuwichitratana study, 70 participants with a mean age of 34 years were randomised to desoximetasone cream (0.25%) or placebo. In the Mancuso study 61 participants with a mean age of 41 years and a ratio of male/female participants of 26/34 were randomised to betamethasone valerate foam (0.1%) or betamethasone dipropionate lotion (0.05%).

The Tosti 2005 study was a within-patient right vs left design in which 34 participants (8 males and 26 females with an age range 27 to 53 years) were randomised to 0.05% clobetasol propionate or placebo foam to the right or left side of the scalp for 12 weeks. The foam was designed as an easy to apply non-greasy topical formulation.

Topical tacrolimus and Intralesional corticosteroids

We found no RCTs on either of these immunosuppressant therapies.

Systemic corticosteroids

There was one trial (Kar 2005) using systemic corticosteroids on participants with severe alopecia areata where 43 participants with an age range of 19 to 40 years were randomised to oral prednisolone (200 mg once weekly) or placebo tablets. The ratio of male/female participants was given for those who completed the trial and not for those randomised.

Systemic ciclosporin

We found no RCTs on the use of systemic ciclosporin.

Topical ciclosporin

There were three trials using topical ciclosporin on participants with severe alopecia areata (Nelson 1994 ; Rongioletti 1992 ; Tosti 1991). In a 3-arm parallel trial by Tosti 1991 26 participants with an age range of 16 to 48 years and male to female ratio of 15/11 were randomised to 10% ciclosporin (in an oily solution) versus psoralen plus UVA phototherapy (PUVA) versus thymopentin (50 mg/ml). In the Rongioletti 1992 trial, 85 participants with an age range of 16 to 62 years and male/female ratio of 38/47 were randomised to 10% ciclosporin A (in a gel) versus the gel alone. Nelson 1994 compared 100 mg/ml ciclosporin A in a liposomal (a vesicle used to transport the drug into the skin) vehicle versus the vehicle alone in a study with 17 participants: 8 males, 9 females with a mean age 37 years.

Photodynamic therapy (PDT)

In a within-patient trial on six participants with severe alopecia areata, 3 different concentrations of 5-aminolaevulinic acid (5%, 10%, 20%) or vehicle were applied to different sites on the scalp followed by exposure to red light (light with a wavelength of between 600-700nm) (Bissonnette 2000). The age range of the 3 males and 3 females was 36 to 64 years.

Topical immunotherapies

There were no RCTs found on the use of dinitrochlorobenzene, diphencyprone or anthralin (dithranol) to treat alopecia areata.

There was one parallel RCT (Pipoli 1995) using squaric acid dibutyl ester (SADBE) on 30 participants who were randomised to one of three groups treated with either SADBE applied at a concentration to maintain a mild eczema or lymphoblastoid interferon-alpha (IFN) or both. The median age of the participants was 28 years and the ratio of male/female was 14/16.

Hair Growth Stimulants

Topical minoxidil

There were five RCTs found on the use of minoxidil (a total of 110 participants) at different concentrations to stimulate hair growth. Of these, three were parallel studies (Khoury 1992 ; Price 1987a ; Price 1987b) and one was a within-patient study (Shapiro 1993). The remaining study was a cross-over study where the participants all had alopecia totalis and had undergone previously unsuccessful treatments with steroids and other therapies (White 1985).

Price 1987a used 3% minoxidil or vehicle (polypropylene glycol, ethanol and water) on 30 participants (7 males and 23 females) ranging in age from 9 to 65 years. Three percent minoxidil was also used in the cross-over study (White 1985) where the 15 participants (5 males and 10 females) with a median age of 40 years were randomised to 3% minoxidil or placebo solution and then crossed over to the alternate treatment.

The highest concentration of 5% minoxidil was used in the remaining three studies: Shapiro 1993 was a within-patient trial of 15 participants (6 males and 9 females) with an age range of 25 to 70 years and where the majority of participants had extensive patchy alopecia involving >50% hair loss. One side of the scalp was sensitised with diphenylcyclopropenone and then randomised to either 5% minoxidil or vehicle. The other side of the scalp received no treatment. In the Price 1987b study 5% minoxidil solution or placebo solution was randomised to 30 participants with an age range of 7 to 63 years. The Khoury 1992 study included four children aged 10 to 15 years amongst the 20 participants (9 males and 11 females with a age range of 10 to 54 years) randomised to 5% minoxidil or vehicle which was polypropylene glycol, alcohol and water.

Other therapies

We found no RCTs on the use of cryotherapy, aromatherapy or anti-viral agents.

Systemic immunomodulation

We found one cross-over study (Galbraith 1987) where 34 participants with alopecia totalis of at least one year's duration

were assigned randomly to inosiplex tablets (initially at a dose of 50mg/kg/day and reducing to 50mg/kg 3 days per week) or identical placebo tablets for 20 weeks, after which they were crossed over to the other intervention.

Psychosocial

On the premise that alopecia areata may be associated with stressful life events and therefore anxiety and depression, an RCT compared the efficacy of an antidepressant treatment, imipramine (Perini 1994). Imipramine (75 mg daily) or placebo pills were administered for 6 months to 13 participants (9 males and 4 females with a mean age of 33 years) who had been diagnosed with alopecia areata or alopecia universalis within the previous 6 months.

Prostaglandin analogues

A side effect of the use of the prostaglandin analogue F2α latanoprost, which is used to treat glaucoma, is excessive hair growth or hypertrichosis. To assess the usefulness of this observation, Ross 2005 conducted a within-patient trial on 11 adults (4 males and 7 females with an age range of 30 to 63 years) with severe eyebrow alopecia areata where one eyebrow was randomly assigned to receive topical latanoprost and the other eyebrow was the control.

Excluded studies

There were five RCTs which we excluded, details of which are in the Characteristics of excluded studies table. These were excluded because when we wrote to ask for the number of participants in each arm of their trial who obtained the outcome of >50% re-growth of the affected area (with normal hair) as a measure of moderate hair growth (as a reasonable, albeit imperfect proxy for clinically significant hair regrowth), as well as the number able to stop wearing a wig, the authors replied but were unable to give us any more information: (Berth-Jones 1991 ; Olsen 1992 ; Price 1987c ; Price 1999 ; Tosti 1986).

Ongoing studies

We identified four ongoing studies from trials registers (NCT00167102 ; NCT00187577 ; CSG 15 ; CSG 30). We hope to be able to assess these in a future update of this review when they have been completed.

Studies awaiting assessment

There are 11 studies which are awaiting assessment and are listed in Studies awaiting classification:
Two studies are from the LILACS database and we have been unable to obtain a copies of the papers by Maia 2003 and Ochoa 1993 .

Vali 2005 published a conference abstract of an RCT comparing the use of onion juice or placebo on participants with mild alopecia areata with <25% scalp involvement. The trial has not been published yet but from correspondence received the trial author reports that at 12 weeks 48.1% of the 60 participants in the onion juice group and 19.2% of the 76 participants in the placebo group had 50% hair regrowth. We await publication of this trial.

The immunomodulator bexarotene has been found to reverse alopecia in participants with cutaneous T-cell lymphoma. In order to assess this Duvic 2004 published a conference abstract of a within-patient RCT comparing topical bexarotene 1% topical gel on one half of the scalp. We await a reply to our request for further information about this study.

We are awaiting replies from six trial authors (Lee 1986 ; Fenton 1983 ; Pigatto 1987 ; Shi 1986 ; Swanson 1981 ; Vestey 1985 ; Vestey 1986) to whom we wrote to ask for the number of
participants in each arm of their trial who obtained the outcome of 50% scalp cover (with normal hair) as a measure of moderate hair growth (as a reasonable, if imperfect proxy for clinically significant hair regrowth), as well as the number able to stop wearing a wig.

lists all the authors we contacted for further information.

Risk of bias in included studies

Our assessment of the risk of bias in the included studies has broadly followed the criteria we set out in the protocol. However, we now consider that the criteria we laid down, specifically; 'aims, interventions and outcome measures clearly defined' and 'use of appropriateness of statistical analyses' do not fully define the quality of these studies. The 'degree of certainty that the participants have alopecia areata, totalis or universalis' was clearly defined in all the included studies. We think in general the quality of the studies was poor for the following reasons:

Randomisation

There were only four studies where the method of generation of the randomisation sequence was clearly stated: Mancuso 2003 and Tosti 2005 used a computer generated randomisation list by Arcus Quickstat, Nelson 1994 used a computer generated code and Kar 2005 used a random numbers table.

Allocation

The method of allocation concealment was considered unclear in all studies except Mancuso 2003 where a phone call centralised procedure was used for each eligible participant.

Blinding

In the majority of the studies blinding of the participants was generally clearly stated but the blinding of the clinicians or assessors was ambiguous. In four of the studies (Bissonnette 2000 ; Charuwichitratana 2000; Pipoli 1995 ; Tosti 1991) the reference to blinding of the participants, the clinicians and the assessors was not stated clearly.

Follow-up and exclusions

There were only two studies where intention-to-treat (ITT) analysis was stated. These were Mancuso 2003 and Tosti 2005 . Participants were analysed according to the intervention group to which they were initially randomised. In several of the studies we were able to extract data which allowed us to use ITT analysis.

Baseline assessment

In most of the studies some reference was made to the characteristics of the treatment and control groups. The majority of the trials involved participants with moderate to severe alopecia at baseline but generally there was a wide age range and disease duration e.g. Price 1987a . The participants in Charuwichitratana 2000 and Mancuso 2003 were assessed as having patchy or mild to moderate hair loss. Four studies had more females than males participating (Mancuso 2003 ; Price 1987a ; Tosti 2005 ; White 1985). In two studies the participants had the disease for longer in the treatment than in the control groups (Charuwichitratana 2000; Kar 2005) but in one study the placebo group had greater age and greater disease duration (Khoury 1992). Ross 2005 only treated those with alopecia of the eyebrows.

Effects of interventions

We did not find the outcome measures we had expected when we wrote the protocol. We had defined our primary outcome measures as the proportion of participants with clinically significant hair growth as rated by the participants or medical practitioners and improvement in quality of life as measured by questionnaires. In all of these studies the measure of hair growth was reported by the clinicians or assessors and not the participants even though in at least one study (Nelson 1994) there was a planned assessment of the global severity of hair loss by the participant and the clinician, but this did not appear to be reported. We did not find any quality of life measurements.

We defined clinically significant hair growth as >50% re-growth of the affected area.

The secondary outcome measures were adverse events either serious enough to require withdrawal of treatment or more minor participant reported effects which did not require withdrawal of treatment; long-term hair regrowth and its pattern and quality. We have described these below and have recorded them in the Characteristics of Included Studies.

The tertiary outcome measure was whether the interventions tested had an effect in preventing further episodes of hair loss. In the study by Price 1987a two of the participants continued using 3% minoxidil in an open-label extension to the study, one for two years and the other for four years. At the end of these time periods they both had 90% scalp coverage, and in the study by Bissonnette 2000 , three of the six participants elected to continue the treatment schedule but there was no report of the effect of this on their hair growth. In neither study did the trial authors indicate whether hair regrowth continued satisfactorily after the participants finished the treatment. We did not find any studies which evaluated whether the interventions could prevent further episodes of hair loss.

Immunosuppressant Therapies

The proportion of participants with clinically significant hair growth, as rated by the clinicians.

Short term assessment of outcome (less than six months)

Topical Corticosteroids:

Three RCTs involving 165 participants assessed the effect of topical corticosteroids on alopecia areata, which included one within-patient study (Tosti 2005). The parallel studies by Charuwichitratana 2000 and Mancuso 2003 could not be pooled due to different treatments being assessed in the studies. Therefore data are presented for individual studies.

Desoximetasone cream versus placebo

In the study by Charuwichitratana 2000 involving 70 participants, short term hair growth (12 weeks) was not significantly better in participants using desoximetasone as compared to those using placebo (RR 1.00, 95%CI 0.67,1.50; Analysis 1.1).

Betamethasone valerate foam versus betamethasone dipropionate lotion

In the Mancuso 2003 study at week 20 (short term), 23/31 of the group receiving betamethasone valerate foam (BVF) achieved a regrowth score of 3 or more compared with 9/30 in the group receiving betamethasone dipropionate lotion (BDL). A score of 3 related to 51 to 75% hair regrowth and a score of four to >75% hair regrowth. Thus, BVF was significantly more effective than BDL in treating mild to moderate alopecia areata, (RR 2.47; 95% CI 1.38, 4.44; Analysis 2.1

). There was no vehicle control in this study and some of the benefit may have been due to the vehicle rather than the active ingredient.

In a 12-week within-patient study by Tosti 2005 , 7/34 on the clobetasol propionate foam-treated sites had hair re-growth scores of >3 compared to 1/34 on the placebo treated sites. A re-growth score of three indicated hair re-growth of >50% on the treated sites. No formal statistical tests were performed in the original paper.

Systemic Corticosteroids:

One study (Kar 2005) involving 43 participants compared systemic corticosteroids with placebo tablets.

Oral prednisolone versus placebo

Oral prednisolone was administered as a weekly 'pulse' of treatment (Kar 2005). This was a short term study. The trial authors stated that ≥31% hair growth was 'a significant regrowth of hair' but this level of hair regrowth did not meet our outcome measure of clinically significant hair growth. However, 2 of the 23 participants on prednisolone had hair regrowth of >60% compared to none of those on placebo (RR 4.38; 95% CI 0.22, 86.08; Analysis 1.2). It is not clear if the two participants on prednisolone who had this substantial hair regrowth were the two who relapsed at three months.

Topical ciclosporin:

There were three studies involving 128 participants which compared topical ciclosporin to placebo (Nelson 1994 , Rongioletti 1992) or other therapies (Tosti 1991).

Ciclosporin A versus liposomal vehicle

The global severity of hair loss was measured in the 17 participants Nelson 1994 ; there was a slight increase in severity in the ciclosporin group and a decrease in severity in the vehicle group: no figures were given but this was reported as not significant in the original publication. However one participant in each group experienced good regrowth which has been taken to mean clinically significant hair growth, but this was not statistically significantly different between the intervention groups (RR 0.89; 95% CI 0.07, 12.00; Analysis 1.3). We classed this as a short term study as it was less than six months.

Photodynamic therapy (PDT):

Two RCTs involving 32 participants were included that assessed photodynamic therapy for treating alopecia areata (Bissonnette 2000 , Tosti 1991).

The Bissonnette 2000 study was a within-patient study on six participants for 10 weeks. Four circular sites on the scalp were randomly allocated to treatment with vehicle or three concentrations of topical aminolaevulinic acid lotion and then photodynamic therapy. Each site was assessed for the aggregated effect of treatment. The original paper reported there was no significant difference in hair growth compared to baseline for any of the three concentrations of aminolaevulinic acid or vehicle. All the participants completed the scheduled treatment sessions and three decided to continue beyond the period of the trial.

The three-armed study by Tosti 1991 (see above) compared photochemotherapy (PUVA) in eight participants with topical ciclosporin in eight participants. There was no cosmetically acceptable improvement seen in any of the participants.

Long-term assessment of outcome (six months or more)

Topical ciclosporin:

Ciclosporin A versus liposomal vehicle

In the Rongioletti 1992 trial, of the 85 participants randomised to ciclosporin A gel or placebo for six months, 6/42 on ciclosporin and 3/43 on placebo had complete regrowth of hair. This was not significantly different between the treatment groups (RR 2.05; 95% CI 0.55, 7.66; Analysis 3.1). We classed this as a long-term study.Twenty six participants who had been unresponsive to other therapies were allocated to ciclosporin or PUVA or thymopentin (Tosti 1991). There was no cosmetically acceptable improvement in hair growth in any of the groups after nine months of treatment.

Adverse effects

Desoximetasone cream (Charuwichitratana 2000) caused mild itching, transient burning and acneiform eruption in 3 participants; there was no report on why 16 participants did not complete the study. In the Mancuso 2003 study self - reporting of adverse reactions by the participants was employed throughout the study but the results of this were not formally documented. They reported that two participants in the BVF group and one participant in the BDL group experienced mild folliculitis (inflammation of the hair follicles). One participant of the BVF group and three participants of the BDL group discontinued their participation due to lack of efficacy of the treatments; it was not clear whether these were the participants who had experienced folliculitis. In the clobetasol propionate foam study (Tosti 2005) one participant experienced folliculitis. It is not clear if this was the reason for the withdrawal of one participant before week 12.

The only report of adverse effects was pilar keratosis (thickening or hyperkeratosis around the hair follicles) and extensive folliculitis in one participant in the Rongioletti 1992 study where there were 29 drop-outs with no explanation. In the Nelson 1994 study three participants were dropped from the study due to non-compliance: one from the topical ciclosporin group

and the other two from the placebo group. Although no side effects were reported the trial authors did find a slightly increased global hair loss in the intervention group. The Tosti 1991 study used several interventions and noticed the development of fibrotic tracts which replaced lost hair follicles; no mention was made of how many participants experienced this effect and whether it affected all three groups.

Photodynamic therapy was given after the topical application of 5-aminolaevulinic acid as a photosensitiser. This caused erythema, pigmentation and moderate burning in three participants in the Bissonnette 2000 study and minor erosions in two participants and pustules in another.

In the Kar 2005 study there were significantly more side effects in the prednisolone group (11/23) than in the placebo group (2/20) (RR 4.78; 95% CI 1.20, 19.05; Analysis 1.4) which manifested initially as a general weakness, then acneiform eruption, weight gain, gastrointestinal upset, moon-like facies and oligomenorrhea. None of these side effects were serious enough to stop the therapy. However seven participants withdrew for 'reasons unrelated to the study'.

Topical immunotherapies

The proportion of participants with clinically significant hair growth, as rated by the clinicians.

Long-term assessment of outcome (six months or more)

Combination immunotherapy versus squaric acid dibutyl ester or interferon

One study (Pipoli 1995) involving 30 participants was included which compared the effects of two immunomodulatory drugs and a combination of the two on hair growth.

Thirty participants with severe alopecia areata were randomly assigned to squaric acid dibutyl ester (SADBE), lymphoblastoid interferon (IFN) or a combination of both. Variable treatment durations were used for the participants which ranged from 12 to 32 weeks. The results were given at a time six months after discontinuation of the particular therapy: 5/10 in the combination group and 2/10 in the SADBE group and 2/10 in the IFN group achieved scores of two or three. A score of two meant full recovery with relapse within the six month period; a score of three was a full and stable recovery with no relapse within a six month period. Results are presented as the combination treatment group versus the two single treatments. The long-term effect on hair growth was more successful with the combination therapy than the individual therapies but the effect was not significant. (RR 2.5; 95% CI 0.63, 10.0; Analysis 4.1).

Adverse Effects

No participants dropped out of this study due to ill effects. Those on interferon experienced 'flu-like symptoms which resolved after a few doses. The participants allocated to SADBE were monitored so that the erythema and mild pruritus that is necessary for this treatment was not allowed to develop into a severe exudative reaction.

Hair Growth Stimulants

The proportion of participants with clinically significant hair growth, as rated by the clinicians.

Short term assessment of outcome (less than six months)

Topical minoxidil:

Five RCTs involving 110 participants were included that compared minoxidil with placebo (Khoury 1992 ; Price 1987a ; Price 1987b ; Shapiro 1993 ; White 1985). Topical minoxidil had little effect on hair growth, especially in the studies under 6 months (Shapiro 1993 ; Khoury 1992 ; Price 1987b ; White 1985).

In the within-patient study by Shapiro 1993 , there were 5 'responders', which was defined as more than 75% hair re-growth. Two of the six participants whose scalps had been allocated to 5% minoxidil after DPCP sensitisation and three of the participants whose scalps had received vehicle only after DPCP sensitisation were responders. However there was no information provided about which group the two participants who withdrew were originally allocated, so we could not include this study in the meta-analysis.

The cross-over study by White 1985 had no wash-out period between phases, so only the data from the first 16 weeks was used. No participant achieved grade four which was 'moderate growth of terminal hair'.

The studies by Khoury 1992 and Price 1987b had outcomes that we interpreted as 50% scalp coverage and were sufficiently similar to pool (RR 0.96; 95% CI 0.44, 2.12; Analysis 5.1), however no significant difference in hair growth was seen between the groups receiving the intervention or the vehicle.

Long-term assessment of outcome (six months or more)

Topical minoxidil:

The study by Price 1987a was the only study where topical minoxidil was applied for greater than six months. The effect on hair growth was not significantly different between the two groups (RR 3.00; 95% CI 0.35, 25.68; Analysis 5.2).

Adverse Effects

In one study where minoxidil was used no report of adverse effects was given (Khoury 1992) but in the others skin irritation and hair growth at sites distant to the area of application, such as ankles and toes, were the main side effects (White 1985 ; Price 1987a ; Shapiro 1993). The skin irritation was sufficiently severe to cause two participants each to drop out of the studies by Price 1987a and Shapiro 1993 .

Other therapies

The proportion of participants with clinically significant hair growth, as rated by the clinicians.

Long-term assessment of outcome (six months or more)

Systemic immunomodulation

There was one cross-over trial (Galbraith 1987) in which the participants were treated with inosiplex tablets or placebo tablets. Twenty-five of the 34 participants randomised completed the full 40 weeks of the trial. Of these 11 had re-growth of terminal hair but none had clinically significant hair re-growth (personal communication with trial authors).

Psychosocial

There was one RCT (Perini 1994) that compared the antidepressant, imipramine with placebo to determine the effect on alopecia areata.

None of the participants in the active or control groups had any clinically significant hair growth at three months. After six months 1/7 in the treatment group and 0/6 in the placebo group had a re-growth rating of three which was defined as 'complete recovery' although this was not defined in terms of scalp coverage and was not statistically significantly different between the intervention groups (RR 2.63; 95% CI 0.13,54.64; Analysis 6.1).

Prostaglandin analogue

There was one within-patient study (Ross 2005) that compared latanoprost with no treatment. Of the 11 participants that enrolled to have topical latanoprost applied to 1 eyebrow for 12 hours per day for 12 weeks, 8 completed the study. One participant had eyebrow growth but in both eyebrows and this was probably due to concomitant prednisone therapy for another problem so the results are not evaluable.

Adverse Effects

No clinically significant adverse reactions to the immunomodulator, inosiplex were encountered. Participants experienced nausea, headache, drowsiness and dry skin but this was in both the drug and placebo phases of the trial.

The trial authors commented that the antidepressant, imipramine was well tolerated and participants reported few adverse events, but they did not state what these were.

Side effects of the prostaglandin analogue latanoprost, were assessed by a non-blinded investigator and the participant. One participant withdrew due to eyelid droop and transient pruritus. Two other participants experienced pruritus (itching) and slight erythema (redness).

DISCUSSION

Discussion

Summary of main results

The overall efficacy of the treatments identified in the review which included immunosuppressant therapies, topical immunotherapies and hair growth stimulants was poor for the pre-specified outcome of clinically significant hair re-growth. Only one study showed a statistically significant effect of the treatment intervention but this compared two different treatments (Mancuso 2003) and the participants only had a mild patchy form of alopecia. Care has to be exercised in not concluding that none of the treatments work when so many of the studies were so small. As indicated by the wide 95% confidence intervals for many of the included study results, many interventions could still prove to have a clinically useful benefit if they were evaluated in an adequately powered study.

Most of the studies were of short-term (less than six months) duration and reported only short-term outcomes. However, where studies reported longer-term outcomes (more than six months), long-term sustainability of the effects of interventions was poor in terms of continued hair growth. This is not completely unexpected because people with alopecia areata have an ongoing predisposition to the disease and the condition tends to be chronic and relapsing. Current treatments are essentially immunosuppressive and do not permanently change the immune system or the genetic predisposition of the individual or any of the potential environmental triggers. Therefore, even if a treatment worked in the first place, it is expected that the disease may relapse when the treatment is stopped. Similarly, long-term cure is unlikely. Perhaps it would be useful in future studies to assess whether;

(i) a treatment is successful while in use
(ii) there is any long-term benefit which persists after the course of treatment has finished.

We regret that we identified several studies which we felt unable to include because we could not discern whether the outcome was clinically significant hair re-growth. If we receive clarification from the trial authors we shall include them in the update to this review.

In our view one true measure of a successful treatment for the person with alopecia areata would be if they reported satisfaction with their hair re-growth for a sustained period of time. Participants undertaking treatment are likely to view the best outcome as sustained hair re-growth and if applicable to stop wearing a wig or to be able to report satisfaction with their appearance. For people with severe sustained hair loss as in alopecia totalis or alopecia universalis, successful treatment outcomes are more difficult for researchers to achieve. However, people may still feel unable to stop wearing a wig despite achieving 'significant hair growth' (Vestey 1986). None of the participants in any of the studies achieved these participant-orientated, clinically meaningful outcomes.

The lack of success of treatment for participants with alopecia areata relates to the severity and duration of the disease (van der Steen 1991). For those in the early stages of the disease or with less than 25% scalp hair loss alopecia areata has a high degree of natural resolution. Mancuso 2003 readily conceded the success of their study comparing two active treatments and no placebo group may be due in some part to the natural history of the disease.

By contrast, participants with long-standing alopecia areata, or those with alopecia totalis/universalis, are less likely to respond to treatment. Data suggest that fewer than 10% of people with severe disease fully recover (MacDonald Hull 2003). Tosti 1991 set out to test whether those participants with alopecia areata who had not responded to other sensitising therapies would respond when randomly allocated to a variety of other treatments. They concluded that transferring these 'non-responder' participants to other therapies was 'useless'.

Most studies included a heterogenous participant population with wide disease severity and duration. Only one study assessed participants with patchy alopecia areata alone (Charuwichitratana 2000) but did not define 'patchy', whilst only Mancuso 2003 assessed participants with <26% hair loss.

Overall completeness and applicability of evidence

Overall, considerable numbers of participants withdrew or were lost to follow up. In some studies no reason was given for this (e.g. Kar 2005), but in others it is clear that participants were disheartened by the lack of efficacy (Mancuso 2003). In others the time commitment expected of the participants was considerable in terms of application of treatments and clinic visits (Nelson 1994) and may have lead to drop-outs or non-compliance. Tosti 1991 expressed concern about the poor skin penetration and therefore lack of efficacy of the drug that they were using in their trial.

Quality of the evidence

Alopecia areata has considerable likelihood of natural remission especially in the early stages of the disease (Madani 2000): this complicates interpretation of a successful response to treatment particularly where numbers of participants in each arm of the trial are so low. Where participants have alopecia areata that involves less than 25% hair loss from the scalp or where they have had the disease for less than a year, up to 50% of successful re-growth may be spontaneous (Mancuso 2003).

Other situations where interpretation of the results may be complicated are where topical treatments for hair growth may have systemic effects, which is especially relevant in within-patient trials. In the Bissonnette 2000 study, hair growth occurred beyond the treatment areas of the scalp. Hair growth may also occur at distant sites e.g. hair growth on face (Price 1987b) or toes (White 1985).

In contrast, other treatments such as topical ciclosporin appeared to be ineffective due to lack of drug penetration (Nelson 1994 ; Rongioletti 1992 ; Tosti 1991), it is not clear whether ciclosporin might be of benefit if the drug could be adequately absorbed into the scalp. There are no RCTs which assess systemic use of ciclosporin in treating alopecia areata.

Potential biases in the review process

The difficulties in determining actual hair growth in clinically significant terms in these studies was due to a lack of any universal measure of successful hair growth. Ideally we were looking for hair growth that was cosmetically acceptable to the participant, but we found no reports of participant evaluation of the treatments. After assessing several of the studies we defined >50% re-growth of the affected area as a measure of clinically significant hair growth. However it was not always possible to extract this information from the studies. Olsen 2004 has tried to address the issue of defining and standardising measurement of hair loss so that results from studies might be more comparable.

Some readers might think that our exclusion of non-randomised controlled studies was a bit harsh, especially for studies of topical diphencyprone where some reports of half scalp application produces a clear half head of hair growth (Monk 1989). Whilst we acknowledge that randomised controlled trials are sometimes not needed for treatments which may have a dramatic and persistent effect (Glasziou 2007), the evidence from trials of topical immunotherapy (including diphencyprone) suggests that response rates vary a lot from dramatic improvement to no regrowth at all. Egger 2003 showed that studies with more positive effects are more likely to be published than those with less conclusive results, or those written in languages other than English. To tackle the problem of publication bias we wrote to authors asking for information, we searched databases of ongoing trials, and we searched the LILACS (Latin American and Carribean Health Science Information) database. Selective reporting of dramatic effects from non-randomised trials without any control group

is likely to be very misleading therefore, and randomised controlled trials are needed to explore short and long-term effects across a group of participants of defined disease severity and duration.

Agreements and disagreements with other studies or reviews

Alopecia areata is a chronic hair loss disease in which it is very difficult to predict whether there will be periods of spontaneous remission or whether the pattern of hair loss will get progressively more severe. The results of our review are in agreement with the comments of Epstein 2001 . There is such a lack of consistent response to the therapies that are available, that the Federal Drugs Administration (USA) does not have an approved list for this disease (Olsen 2004).

It is a condition that can cause psychosocial problems and more severe psychological effects on some individuals (Schmidt 2001 , Firooz 2005). We agree with the conclusions of MacDonald Hull 2003 that considering the possibility of spontaneous remission and lack of efficacy of treatments the option of not treating with medications may be the best one for many participants. This discussion about choosing no therapy for alopecia areata has been ongoing for some time (Hutchinson 1987).

MacDonald Hull 2003 recommends intralesional corticosteroids for patchy hair loss: we found no evidence to support this because randomised trials have not been performed. We also found little evidence to support the use of contact immunotherapy for more extensive hair loss, and although diphencyprone is frequently used for severe alopecia areata we could find no RCTs, fulfilling our inclusion criteria, assessing its use.

AUTHORS' CONCLUSIONS

Implications for practice

Few treatments for alopecia areata have been well evaluated in randomised trials: there is no RCT evidence that steroids, whether topical, intralesional or systemic, are of benefit in treating alopecia areata. Systemic steroids have the potential to produce serious side effects. Similarly, there is insufficient evidence on use of topical minoxidil, topical ciclosporin, PDT, hair growth stimulants, or other immunotherapies for the treatment of alopecia areata.

Before starting treatment for alopecia areata, and especially in the early stages of the disease people should be informed of its natural history and the possibility of spontaneous remission and the lack of evidence for different treatments. We found no RCTs on the use of diphencyprone to treat alopecia areata, but it is frequently used and recommended for the treatment of extensive alopecia areata and alopecia totalis/universalis (MacDonald Hull 2003). Similarly although topical steroids and minoxidil are widely prescribed by dermatologists for limited patchy alopecia areata, and appear to be safe, there is no convincing evidence that they are beneficial. MacDonald Hull 2003 concluded that there was poor evidence to support the use of topical steroids and topical minoxidil.

It is clinically challenging when a patient with alopecia areata is desperately seeking treatment, to tell them that the evidence suggests that current treatment confers no long-term benefit. Considering the possibility of spontaneous remission and lack of efficacy of treatments, the option of not treating may be the best option for many patients. For some participants with extensive alopecia areata, wearing a wig might be a reasonable option. Healthcare practitioners can still play an important role in providing psycho-social support and information, and self help groups both online and face-to-face can be beneficial for some people.

Implications for research

Few treatments for alopecia areata have been well evaluated in randomised trials and we found none that addressed participant-focussed measures of success or measurements of quality of life. Addressing these deficiencies by means of high quality clinical trials has to be a priority and main conclusion from our review.

Future studies need to be much bigger than the current largely inconclusive small studies performed to date, and they should ideally include a placebo or vehicle group given the current uncertainty around whether any treatment works. In order that studies can be comparable there needs to be a clear definition of baseline measures of hair loss as well as success in terms of measuring scalp coverage, measurement of sustained hair re-growth and participant satisfaction. Future research should incorporate outcome measures that are clinically meaningful to participants.

Future trials should be designed to recruit participants who are clinically homogeneous, for example of similar disease severity or duration, or both, so that clinically meaningful outcomes can be used to better direct clinical practice. Similarly, because short-term interventions may not 'cure' alopecia areata or result in long-term benefit, trials should focus on assessing safe and sustainable treatments.

There have been no trials involving the use of good quality wigs or alternative supportive therapies versus pharmaceutical interventions for alopecia areata. Such trials using patient satisfaction outcomes would be invaluable. There seems little point in doing more trials on topical ciclosporin and topical minoxidil. Long-term use of topical corticosteroids, topical tacrolimus and topical immunotherapy with diphencyprone are possible future trial priorities.

Although there are 'new' topical immunomodulating drugs and biologic therapies for the treatment of other immune-mediated inflammatory skin diseases (Price 2003 ; McMichael 2003), evidence from randomised controlled trials is needed to support their effectiveness in alopecia areata. However, reports of alopecia areata occurring during treatment with biologic agents (Tosti 2006 ; Garcia Bartels 2006) suggest that their utility will be limited.

If more high quality RCTs were to be conducted comparing the variety of possible interventions for alopecia areata, there might be consensus about which treatment would be most effective at different stages of patchy hair loss and disease severity. A pseudo (non)- randomised study of aromatherapy showed promise but this warrants further study in RCTs (Hay 1998)

A C K N O W L E D G E M E N T S

Acknowledgements

The editorial base would like to thank the the external peer referees Hugh Rushton, David de Berker and Shirley Manknell

R E V I E W _ C H A R A C T E R I S T I C S _ O F _ S T U D I E S

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Bissonnette 2000

Methods	A within-patient study	
Participants	Incl: Extensive AA baseline scalp hair loss 76 to 100% Excl: n/s Set: Hospital, Vancouver, Canada Age: 36 to 64 yrs Randomised: 6 m/f: 3/3 Evaluable: 6 Duration of condition: 4-35 yrs	
Interventions	a: 5% ALA (5-aminolaevulinic acid) b: 10% ALA c: 20% ALA d: hydroalcoholic vehicle only Freq: x2 weekly for 10 weeks Applicns: 200ul of each soln applied to 4x3cm sites on the scalp then scalp covered with Tegaderm and hat for 3 hrs until scalp exposed to red light	
Outcomes	1. Clinical Outcomes: clinically significant hair growth which was graded from 0 to 5. 0=no hair loss, 1</=25% hair loss, 2= 26-50%, 3=51-75%, 4= 76-99%, 5=100% (total hair loss) 2. Adverse outcomes: erythema, mild to moderate burning sensation during light exposure in 3 Px. Minor erosions (2 Px), pustules (1 Px) - were sometimes noted on the treated sites	
Notes	Sp: Grants from National Alopecia Areata Foundation and DUSA pharamaceuticals	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear. No third party mentioned for preparation of solutions
Blinding? All outcomes	Unclear	Says double blind. Interpreted as Px, clinicians but not assessors
Randomisation?	Yes	Table of random numbers.Patches randomly allocated to receive interventions.
Intention-to-		

treat/Drop-outs?	No	0 out of 6

Charuwichitratana

Methods	Parallel group randomised study	
Participants	Incl: Patchy AA Excl: <15yrs of age and pregnant females. No Tx for 1 mth prior to study Set: Hospital outpatients, Thailand Age: 15 to 61(34) yrs Randomised: 70 m/f: n/s Evaluable: 54 Duration of condition: 0.14 to 104 weeks Baseline Comparison: Tx group had AA for up to 2 years. Placebo group had AA for up to 1 year.	
Interventions	a: 0.25% desoximetasone cream b: Placebo Freq: BD for 12 weeks Applicn: to the head -not sure of the quantity of cream applied.	
Outcomes	1. Clinical outcomes: complete hair growth was defined as 100% growth; partial hair growth as 75-100% good; 50-74% moderate; 25-49% mild; 0-24% no improvement 3. Adverse outcomes: mild itching, transient burning and acneiform eruption in 3 Px treated with desoximetasone	
Notes	Sp: n/s Sample size calculations done. It is not clear if the range given for duration is for the disease or the current episode of the disease	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	It states 'double blind' in the Abstract but unsure to whom this refers,probably the Px and clinician.
Randomisation?	Unclear	Px were 'assigned randomly'
Intention-to-treat/Drop-outs?	No	16 out of 70

Galbraith 1987

Methods	Randomized placebo controlled trial, crossover study
Participants	Incl: 34 Px with AT of at leasy one year and with documented evidence of cell-mediated immune disfunction. Excl: n/s Set: USA Age: 18 to 44years Randomised: 34 m/f: 17/17 Evaluable: 25 Durn: at least 1 yr
	a: 500mg tablets containing inosiplex: inosine 3:1 (n=34)

Interventions	b: identical tablets containing avicel, lactose and stearic acid (n-34) Freqy: Inosiplex tablets given as 50mg/kg/day up to 5gm/day for wks 0 to 2 and 9-20. Dose redn to 50mg/kg/day for 3 days per wk for wks 3 to 8
Outcomes	Terminal growth of scalp hair to >1cm Terminal growth of terminal body hair, brows and lashes.
Notes	Sp: Grant from Newport Pharmaceuticals International Non-compliance in 7 Px Personal communication: none of the Px achieved clinically meaningful re-growth of hair

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Px -yes; clinicians-yes; assessors-unsure.
Randomisation?	Yes	random sequence held by the sponsor who held the code until all Px had completed the trial
Intention-to-treat/Drop-outs?	No	7 out of 34

Kar 2005

Methods	Parallel group randomised study
Participants	Incl: Severe AA with >40% hair loss or >10 patches over scalp & body Excl: Diabetes, thyroid disorders, peptic ulcers, hypertension, cardiac failure, active infection, nephropathy, alopecia universalis, steroid use within the last three mths and those pregnant Set: Dermatology Dept, Chandigarh, India Age: Group A 26.3yrs; Group B 30.2 years (these mean ages from Table 1 relate only to final patients evaluable) Randomised: 43 m/f: 26/10 (these from Table 1 relate only to final patients evaluable) Evaluable: 36 Duration of condition: 0.8 to 4.37yrs (these from Table 1 relate only to final patients evaluable) Baseline Comparison:it was the first episode of disease for 6 in the Tx group and 3 in the placebo group
Interventions	a: Oral prednisolone tablets (n= 23) b: Placebo tablets (n=20) Freq: x1 wkly for 3 mths Applicns: 5x40mg tablets
Outcomes	1. Clinical outcomes: hair re-growth at three mths. >60% classed as marked; 31 to 60% classed as moderate; <30% classed as poor Follow up three mths later 2. Adverse outcomes: general weakness for 1 to 2 days after the start of therapy. Also acneiform eruption, weight gain, gastrointestinal upset, facial mooning and oligomenorhea
Notes	Sp:None Withdrawals: seven for 'reasons unrelated to the study' which may introduce bias because these excluded Px may be systematically different to the other remaining Px. Comment: More with first episode AA in active group (6 vs3); these are more likely to respond/improve This paper was reviewed by one of the authors- M Sladden, P Hutchinson. Is oral

	pulsed prednisolone useful in alopecia areata: critical appraisal of a randomised trial? J Am Acad Dermatol 2005; 53: 1100-1
Risk of bias	

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Px- yes; clinicans and assessors - unsure
Randomisation?	Yes	random number table
Intention-to-treat/Drop-outs?	No	7 out of 43

Khoury 1992

Methods	Parallel group randomised study
Participants	Incl: Diagnosis of AA. involving hair loss on 26 to 99% of scalp. Biopsies taken at baseline. Excl: Previous receipt of minoxidil or any topical or systemic Tx in the previous three mths. Set: USA hospital department . Age: 10 to 54 yrs (4 children included aged10,11,13 & 15 yrs) Randomised: 20 m/f: 9/11 Evaluable: 20 Duration of condition: 0.1 to 42 yrs Baseline comparison: placeb group had a greater range of age/disease duration
Interventions	a: 5% minoxidil in polypropylene glycol, alcohol & water. (n=9; m/f 5/4 age range 13 to 48yrs; duration 1 to 24yrs) b: Vehicle alone (n=11; m/f 4/7; age range 10 to 54yrs; duration 0.1 to 42 yrs) Freq: 1 ml BD for 12 weeks Applicns: Topical solution applied without occlusion
Outcomes	1. Clinical outcomes: cosmetically acceptable hair re-growth was defined as hair loss not greater than 25%. Hair loss was determined by dividing the scalp into 4 & categorising hair loss as 0 to 25%; 26 to 50%; 51 to 75%; 76 to 99% or 100%. 2. Adverse outcomes: none reported
Notes	Sp: Grant from The Upjohn Company ITT: n/s Short term study 12 weeks
Risk of bias	

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Px Y; clinicians Y; outcome assessors Y (for biopsies).
Randomisation?	Unclear	Px were 'randomly assigned'

Intention-to-treat/Drop-outs?	Yes	0 out of 20

Mancuso 2003

Methods	Parallel group randomised study	
Participants	Incl:Mild to moderate AA with <26% hair loss all >18yrs age Excl: >26% hair loss, previous steroid treatment for AA in last 4 weeks, history of steroid allergy, pregnant or lactating women Set: Unsure, Italy Age: 41 (+/- 13) yrs Randomised: 61 m/f: 26/35 Evaluable: 61 Duration of condition: n/s Baseline comparison: more females than males	
Interventions	a: 0.1% betamethasone valerate in a foam (n=31) b: 0.05% betamethasone dipropionate as a lotion (n=30) Freq: BD for 12 wks Applicns: to the affected areas but the quantity used was not stated	
Outcomes	1. Clinical outcomes: comparison of hair re-growth rate. Scale ranging from 0 (re-growth <10%) to 4 (re-growth > 75%) known as the RGS (re-growth score) 2. Adverse outcomes: safety and tolerability were assessed by self-reported adverse reactions at each visit : mild folliculitis in three Px	
Notes	Sp: Unsure probably by MiPharm, Italy ITT: Y . LOCF (last observation carried forward method). A power calculation done to ensure adequacy of sample size. Withdrawals: Although none were lost to follow-up, 4 due to lack of efficacy	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate. Phone call centralized procedure
Blinding? All outcomes	Yes	Px -no; clinicians -yes; Assessors -yes
Randomisation?	Yes	Computer generated randomisation list (Arcus Quickstat)
Intention-to-treat/Drop-outs?	Yes	0 out of 61

Nelson 1994

Methods	Parallel group randomised study
Participants	Incl: Clinical diagnosis of AA with >/= 6 months refractory to other therapies. Px must have discontinued all other medications for AA 4 weeks prior to study entry Excl: n/s Set: Dermatology Dept, USA Age: 22 to 61 years (mean 37 years) Duration of condition: > 6 months Randomised: 17 m/f: 8/9 Evaluable: 14 Baseline comparison: only the mean age given for the 2 groups

Interventions	a: 100mg/ml of a topical solution of ciclosporin A in a liposomal vehicle b: the liposomal vehicle alone Freq: Twice daily for four months Applicns: 0.5ml to a 1cm2 patch marked with ink
Outcomes	1. Clinical outcomes: Px and clinician assessment of global severity of hair loss on a 4 point scale: 0=mild,1=mild to moderate; 2= moderate; 3=moderate to mild; 4= severe alopecia. 2. Adverse outcomes: topical cyclosporin applied to avoid side effects associated with systemic admin - but no side effects reported
Notes	Sp: This was a physician-sponsored investigation approved by the University of Michigan Medical Center Institutional review Board and the Food & Drug Administration. Sandimmune, Sandoz Pharmaceuticals Hanover, New Jersey, USA prepared the ciclosporin A preparation. Withdrawn: three due to non-compliance

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Px-no; clinicians - unsure; assessors-unsure.
Randomisation?	Yes	computer generated code
Intention-to-treat/Drop-outs?	No	3 out of 17

Perini 1994

Methods	D: Parallel group randomised study
Participants	Incl: 6 had AA; 7 had AU of < 6mths duration Excl: > 6mths alopecia Set: Dermatology Clinic, University Hospital, Italy Age: 20 to 55 (33) yrs Randomised: 13 m/f: 9/4 Evaluable: 13 Duration of condition: less than six mths Baseline comparison: All had disease for <6months. The Tx and placebo groups did not differ in sociodemographic variables except sex as all in the placebo group were males.
Interventions	a: Imipramine tablets (n=7) b: Placebo tablets identical (n=6) Freq: OD for six mths Applicns: 75mg imipramine dose
Outcomes	1. Clinical outcomes: hair growth at 3 & 6 mths. Assessed by a 4-step scale: 0=no growth; 1=vellus; 2=terminal; 3=complete 2. Adverse outcomes: they state that the treatment was well tolerated and the Px reported few adverse events
Notes	Sp: Ciba-Geigy for supplying imipramine & placebo tablets Comment: unequal distribution of the sexes The outcome scale two does not indicate how much terminal growth and three does not define 'complete'

Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Px-Yes; clinicians-unsure; assessors - yes
Intention-to-treat/Drop-outs?	No	0 out of 13

Pipoli 1995

Methods	Parallel group randomised study	
Participants	Incl: severe AA of the scalp with >/= 70% hair loss (AA=13, AT=17) Excl: Those with serious illness or with AA <3yrs or ophiasic pattern Set: Dermatology Dept, University, Italy Age: 18 to 60yrs (median 28) Randomised: 30 Evaluable: 30 Duration of condition: 3.1 to 7.8 yrs Baseline comparison: similar scalp involvement	
Interventions	a: Topical immunotherapy (TI) with Squaric acid dibutylester (SADBE) (n=10) b: Lymphoblastoid interferon alpha (IFN) (n=10) c: IT and IFN Freq & Applicn: a:SADBE was prepd in acetone at 7 doubling dilns from 2%. Initially 1ml of the soln was applied to a bald area and left for 48 hrs. Then wkly the min conc was applied to a wider area to maintain a mild eczema. Admin for at least 12 wks for a max of 32 wks b: Intramuscular injections of 3x10-6 IU were given OD for 15 days thenx3 wkly for 2 wks then x1 wkly for 2 mths c: Px were given both. No information about how the applications were combined	
Outcomes	1. Clinical outcomes: at six mths after completion of therapy the results were categorised. Scoring system: 0=no disease progression; 1=partial recovery, not cosmetically acceptable; 2= full recovery with relapse within six mths; 3=full & stable recovery with a six mth relapse-free period. It does not clearly define 'full recovery' in terms of hair growth but it is implied that it is cosmetically acceptable. 2. Adverse outcomes: those treated with interferon had mild flu symptoms, myalgia & headache after the initial few doses. Those with SADBE had mild erythema, mild scaling and pruritis.	
Notes	Sp: unsure	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	No mention of blinding
Randomisation?	Unclear	randomly assigned but to three equal sized groups

Intention-to-treat/Drop-outs?	No	0 out of 30

Price 1987a

Methods	Parallel group randomised study	
Participants	Incl: AA, AT or AU with > 50% hair loss Excl: < 50% hair loss, cardiovascular disease, hypertension, severe systemic illness. Set: USA hospital, outpatient dept. Age: 9 to 65 yrs Randomised: 30 m/f: 7/23 Evaluable: 25 Duration of condition: 2 mths to 12 yrs Baseline comparison: more females than males. Wide age range and disease duration range for both groups.	
Interventions	a: 3% minoxidil in a vehicle of propylene glycol, ethanol and water (n=15) b: Vehicle only (n=15) Freq: 1ml. BD for one year Applicn: to affected area of half scalp with petrolatum occlusion overnight.	
Outcomes	1. Clinical outcomes: at the end of the study hair growth was assessed as none, partial and cosmetically acceptable. 2. Adverse outcomes: Itchy scalp rash	
Notes	Withdrawn: three failed to attend after the initial visit. 2- adverse effects Specific details about child Px not included in report Study for one year therefore long term	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Px-yes; clinicians -yes;outcome assessor N.
Randomisation?	Unclear	randomly assigned but the numbers correspond to medication numbers
Intention-to-treat/Drop-outs?	No	5 out of 30

Price 1987b

Methods	Parallel group randomised study
Participants	Incl: AA affecting 25 to 100% scalp Excl: anyone who had previously been enrolled in a minoxidil study. Also those with hypertension, cardiovascular disease or severe systemic illness Set: Medical Center, USA Age: 7 to 63 yrs Randomised: 30 m/f: n/s Evaluable: 29 Duration of condition: not stated Baseline comparison: more of the Px in the minoxidil group had 100% hair loss at

	baseline.
Interventions	a: 5% topical minoxidil soln b: Placebo soln Freq: 1ml soln applied approx every 12 hrs Applicns: Soln applied to scalp
Outcomes	1. Clinical outcomes: hair growth was assessed as 1.none 2.slight 3. incomplete 4. cosmetically acceptable 2. Adverse effects: Px questioned about itching, stinging, burning and scalp inflammation and folliculitis- abnormal facial hair.
Notes	Study for 12 weeks. After 12 wks all Px received 5% minoxidil

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Px-yes; clinicians - yes; assessors-no.
Randomisation?	Unclear	not stated
Intention-to-treat/Drop-outs?	No	1 out of 30

Rongioletti 1992

Methods	Parallel group randomised study
Participants	Incl: All AA: AU=40 and AT=19 Excl: All Tx stopped three mths prior to start of trial Set: Dermatology Department, Italy Age: 16 to 62 yrs Randomised: 85 m/f: 38/47 Evaluable: 56 Duration of condition: 8mths to 42 yrs (mean= 9.7yrs) Baseline comparison: no details other than all Px in good health wiht no history of atopy.
Interventions	a: 10% ciclosporin A in a gel (olive oil 10%, ethanol 10%, other vehicles 70%) (n=42) b: placebo -only the gel (n= 43) Freq: once a day for six mths Applicns: two cm (equivalent to 42 mg ciclosporin A) to the alopecic patch
Outcomes	1.Clinical outcomes: no re-growth, re-growth of no cosmetic value and full re-growth which was also referred to as complete hair re-growth 2. Adverse outcomes: pilar keratosis and extensive folliculitis
Notes	The authors thought the lack of detectable blood levels of the drug suggested poor transcutaneous absorption.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Px -yes; observer (probably the clinician) - yes

Randomisation?	Unclear	not stated
Intention-to-treat/Drop-outs?	No	29 out of 85

Ross 2005

Methods	Within-patient randomised study: right-left eyebrow study	
Participants	Incl: All severe eyebrow AA Excl: No drugs for 10 weeks prior to RCT. Topical Tx to non-eyebrow areas allowed Set: Dermatology and Laser Centre, USA Age: 30 to 63 years Randomised: 11 m/f: 4/7 Evaluable: 8 Duration of condition: 3 months to 20 years	
Interventions	a: 3ug topical latanoprost b: not sure but does mention vehicle Freq: 12 hours daily for 12 weeks Applicns: no details given	
Outcomes	1. Clinical outcomes: eyebrow growth rated as negative (0 to 75% coverage) or positive (76 to 100% coverge) 2. Adverse outcomes: eyelid droop, transient pruritis and slight erythema	
Notes	Sp: Pfizer 3 withdrew	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Px-unsure; clinician-yes; assessor -unsure.
Randomisation?	Unclear	not stated
Intention-to-treat/Drop-outs?	No	3 out of 11

Shapiro 1993

Methods	Within-patient randomised study: right-left scalp study
Participants	Incl: AA for more than two years affecting > 50% scalp Excl: hypertension, cardiovascular disease or serious medical illness Set: hair clinic, Canada Age: 25 to 70 years Randomised: 15 m/f: 6/9 Evaluable: 13 Duration of condition: 2 to 55 years (mean 12 years)
Interventions	a: four cm circle of Tx side of scalp sensitised with 2% Diphenylcyclopropenone (DPCP). Then 24 weeks of inc concs DPCP until inflammation. Also 0.5ml 5% minoxidil or vehicle applied to the same area of scalp that received DPCP. Topical fluocinonide (0.05%) given if reaction was severe b: unclear any Tx given to the control side of head. Freq: DPCP applied once weekly and minoxidil or vehicle applied x2 daily

	Applicns: see a and b
Outcomes	1. Clinical outcomes: responders classed as showing >75% terminal hair growth on treated side. 2. Adverse outcomes: localized adenopathy in all Px, severe generalised dermatitis.
Notes	Study for 24 weeks therefore defined as short term

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Px-yes; clinicians-yes; assessors - unclear
Intention-to-treat/Drop-outs?	No	2 out of 15

Tosti 1991

Methods	Parallel group randomised study
Participants	Incl: severe AT or AU. All unresponsive to one yr of sensitising therapies Excl: those who showed any reponse to sensitising therapies Set: Dermatology Dept, Hospital, Italy Age: 16 to 48yrs and no Tx for six mths Randomised: 26 m/f: 15/11 Evaluable: 26 Duration of condition: not stated but all with 100% hair loss Baseline comparison: The three groups were fairly well matched on sex and age range
Interventions	a: 10% ciclosporin in an oily soln (n=8) Freqy & Applcn: 2ml applied to the scalp daily for 9 mths b: Photochemotherapy PUVA (n=8) Freq & Applicn: x3 per week for 9 mths c: 50mg/ml Thymopentin in saline. (n=10) Freqy & Applicns: The 1ml vial was dild to 10 ml and injected IV in 10 mins. x3 per week for 3weeks, every 3 mths for 9 mths (-so 3wks Tx then 2mths and 1 wk rest)
Outcomes	1. Clinical outcomes: cosmetic clinical improvement determined by examination of re-growth of terminal. Scalp biopsy from 10/26 Px 2.Adverse outcomes: fibrotic tracts
Notes	Sp: unsure The authors set out to test whether those with 100% hair loss & with a history of poor response to treatment were likely to respond to different Tx

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	not stated
Randomisation?	Unclear	not stated
Intention-to-treat/Drop-	No	0 out of 26

outs?		

Tosti 2005

Methods	Within-patient randomised study: right-left scalp study	
Participants	Incl: Moderate to severe AA (of which 55% had AT) Excl: n/s Set: Dermatology Clinic; Bologna, Italy Age: 40 +/- 13 years Randomised: 34 m/f: 8/26 Evaluable: 34 Duration of condition: n/s	
Interventions	a: 0.05% clobetasol propionate foam b: placebo foam in an identical container Freq: Applied BD for 5 days/wk for 12 weeks Applicns: foam sprayed from pressurised containers	
Outcomes	1.Clinical outcomes: hair re-growth measured in a 5-point semi-quantitative score from 0= <10% re-growth to 4= > 75% regrowth 2. Adverse outcomes: folliculitis	
Notes	Sp: Olux, MiPharm, Italy 1 Px withdrew before week 12.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - clear.The Rx numbers were allocated sequentially in the order in which the Px were enrolled
Blinding? All outcomes	Unclear	Px- yes; clinicians- yes; assessors- unsure
Randomisation?	Yes	Computer generated Arcus Quickstat.
Intention-to-treat/Drop-outs?	Yes	(LOCFmethod used). 1 out of 34

White 1985

Methods	Cross-over randomised study
Participants	Incl: AT all Px had previous unsuccessful Tx with steroids & other Tx Excl: AT Px who had had no Tx Set: UK hospital outpatients (monthly assessments) Age: 18 to 67 yrs(median 39.9yrs) Randomised: 15 m/f: 5/10 Evaluable: 12 Duration of condition: 1.5 to 40yrs(median 17.7yrs) Baseline comparison: more females than males. Wide age range and disease duration
Interventions	a: 3% minoxidil soln. (n=8) b: placebo soln (n=7) Freq: x2 daily for 16wks (then cross-over to the other Tx) Applicns: scalp
Outcomes	1.Clinical outcomes: therapeutically useful regrowth of hair graded by the clinician from 0=no new hair growth; 1=new growth of vellus hair; 2= new growth of intermediate hair; 3=minimal new growth of terminal hair, 4=moderate growth of terminal hair; 5= dense new

	growth of terminal hair. 2. Adverse outcomes: hair growth occured at distant sites; ankle oedema
Notes	Sp: unsure 3 withdrawals in the placebo grp in the first 16 wks Only data from the first phase of this study was used at 16 weeks

Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Px-yes; clinicians-yes; assessors - no.
Randomisation?	Unclear	not stated
Intention-to-treat/Drop-outs?	No	3 out of 15

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Berth-Jones 1991	The scoring system for hair growth was too broad ('good' was defined as 20 to 100% hair growth). Therefore we were not able to extract meaningful data relevant to our outcome measure of >50%. We were unable to get any further data from the author.
Olsen 1992	It is unclear from the data shown how many patients in the treatment and control groups had 'cosmetically acceptable hair growth' or hair growth covering >50% of the scalp at the end of 12 and 20 weeks. We were unable to get any further explanation from the author.
Price 1987c	This paper included an RCT where subjects were assigned to 5% minoxidil or placebo for 12 weeks. No results were given in the paper and we were unable to get any further information from the author.
Price 1999	The trial ceases to be an RCT after 12 weeks, after which all the patients were given minoxidil. There were no clinically meaningful results reported at this 12 week time point. Cosmetically acceptable results were reported after 48 weeks when all patients were using minoxidil. Our request for the full paper was not successful.
Tosti 1986	The data on the 40 participants of the RCT was not presented separately from the total group in the study who were not randomised. The author was unable to give us any further data.

Characteristics of ongoing studies [ordered by study ID]

CSG 15

Trial name or title	A randomised active-controlled double-blind study of topical tacrolimus 0.1% ointment versus conventional treatment with mid-potency topical steroid ointment in alopecia areata
Methods	
Participants	Above 12 years of age with at least 2 patches of localised alopecia areata
Interventions	One patch randomised to tacrolimus ointment and one to topical steroid
Outcomes	Hair growth
Starting date	Start date 1/12/2003
Contact	S Amladi TN Medical College & BYL Nair Hospital, Mumbai, India

information	s_amladi@hotmail.com
Notes	Planned end date was 1/8/2004

CSG 30

Trial name or title	Effect of laser examination in alopecia areata
Methods	
Participants	
Interventions	
Outcomes	
Starting date	Start date 1/1/2003
Contact information	Mohsen Sharifi Moscow Medical Academy mohsen_ima@yahoo.com
Notes	Planned end date was 1/1/2005

NCT00167102

Trial name or title	A double-blind placebo controlled randomized multicenter study to evaluate the safety and therapeutic efficacy of intramuscular administration of alefacept (LFA-3IgG1 Fusion protein) in patients with chronic severe scalp alopecia areata
Methods	
Participants	Diagnosis of AA by study investigator . Must have 50 to 95% patchy scalp hair loss of >1yr. 18 to 65 yrs male or female. n=20
Interventions	12 weeks. Weekly IM of alefacept
Outcomes	Safet y & therapeutic efficacy of alefacept. No statement about hair growth
Starting date	July 2005
Contact information	Cathleen Boeck boeck001@umn.edu
Notes	This trial start was delayed. Due to start 10/06.

NCT00187577

Trial name or title	Efficacy study of latanoprost and bimatoprost solutions in promoting eyelash growth in patients with Alopecia Areata
Methods	
Participants	Males and females 18 to 70yrs with AA and 50% eyelash loss for >6mths. n=20
Interventions	Latanoprost or bimatoprost opthalmic solns applied to the eyelid marginsof one eye once per day
Outcomes	Eyelash growth to be documented at eight wk intervals when eyelids to be photographed and eyelash length to be measured.
Starting date	June 2005
Contact information	Ingrid Roseborough roseborough@derm.ucsf.edu
Notes	Expected completion May 2006. Wrote 10/10/06 to ask for pubn.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Skin Group search strategy

Search methods for identification of studies Electronic searches
We searched The Cochrane Skin Group Specialised Register in February 2006 using the following terms:
(alopecia and areata) or (alopecia and totalis) or (alopecia and universalis) or (alopecia and celsi) or (nonscarring and hair and loss) or ophia*

We searched The Cochrane Central Register of Controlled Clinical Trials (The Cochrane Library Issue1,2006) using the search strategy in Appendix 1 :

We searched MEDLINE (OVID) (from 2003 to February 2006) using the strategy in Appendix 2 which included the search strategy to locate RCTs with the search terms 1-29 as given in the Cochrane Handbook (Higgins 2005), Appendix 5b.2.

We searched EMBASE (from 2005 to February 2006) using the strategy in Appendix 3 .

We searched PsycINFO (from 1806 to February 2006) using the strategy in Appendix 4 .

We searched AMED (Allied and Complementary Medicine,1985 to February 2006) using the strategy in Appendix 5 .

We searched LILACS (Latin American and Caribbean Health Science Information database, from 1982 to February 2006) using the strategy in Appendix 6 .

Searching other resources References from published studies
The bibliographies of included and excluded RCTs were checked for possible references to further RCTs.

Unpublished literature
Trial authors of papers and abstracts were contacted where possible to ask for more information about their studies.

The following ongoing trials registries were searched in February 2006:
www.nottingham.ac.uk/ongoingskintrials and www.clinicaltrials.gov using the term 'alopecia areata' and www.controlled-trials.com using the terms areata, totalis and universalis. Identified studies have been placed in the 'Studies Awaiting Assessment' section

Conference proceedings
The abstracts from the International Research Workshops 1999 and 2003 on alopecia areata were scanned for RCTs.

Adverse effects
All the adverse events detailed in the included studies were extracted and are summarised in the body of the review.

Searches were made of the websites of the Regulatory Agencies in October 2006: www.emea.eu; http://medicines.mhra.gov.uk; www.fda.gov/medwatch and www.tga.gov.au for reports of adverse events associated with minoxidil, 5-ALA, desoximetasone cream, prednisolone cream, betamethasone, ciclosporin A, SADBE, interferon, DPCP, DNCB, latanoprost, PUVA, thymopentin, clobetasol propionate, inosiplex and croton oil. These searches did not yield any additional data

Language
No language restrictions were imposed and translations were sought for several papers.

REVIEW_APPENDICES

Appendix 1. Cochrane Controlled Trials Search Strategy

#1 alopecia areata in All Fields in all products
#2 MeSH descriptor Alopecia Areata, this term only in MeSH products
#3 alopecia totalis in All Fields in all products
#4 alopecia universalis in All Fields in all products
#5 alopecia celsi in All Fields in all products
#6 ophia$ in All Fields in all products
#7 nonscarr* NEAR hair NEAR loss in All Fields in all products
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

Appendix 2. MEDLINE (OVID) search strategy

(i) Search strategy to locate RCTs
Search terms 1-29, as given in the Cochrane Handbook (Higgins 2005), Appendix 5b.2
(ii) Search strategy to locate alopecia areata.
30. exp Alopecia Areata/
31. alopecia areata.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32. (alopecia adj totalis).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
33. (alopecia adj universalis).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

34. (alopecia adj celsi).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
35. ophia$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
36. (nonscarring adj hair adj loss).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
37. 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 29 and 37

The results of searches (i) and (ii) were combined with the Boolean operator AND.

Appendix 3. EMBASE (OVID) search strategy

1. random$.mp.
2. crossover procedure/ or double blind procedure/ or single blind procedure/
3. comparative study/ or controlled study/ or clinical trial/
4. factorial$.mp.
5. PLACEBO/ or placebo$.mp.
6. versus.mp.
7. (single or double or treble or triple).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
8. (blind or mask).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
9. Alopecia Areata/ or alopecia areata.mp.
10. Alopecia Areata/th, dt [Therapy, Drug Therapy]
11. alopecia totalis.mp.
12. alopecia universalis.mp.
13. alopecia celsi.mp.
14. ophiasis.mp.
15. nonscarring hair loss.mp.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
17. 9 or 10 or 11 or 12 or 13 or 14 or 15
18. 16 and 17

Appendix 4. PsychINFO search strategy

1. alopecia areata.mp.
2. exp ALOPECIA/
3. exp Clinical Trials/
4. 1 or 2
5. 3 and 4

Appendix 5. AMED Search Strategy

1. randomised controlled trial$/
2. random allocation/
3. double blind method/
4. single blind method.mp.
5. exp Clinical trials/
6. (clin$ adj25 trial$).mp. [mp=abstract, heading words, title]
7. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$ or dummy)).mp. [mp=abstract, heading words, title]
8. (placebo$ or random$).mp. [mp=abstract, heading words, title]
9. research design/ or clinical trials/ or comparative study/ or double blind method/ or random allocation/
10. prospective studies.mp.
11. cross over studies.mp.
12. Follow up studies/
13. control$.mp.
14. (multicent$ or multi-cent$).mp. [mp=abstract, heading words, title]
15. ((stud or design$) adj25 (factorial or prospective or intervention or crossver or cross-over or quasi-experiment$)).mp. [mp=abstract, heading words, title]
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. alopecia areata.mp.
18. alopecia universalis.mp.
19. ophia$.mp.
20. (nonscarring ajd hair adj loss).mp. [mp=abstract, heading words, title]
21. alopecia celsi.mp.
22. 17 or 18 or 18 or 19 or 20 or 21
23. 16 and 22

Appendix 6. LILACS Search Strategy

((Pt randomised controlled trial OR Pt controlled clinical trial OR Mh randomised controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt

clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words] and alopecia and (areata or universalis or totalis or celsi) or (nonscarring and hair and loss) [Words]

REVIEW_DECLARATIONS

Declarations of interest

None known.

REVIEW_DIFFERENCES

Differences between protocol and review

We added a sentence to the first of the primary outcome measures: We have taken >50% re-growth of the affected area as the measure of moderate hair growth and thus as a clinically significant improvement.

In the Methods section under 'Measures of treatment effect', the results have been expressed as risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes which were deemed to be more suitable for pharmaceutical interventions than expressing the results as odds ratios which was the original plan.

In the Methods section under 'Unit of analysis issues' we explained why we did not list non-randomised controlled studies.

In the Methods section under 'Data synthesis' we gave our reasons for using an outcome measure of >50% re-growth of the affected area as the measure of moderate hair growth and thus as a clinically significant improvement. This was because once we started data extraction we became aware that many of the studies did not report on 'clinically significant hair growth' and we thought that this measure would be a pragmatic means to indicate treatment benefit with those with this hair loss condition.

REFERENCES

References to studies included in this review

Bissonnette 2000 *{published data only}*

Bissonnette R, Shapiro J, Zeng H, McLean DI, Lui H. Topical photodynamic therapy with 5-aminolaevulinic acid does not induce hair regrowth in patients with extensive alopecia areata. British Journal of Dermatology 2000 issue: 5;143:1032-5.

Charuwichitratana *{published data only}*

Charuwichitratana S WPTS. Randomized double-blind placebo-controlled trial in the treatment of alopecia areata with 0.25% desoximetasone cream. Archives of Dermatology issue: 10;136:1276-7.

Galbraith 1987 *{published data only}*

Galbraith GM, Thiers BH, Jensen J, Hoehler F. A randomized double-blind study of inosiplex (isoprinosine) therapy in patients with alopecia totalis. Journal of the American Academy of Dermatology 1987 issue: 5 Pt 1;16:977-83.

Kar 2005 *{published data only}*

Kar BR, Handa S, Dogra S, Kumar B. Placebo-controlled oral pulse prednisolone therapy in alopecia areata. Journal of the American Academy of Dermatology 2005 issue: 2;52:287-90.

Khoury 1992 *{published data only}*

Khoury EL, Price VH, Abdel-Salam MM, Stern M, Greenspan JS. Topical minoxidil in alopecia areata: no effect on the perifollicular lymphoid infiltration. Journal of Investigative Dermatology 1992 issue: 1;99:40-7.

Khoury EL, Price VH, Abdel-Salim MM, Stern M, Greenspan JSD. Topical minoxidil in alopecia areata: immunopathologic studies. Abstract. Journal of Investigative Dermatology 1988 issue: 4;90.

Mancuso 2003 *{published data only}*

Mancuso G, Balducci A, Casadio C, Farina P, Staffa M, Valenti L. Efficacy of betamethasone valerate foam formulation in comparison with betamethasone dipropionate lotion in the treatment of mild-to-moderate

alopecia areata: A multicenter, prospective, randomized, controlled, investigator-blinded trial. International Journal of Dermatology 2003 issue: 7;42:572-5.

Nelson 1994 *{published data only}*

Nelson BR, Ratner D, Weiner ND, Egbaria K, Hamilton TA, Johnson TM. Efficacy of topical cyclosporin A in the treatment of alopecia areata. Journal of Dermatological Treatment 1994 issue: 2;5:77-9.

Perini 1994 *{published data only}*

Perini G, Zara M, Cipriani R, Carraro C, Preti A. Imipramine in alopecia areata. A double-blind, placebo-controlled study. Psychotherapy & Psychosomatics 1994 issue: 3-4;61:195-8.

Pipoli 1995 *{published data only}*

Pipoli M, D'Argento V, Coviello C, Dell'Osso A, Mastrolanardo M, Vena GA. Evaluation of topical immunotherapy with squaric acid dibutylester, systemic interferon alpha and the combination of both in the treatment of chronic severe alopecia areata. Journal of Dermatological Treatment 1995 issue: 2;6:95-8.

Price 1987a *{published data only}*

Price VH. Double-blind, placebo-controlled evaluation of topical minoxidil in extensive alopecia areata. Journal of the American Academy of Dermatology 1987 issue: 3 Pt 2;16:730-6.

Price 1987b *{published data only}*

Price VH. Topical minoxidil (3%) in extensive alopecia areata, including long-term efficacy. Journal of the American Academy of Dermatology 1987 issue: 3 Pt 2;16:737-44.

Rongioletti 1992 *{published data only}*

Rongioletti F, Guarrera M, Tosti A, Guerra L, Pigatto P. Topical cyclosporin A fails to improve alopecia areata - A double blind study. Journal of Dermatological Treatment 1992 issue: 1;3:13-4.

Ross 2005 *{published data only}*

Ross EK, Bolduc C, Lui H, Shapiro J. Lack of efficacy of topical latanoprost in the treatment of eyebrow alopecia areata [9]. Journal of the American Academy of Dermatology 2005 issue: 6;53:1095-6.

Shapiro 1993 *{published data only}*

Shapiro J, Tan J, Ho V, Abbott F, Tron V. Treatment of chronic severe alopecia areata with topical diphenylcyclopropenone and 5% minoxidil: a clinical and immunopathologic evaluation. Journal of the American Academy of Dermatology 1993 issue: 5 Pt 1;29:729-35.

Shapiro J, Tan J, Ho V, Tron V. Treatment of severe alopecia areata with topical diphenylcyclopropenone and 5% minoxidil: a clinical and immunopathologic evaluation. Journal of Investigative Dermatology 1995 issue: Suppl:;104.

Shapiro J, Tan J, Tron V. Diphencyprone and minoxidil in alopecia areata: a clinical and immunopathologic evaluation. Abstract 66. Journal of Investigative Dermatology 1992 issue: 4;98.

Tosti 1991 *{published data only}*

Tosti A, Bardazzi F, Guerra L. Alopecia totalis: is treating nonresponder patients useful?. Journal of the American Academy of Dermatology 1991 issue: 3;24:455-6.

Tosti 2005 *{published data only}*

Tosti A, Iorizzo M, Milani M. Efficacy and safety of a new clobetasol propionate 0.05% foam in Alopecia areata: A randomised, double-blind placebo controlled trial. Abstract P08.17. Journal of the European Academy of Dermatology and Venereology 2005 issue: Suppl 2;19:222-3.

White 1985 *{published data only}*

White SI, Friedmann PS. Topical minoxidil lacks efficacy in alopecia areata [letter]. Archives of Dermatology 1985 issue: 5;121.

** indicates the major publication for the study*

References to studies excluded from this review

Berth-Jones 1991 *{published data only}*

Berth-Jones J, Hutchinson PE. Treatment of alopecia totalis with a combination of inosine pranobex and diphencyprone compared to each treatment alone. Clinical & Experimental Dermatology 1991 issue:

3;16:172-5.

Olsen 1992 *{published data only}*

Olsen EA, Carson SC, Turney EA. Systemic steroids with or without 2% topical minoxidil in the treatment of alopecia areata. Archives of Dermatology 1992 issue: 11;128:1467-73.

Price 1987c *{published data only}*

Price VH. Topical minoxidil in extensive alopecia areata, including 3-year follow-up. Dermatologica issue: Suppl 2;175:36-41.

Price 1999 *{published data only}*

Price, VH. Trancik, R. Rundegren, J. Topical Minoxidil 5% in the treatment of Alopecia Areata. The 3rd International Research Workshop on Alopecia Areata and 2nd Intercontinental Meeting of Hair Research Societies Journal of Investigative Dermatology Symposium Proceedings. 1999; Vol. 4, issue 3:252.

Tosti 1986 *{published data only}*

Tosti A, Padova MP, Minghetti G, Veronesi S. Therapies versus placebo in the treatment of patchy alopecia areata. Journal of the American Academy of Dermatology 1986 issue: 2 Pt 1;15:209-10.

Additional references

Colombe 1999

Colombe BW, Lou CD, Price VH. The genetic basis of alopecia areata: HLA associations with patchy alopecia areata versus alopecia totalis and alopecia universalis. Journal of Investigative Dermatology. Symposium proceedings 1999 issue: 3;4:216-9.

Egger 2003

Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews?. Health Technology Assessment 2003 ;7:1-76.

Epstein 2001

Epstein E. Evidence-based treatment of alopecia areata.[comment]. Journal of the American Academy of Dermatology issue: 4;45:640-2.

Firooz 2005

Firooz A, Firoozabadi MR, Ghazisaidi B, Dowlati Y. Concepts of patients with alopecia areata about their disease. BMC Dermatology. 2005 issue: 1;5:1-5.

Garcia Bartels 2006

Garcia Bartels N, Lee HH, Worm M, Burmester GR, Sterry W, Blume-Peytavi U. Development of alopecia areata universalis in a patient receiving adalimumab. Archives of Dermatology 2006 ;142:1654-5.

Glasziou 2007

Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise.[see comment]. BMJ issue: 7589;334:349-51.

Green 2000

Green J, Sinclair R. Genetics of Alopecia Areata. Australian Journal of Dermatology 2000 ;41:213-8.

Hay 1998

Hay IC, Jamieson M, Ormerod AD. Randomized trial of aromatherapy. Successful treatment for alopecia areata.. Archives of Dermatology 1998 issue: 11;134:1349-52.

Higgins 2005

Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]. In: The Cochrane Library, Issue 3 Chichester, UK: John Wiley & Sons Ltd, 2005.

Hutchinson 1987

Hutchinson E. Therapy versus placebo for alopecia areata. Journal of the American Academy of Dermatology issue: 3;17:516-7.

Juni 2001

Juni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ 2001 ;323:42-6.

MacDonald Hull 2003

MacDonald Hull SP, Wood ML, Hutchinson PE, Sladden M, Messenger AG. British Association of Dermatologists Guidelines for the management of alopecia areata.[see comment]. British Journal of Dermatology issue: 4;149:692-9.

Madani 2000

Madani S, Shapiro J. Alopecia areata update. Journal of the American Academy of Dermatology 2000 issue: 4;42:549-66.

McMichael 1998

McMichael A. Impact of hair disorders and pigment disorders on quality of life. In: Rajagopalan R, Sherertz E, Anderson R, editor(s). Care Management of Skin Diseases, Life Quality and Economic Impact New York: Marcel Dekker, 1998:207-23.

McMichael 2003

McMichael AJ. The new biologics in psoriasis: possible treatments for alopecia areata. Journal of Investigative Dermatology Symposium Proceedings. 2003; Vol. 8:217-8.

Monk 1989

Monk B. Induction of hair growth in alopecia totalis with diphencyprone sensitization. Clinical & Experimental Dermatology issue: 2;14:154-7.

Muller 1963

Muller SA, Winkelmann RK. Alopecia areata: an evaluation of 736 patients. Archives of Dermatology 1963 ;88:290-297.

Olsen 2004

Olsen E A. Alpecia areata investigational assessment guidelines -Part II. Journal of the American Academy of Dermatology 2004 ;51:440-7.

Price 2003

Price VH. Therapy of alopecia areata: on the cusp and in the future. Journal of Investigative Dermatology Symposium Proceedings. 2003; Vol. 8:207-11.

Safavi 1995

Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ. Incidence of alopecia areata in Olmsted county, Minnesota, 1975 through 1989. Mayo Clinic Proceedings 1995 issue: 7;70:628-33.

Schmidt 2001

Schmidt S, Fischer TW, Chren MM, Strauss BM, Elsner P. Strategies of coping and quality of life in women with alopecia. British Journal of Dermatology issue: 5;144:1038-43.

Sinclair 1999

Sinclair RD. Alopecia areata. In: Sinclair R, Banfield C, Dawber R, editor(s). Handbook of diseases of the hair and scalp London: Blackwell Science, 1999:75-84.

Tosti 2006

Tosti A, Pazzaglia M, Starace M, Bellavista S, Vincenzi C, Tonelli G. Alopecia areata during treatment with biologic agents. Archives of Dermatology 2006 ;142:1653-4.

van der Steen 1991

Steen PH. Prognostic factors in the treatment of alopecia areata with diphenylcyclopropenone. Journal of the American Academy of Dermatology 1991 issue: 2;24:227-30.

GRAPHS

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

Immunosuppressant therapies vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinician rated clinically signif hair growth. Short term outcome <6mths	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Clinician rated clinically signif hair growth. Short term outcome <6mths	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Clinician rated clinically signif hair growth. Short term outcome <6mths	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse effects of corticosteroid (oral prednisolone) therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Immunosuppressant therapy active vs active treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinician rated clinically signif hair growth. Short term outcome <6mths	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Immunosuppressant therapy vs vehicle

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinician rated clinically signif hair growth. Long term outcome - 6mths or more	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Topical Immunotherapies

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinician rated clinically signif hair growth. Long term outcome - 6mths or more	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Combination immunotherapy vs squaric acid dibutyl ester.	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Combination immunotherapy vs interferon.	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

Hair Growth Stimulant: topical minoxidil vs vehicle

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinician rated clinically signif hair growth. Short term outcome <6mths	2	50	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.44, 2.12]
2 Clinician rated clinically signif hair growth. Long term outcome (6 mths or more)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Antidepressant therapy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinician rated clinically signif hair growth. Long term			Risk Ratio (M-H,	Totals not

outcome (6 mths or more)	1	Random, 95% CI)	selected

COVER SHEET

Interventions for alopecia areata

Reviewer(s)	Delamere Finola M, Sladden Michael J, Dobbins Helen M, Leonardi-Bee Jo
Contribution of Reviewer(s)	
Issue protocol first published	2003 issue 4
Issue review first published	2008 issue 2
Date of last minor amendment	Information not supplied by reviewer
Date of last substantive amendment	Information not supplied by reviewer
Most recent changes	
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	Information not supplied by reviewer
Date reviewers' conclusions section amended	Information not supplied by reviewer
Contact address	Delamere Room A103, King's Meadow Campus Lenton Lane Launceston General Hospital Clinical Sciences Building Nottingham City Hospital NHS Trust Campus, Hucknall Road Nottingham Launceston Nottingham Nottingham Tasmania UK Australia UK UK NG7 2NR 7250 NG7 2UH NG5 1PB Telephone: Facsimile: E-mail: finola.delamere@nottingham.ac.uk
Cochrane Library number	CD004413
Editorial group	Cochrane Skin Group
Editorial group code	HM-SKIN

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Nottingham University, UK.
- Leicester Royal Infirmary -NHS, UK.
- University of Tasmania, Australia.

KEYWORDS

Humans; Alopecia Areata [*therapy] ; Randomized Controlled Trials as Topic ; Treatment Outcome

HISTORY

History
Protocol first published: Issue 4, 2003
Review first published: Issue 2, 2008

Date	Event	Description
5 December 2007	New citation required and conclusions have changed	Substantive amendment

Imprimir | Fechar