Title Page

Systemic Treatments for Alopecia Areata: A Systematic Review

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Main Text

Systemic Treatments for Alopecia Areata: A Systematic Review

Abstract

A range of systemic treatments are used for alopecia areata (AA) with variable evidence supporting efficacy. In this systematic review, we evaluated the evidence surrounding systemic treatments for alopecia areata, alopecia totalis (AT) and alopecia universalis (AU). A systematic search was conducted of the peer-reviewed literature published between 1946 and March 2018 via Medline, Embase, Amed, the Cochrane Central Register of Controlled Trials, PsychINFO and Lilacs. All randomised controlled trials (RCTs) that evaluated the effectiveness of systemic treatments for individuals with AA, AT or AU were included. Sixteen studies were included with a total of 768 participants. We found 8 placebo-controlled RCTs, 3 RCTs comparing 2 systemic treatments and 5 RCTs comparing 3 treatments. A total of 15 different systemic therapies were investigated. The most frequently investigated therapy was oral prednisolone pulse therapy and oral inosiplex. There was significant variability in the definition of treatment success. No study evaluated the impact of pharmacotherapy on quality of life using complete quantitative quality of life instruments. Adverse events were reported in 13 studies and were corticosteroid-related or otherwise well tolerated. Relapse rates were considerable in the 4 studies that reported this outcome. There is currently no specific systemic therapy that is supported by robust body of evidence from RCTs. The current evidence suggests efficacy of oral prednisolone pulse therapy and oral inosiplex. Evidence does not support the use of oral zinc sulphate, alefacept and efalizumab. Future RCTs should be adequately powered and employ clearly defined clinical response endpoints to allow future meta-analyses.

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Key Words:
Alopecia Areata, Hair Diseases, Review, Drug Therapy, Glucocorticoids, Biological Therapy, Immunomodulation

Learning Points:

- There are few published RCTs investigating systemic treatments for alopecia areata. Those published are of small to moderate sample size.
- No systemic treatment is currently supported by a robust body of evidence from multiple RCTs.

Introduction

Alopecia areata (AA) is an autoimmune disease of the hair follicle, resulting in acute or chronic patches of hair loss, total hair loss of the scalp (alopecia totalis, AT), or complete hair loss of entire body and scalp (alopecia universalis, AU). It is a disease with significant impact on health-related quality of life, in particular to the domains of role-emotional, mental health and vitality (1, 2).

While it is difficult to determine how an individual's AA will fare, without treatment a large number of patients will experience disease progression. Ikeda et al.(3) studied 1,987 individuals with AA and showed a 65% risk of progression to chronic AA in participants with a solitary stable patch of AA for between 6 to 12 months in duration. Importantly, those with disease beyond 12 months had a 50% risk of progression to AT/AU.

Treatment goals include halting disease progression and achieving satisfactory hair regrowth. However, current management of AA, AT and AU is sub-optimal with uncertainties surrounding treatment choice, duration, indication and efficacy. Initial therapy often involves use of topical and intralesional corticosteroids. In extensive and refractory cases, systemic agents are trialled, with choice largely dependent on clinician experience. In a consensus between patients, carers, relatives and health professionals, quantifying the efficacy of systemic therapies, both immunosuppressant and biological, represented 2 of the top 3 research uncertainties to be prioritised (4). So far, there has only been one systematic review (5) published a decade ago evaluating treatments for alopecia areata, in which 3 randomised controlled trials (RCTs) of systemic agents were identified. Since that review, there has been greater acknowledgement of the much needed research into AA with further trials being conducted to evaluate systemic therapies. Newer medications, such as JAK

inhibitors, have regenerated attention toward treatment options for this disease, and thus it is timely in this current era for an updated review on the trials that have been conducted and the trials currently underway.

This systematic review aims to identify studies that have investigated the use of a systemic agent for treatment of AA, AT or AU. More specifically, the objectives of this review are: (1) to identify randomized controlled trials (RCTs) of systemic treatments for AA, AT or AU, (2) to evaluate the corresponding efficacy of systemic treatments, (3) to identify how efficacy is being measured, and (4) to assess the corresponding side effects of systemic treatments. To the best of our knowledge, this is the most updated systematic review since Delamere et al. (5) that will comprehensively assess systemic treatments being used.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (6) and registered on PROSPERO in advance (CRD42018088758). All RCTs that evaluated the effectiveness of systemic treatments for AA, AT or AU were included. We included all comparators of a systemic treatment to: placebo, other systemic treatment and non-systemic treatment.

Medline (1946 to present), Embase (1974 to present), Allied and Complementary Medicine Database (1985 to present), the Cochrane Central Register of Controlled Trials (1999 to present), PsychINFO (1806 to present) and Latin American and Caribbean Health Sciences Literature (1987 to present) were searched through March 4, 2018 using a combination of free-text terms and medical subject headings (e.g. 'alopecia areata', 'randomised controlled trial'). (Supplementary Materials: Appendix 1).

Ongoing trials were searched through the following databases: Clinical-Trials.gov, metaRegister of Controlled Trials, the Australian New Zealand Clinical Trials Registry, the EU Clinical Trials register, and the World Health Organisation International Clinical Trials Registry Platform.

Both forward and backward hand-searching were employed to identify additional studies that satisfied the inclusion criteria. Abstracts and/or titles of every record retrieved were scanned and the full text of all potentially relevant articles were examined. Risk of bias in included studies was assessed using the guidelines of the Cochrane Handbook of Systematic

Reviews of Interventions (6). Reporting bias was assessed through funnel plot analysis using Stata version 12 software for symmetry on visual inspection and Egger's test.

Results

Study Selection

A total of 2,830 articles were identified from the search strategy (Supplementary Figure 1). After inclusion and exclusion criteria, 16 studies involving 768 randomised participants were included in the review (Table 1).

Study Characteristics

There were 14 RCTs, 1 quasi-RCT and 1 cross-over RCT. The included studies involved 768 randomised participants. All inclusion criteria entailed some form of AA, AT or AU, with variation across studies as to specificity of severity and duration. The age range of participants across all included studies was 2 – 66 years.

A total of 15 different systemic interventions were examined across the 16 included studies. The most frequently examined intervention was oral prednisolone pulse therapy (PT) (7-9) and oral inosiplex (10-12). Eight studies were placebo-controlled RCTs, 3 studies compared 2 different systemic treatments and 5 studies compared 3 different treatments.

All studies included a categorical endpoint for efficacy, while only 4 studies included a numerical endpoint (10, 13-15). There was large variation in the definition of treatment 'response' (Table 2) with little consistency between studies.

Thirteen studies reported adverse events (Table 3). Relapse rate following cessation of treatment was reported in 4 studies (Table 4) which was considerable across these studies (9, 10, 16, 17). Only 3 studies performed scalp biopsies to determine histological changes from treatment (10, 15, 18).

Risk of bias within studies

The most robust studies were Strober et al. (14) and Price et al. (15) which scored low across all domains on risk of bias assessment (Supplementary Materials: Appendix 2). Many studies had significant bias in blinding of participants and personnel and uncertainties in allocation concealment and blinding of outcome assessment.

Results of individual studies

There were no studies sufficiently similar to support pooling of data in a meta-analysis. We present a summarised discussion of the evidence on systemic interventions in the included studies below.

Evidence for Systemic Glucocorticoids

Five RCTs evaluated systemic glucocorticoids: 1 placebo-controlled RCT (9) and 4 comparative RCTs (8, 16, 17, 19) with at least 1 treatment arm involving a systemic glucocorticoid.

Kar et al. (9) found a statistically significant response rate of 40% (8/20) in participants treated with oral prednisolone PT (200mg once weekly) for 3 months when compared to identical placebo tablets. In comparative studies, there were significantly greater response rates with intramuscular triamcinolone, intravenous methylprednisolonse and oral betamethasone minipulse therapy with liquid phenol, when compared to oral dexamethasone (16), oral prednisolone pulse therapy (PT) (8) and liquid phenol with and without topical minoxidil respectively (19).

Evidence for Immunomodulator Agents

Oral Inosiplex

Oral inosiplex (isoprinosine, inosine pranobex) is a synthetic immunomodulator with anti-viral effects. Three studies evaluated oral inosiplex for treatment of AA. Of these, 2 were placebo-controlled trials. One placebo-controlled trial was a cross-over trial which only reported inosiplex response rates for the first phase, and not placebo, making it difficult to draw solid conclusions on the efficacy of inosiplex from the trial (10). The other placebo-controlled study found complete hair regrowth in 33.3% (5/15) of patients in the oral inosiplex group which was statistically significant on intention to treat analysis (11). Oral inosiplex was also compared to topical diphencyprone or both for 6 months by Berth-Jones et al. (12), with poor response for all 3 treatment arms. This study recruited only participants with AT of at least 12 months duration which may explain the low response rates for all 3 treatments.

Intravenous Thymopentin

Intravenous thymopentin is a synthetic immunostimulant studied in primary immunodeficiencies, such as AIDs. It was investigated in a comparative trial to topical 10%

cyclosporin or photochemotherapy in 26 patients with AT/AU non-responsive to sensitising therapy for at least 1 year. No participants had any regrowth.

Evidence for Biologics

Intramuscular Alefacept

Alefacept is an immunosuppressive biological agent that inhibits T cell activation. A multi-centre, double-blind, placebo-controlled RCT of 45 participants, found no statistically significant difference between intramuscular alefacept and placebo.

Subcutaneous Efalizumab

Efalizumab is a humanised monoclonal antibody and T cell blocker. A phase II, placebo-controlled trial of 62 participants found no statistically significant difference between subcutaneous efalizumab and placebo.

Evidence for Antidepressants

Oral Imipramine

One double-blind placebo-controlled trial evaluated oral imipramine, a tricyclic antidepressant for AA (20). While the results were favourable for oral imipramine, inducing a regrowth rate of 71% (5/7), the relatively small sample size of 13 randomised participants make these findings difficult to generalise to the AA population.

Oral Paroxetine

Paroxetine is a selective serotonin reuptake inhibitor. One double-blind placebo-controlled RCT found a complete regrowth in 25% (2/8) of patients on oral paroxetine compared to 20% (1/5) on placebo. 50% (4/8) of patients showed partial regrowth, however this was not reported in the placebo group. While the trial reported a ‘clear beneficial effect’ of oral paroxetine, the small sample size makes these figures less reliable.

Evidence for Complementary and Alternative Medicine

Oral Zinc Sulphate

Ead et al. (21) evaluated oral zinc sulphate in 42 participants with AA, AT or AU and found no difference compared to placebo.

Oral Total Glucosides of Paeony Capsule (TGPC) and Oral Compound Glycyrrhizin Tablets (CGT)

Oral TGPC and oral CGT are plant extracts of glycosides with proposed immunoregulatory functions. Two studies evaluated oral TGPC and oral CGT at the same hospital, with the same lead author, but across different time periods and AA populations. The first study (22) compared oral TGPC to oral CGT and found similar efficacy of around 70% 'cured' or 'markedly effective' for both. The second study compared oral TGPC plus oral CGT with oral CGT alone in children aged 2 to 14 years old (13). After 6 and 12 months, combination oral TGPC and oral CGT were significantly more effective than oral CGT alone – 82% effective rate compared to 54% at 12 months respectively.

Risk of Bias Across Studies

To explore risk of publication bias, funnel plot analysis was conducted (Supplementary Figure 2). For construction of the funnel plot we could only include double-arm trials, studies with complete data and studies reporting outcomes translatable to odds ratios. This resulted in analysis of 9 studies (8, 9, 11, 13-15, 20, 22, 23).

We found symmetry of the funnel plot both on visual inspection and with Egger's test. This indicates that risk of publication bias amongst our analysed studies is low.

Ongoing Trials

We identified 4 ongoing RCTs from trial registries (Supplementary Materials: Appendix 3). Systemic therapies being evaluated by these trials are: apremilast, tralokinumab, 'PF-06651600' and 'PF-06700841', 'CTP-543' and 'TS-133'.

Discussion

Summary of Evidence

Overall, we identified 16 RCTs, cross-over RCTs or quasi-RCTs evaluating systemic therapy for AA, AT or AU. There was no systemic therapy that clearly had a robust body of high-quality clinical trials to support its efficacy. Overall, the evidence was not sufficiently vigorous to conclude percentage efficacy nor comparative efficacy for many of the investigated treatments. This is particularly pertinent when considering smaller sample sizes of certain studies in which power calculations have not been reported. A summarised table of response rates where data was available in presented in Table 5.

Of the trials conducted to determine comparative efficacy between treatments, 4 studies found a superior treatment arm (8, 13, 16, 19), whereas 3 studies found no difference between treatment arms (12, 17, 18). Combination oral TGPC and CGT, intramuscular triamcinolone, intravenous methylprednisolone and liquid phenol (20%) with oral betamethasone minipulse therapy were found to be superior to oral CGT alone, oral dexamethasone, oral prednisolone and liquid phenol (20%) respectively. There was no difference between inosiplex, diphencyprone or inosiplex with diphencyprone; intravenous thymopentin, topical cyclosporin or photochemotherapy; oral methylprednisolone pulse therapy with 3 consecutive pulses every 2 weeks, 2 consecutive pulses every 3 weeks or 3 consecutive pulses every 3 weeks. These 3 trials recruited patients with AT or AU. When compared to studies recruiting AA participants (24-30), the results suggest that AT patients have lower response rates than AA patients to similar treatments.

Apart from trials investigating systemic corticosteroids, most other systemic treatments were well tolerated with few side effects (Table 3). In Kar et al. (9), 55% of patients on oral prednisolone PT developed side effects, while in Saif et al. (17), 95% of patients on oral methylprednisolone PT developed side effects. Dehghan et al. (8) found no significant difference in adverse events when comparing participants on oral prednisolone PT with intravenous methylprednisolone PT.

Quality of the Evidence

There was considerable difference in the recruitment, conduct and evaluation of systemic treatment for each RCT. For this reason, we could not perform a meta-analysis.

In AA Investigational Assessment Guidelines, Olsen et al. (31) sets a series of criteria for selecting subjects for clinical and laboratory studies of AA to facilitate interpretation and comparability of data. Extent of involvement (percentage hair loss), medical history (including atopic or autoimmune disease), AA disease history (e.g. age at onset of first episode, duration of current episode) and demography (age, ethnicity) (31), were considered important data to identify in a study population. Of the 16 included studies in our systematic review, only Price et al. (15) and Saif et al. (17) gathered and presented extensive background close to the detail described by Olsen et al. (31). For Saif et al. (17), subgroup analyses showed that adequate responders were significantly older, had shorter duration of disease and had lower incidence of subclinical hypothyroidism (17). Detailed demography may therefore help identify potential prognostic and influencing factors in AA treatment.

We found large variation in the preciseness of endpoints (Table 2). Many studies lacked well-defined quantitative endpoints. Six studies did not provide a definition for what they considered a 'response' or 'grade of improvement' (10, 18-21, 23). This is a significant barrier to attaining precise and comparable data on efficacy. Numerical outcomes provide more exact quantification of response, however were only used in 4 studies (10, 13-15). Efficacy may be recorded through percentage change in the Severity of Alopecia Tool (SALT) score, a visual quantification of hair loss through summation of percentage hair loss from 4 views of the scalp (32). A $SALT_{50}$, i.e. 50% improvement, is an acceptable definition of 'response' to use as an endpoint in clinical trials evaluating systemic therapy for participants with extensive AA (32). Only Strober et al. (14) and Price et al. (15) employed $SALT_{50}$ as an endpoint. As measurement of efficacy was diverse, a meta-analysis was not feasible. More consistent measures would allow meta-analyses in the future.

In conjunction with hair regrowth, an important measurement of efficacy is an improvement in quantitative measurements of quality of life. AA is associated with a marked burden on utility (1, 2). Therefore, an effective treatment should be measured through both percentage hair regrowth and a satisfactory improvement in quality of life. No studies completely evaluated quality of life. Two studies investigated anti-depressants (20, 23) and used psychometric measures traditionally for depression and anxiety. A third study, Price et al. (15), did not use the complete Dermatology Quality of Life Scales tool, employing only the first 17 questions. The validity of this tool may therefore be impaired. None of these measures are currently validated in the AA population.

No intervention reported long-term maintenance of hair regrowth following cessation of treatment. 4 studies reported relapse rate (9, 10, 16, 17) which ranged from 25% to 75%. There is still currently no evidence from RCTs of any systemic treatment that will produce long-term benefit following use.

Very few studies scored low across all domains on risk of bias assessment. Blinding of participants and personnel was the most concerning domain to cause a high risk of bias in a large number of studies.

Relationship with Previous Literature

Delamere et al. (5) performed a Cochrane review of all interventions for AA in 2008. There was a strict criterion for studies to have primary outcome measured through response defined as >50% regrowth of affected area. Kar et al. (9), Perini et al. (20) and Galbraith et al. (10) were the only 3 studies included that evaluated systemic therapy. One of the ongoing trials identified was Strober et al.'s (14) study, which we include in our systematic review.

Seven RCTs have been published since 2008 included in our review. These trials conclude that intramuscular alefacept and subcutaneous efalizumab are ineffective. Overall evaluation of systemic therapies in AA remains sub-optimal. Comparable findings include: no RCTs evaluating steroid-sparing agents, few studies conducted with a large sample size, few studies evaluating interventional impact on quality of life and few studies with rigorous methodology limiting bias.

Study Implications

Implications for practice

Current choice of systemic agent is based on clinician experience and preference. Unfortunately, there is still insufficient evidence from RCTs supporting a particular systemic therapy for AA. Many different systemic therapies have been trialled with varying success.

The need to evaluate the impact of pharmacotherapy on quality of life is important to our understanding of how best to treat patients. While there is a possibility for spontaneous remission, for a patient with significant psychological distress or continued hair loss, the option of conservative management may not be viable. In the context where evidence supporting certain systemic therapies, albeit variable, exists from some RCTs and non-randomised studies, a management plan developed from an understanding of potential, but not certain success may be an option for clinicians and patients, where some evidence is available but not perfect.

Implications for research

There remains a need for high quality RCTs to be conducted involving systemic treatments for AA to define efficacy, guide treatment in an evidence-based fashion and compare treatments currently used in practice.

For future meta-analyses, there is a need for standardised measures of outcome and endpoints. This has been addressed by Olsen et al. (32), with a suggestion for >50% reduction in hair loss as an appropriate endpoint for moderate to severe AA treated with systemic therapy. Using SALT score to more accurately define percentage hair loss would aid this process. An inclusion criterion that creates a more homogenous cohort of participants may make evidence more clinically specific and relevant. This may be achieved through defining duration, severity and history of AA, and attaining a comprehensive medical history.

Additionally, quantitative measures of quality of life translate hair regrowth into clinically meaningful outcomes for AA patients. Both disease-specific and generic measures should be employed to capture impact of pharmacotherapy on quality of life and allow economic evaluation. This may enable evidence from RCTs to guide decision makers on allocation of healthcare resources, which is pertinent in a disease where there is currently no systemic treatment subsidised on the Pharmaceutical Benefits Scheme in Australia.

Strengths and Limitations

We used a systematic search strategy that was unlikely to introduce bias. A large number of databases were searched, and our search terms were broad to allow detection of all relevant studies (Supplementary Materials: Appendix 1). As a means to reduce publication bias we did not limit publications based on date published or language. Additionally, we searched registries for ongoing trials (Supplementary Materials: Appendix 3). Our protocol was created and registered on PROSPERO prior to commencement to reduce bias during conduct of the systematic review. We were comprehensive in our inclusion of RCTs by considering all outcome measures and comparators.

However, this review has several limitations. Due to the heterogeneity of studies, particularly in regard to outcome measurement, we were unable to perform a meta-analysis. This was an unavoidable limitation due to the studies themselves, rather than our inclusion criteria as we analysed that even a small meta-analysis with a subgroup of relatively similar studies would still contain significance differences affecting a pooled result.

We only considered RCTs for inclusion in this systematic review. Evidence from non-RCTs may be relevant, particularly for other systemic treatments. However, in view of performing a systematic review to answer questions regarding efficacy of systemic treatments, we chose to limit studies to RCTs designed to answer such questions.

Conclusions

There remains no systemic therapy that is supported by robust evidence from high quality RCTs. Some RCTs suggest efficacy of oral prednisolone PT and oral inosiplex. Oral zinc sulphate, intramuscular alefacept and subcutaneous efalizumab are ineffective. To further define efficacy of systemic treatments in AA, there is a need for higher quality RCTs with clearly defined endpoints to be conducted in the future.

Word Count: 3349 (main text)

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Table 1. Characteristics of Included Studies

Berth-Jones et al	1990	RCT	UK	At 1, 2, 4 and 6 months	33	17-66 years	AT or AU of at least 12 months duration	1. Oral inosiplex 50 mg/kg/day divided into 3 doses for 6 months 2. Diphencyprone 1% solution 3. Both oral inosine pranobex and diphencyprone for 6 months
Cipriani et al	2001	RCT	Italy	Every month	13	21-62 years	AA and psychiatric comorbidity	1. Oral paroxetine 20mg daily for 3 months 2. Placebo for 3 months
Dehghan et al	2013	RCT	Iran	-	40	-	AA with at least 30% scalp affected or more than 10 patches of alopecia in scalp and body	1. Oral prednisolone PT 200 mg in one dose every week for 3 months 2. Intravenous methylprednisolone PT 500 mg on 3 continuous days each month for 6 months
Ead et al	1981	RCT	UK	-	42	-	AA, AT or AU	1. Oral zinc sulphate, one capsule twice daily for 3 months 2. Placebo for 3 months
Galbraith et al	1986	Cross-over RCT	America	At 0, 2, 8, 14, 20, 22, 28, 34, and 40 weeks	34	-	AT of at least 1 year duration and cell-mediated immune dysfunction	1. Oral inosiplex for 20 weeks in total at 50 mg/kg/day up to a maximum of 5 gm per day from week 0-2 and week 9-20, with dose reduction to 50 mg/kg 3 days a week from week 3-8 2. Placebo in equivalent tablet dosage for 20 weeks Cross-over after 20 weeks.
Georgala et al	2006	RCT	Greece	Every month	32	16-48 years	AA of at least 12 months duration and refractory to at least one conventional therapy	1. Oral inosiplex 50 mg/kg/day in five divided doses for 12 weeks 2. Placebo for 12 weeks
Kar et al	2005	RCT	India	Every month	43	-	AA with at least 40% scalp affected or 10 patches scattered over the scalp and body	1. Oral prednisolone PT 200 mg once weekly for 3 months 2. Placebo for 3 months
Kurosawa et al	2005	Quasi-RCT	Japan	Every month	89	16-63 years	AA (single or multiple), AT or AU	1. Oral prednisolone PT 80 mg for 3 consecutive days once every 3 months for 12 months 2. Intramuscular triamcinolone 40 mg once a month for 6 months followed by 40 mg once every 1.5 months for 1 year 3. Oral dexamethasone 0.5 mg/day for 6 months
Mehta et al	2012	RCT	India	Every week	51	5-60 years	AA	1. Liquid phenol (20%) applied weekly and oral betamethasone minipulse therapy (5mg twice weekly) for 3 months 2. Liquid phenol (20%) applied weekly with topical minoxidil (2%)

								applied twice daily for 3 months 3. Liquid phenol (20%) applied weekly for 3 months
Perini et al	1994	RCT	Italy	-	13	20-55 years	AT or AU less than 6 months duration	1. Imipramine 75mg daily for 6 months 2. Placebo for 6 months
Price et al	2008	RCT	America	-	62	18-59 years	AA with: 50% to 95% scalp affected and positive pull test; at least 95% scalp affected up to 24 months; or AT up to 12 months. Non-responsive to other therapies. Aged 18 to 70 years.	1. Subcutaneous efalizumab 1.0 mg/kg weekly for 12 weeks 2. Placebo weekly for 12 weeks
Saif et al	2012	RCT	Saudi Arabia	-	42	-	AT, AU or OA	Daily dose of 15mg/kg oral methylprednisolone PT in the following 3 regimens: 1. 3 consecutive days once every 2 weeks for 24 weeks. 2. 2 consecutive days every 3 weeks for 24 weeks. 3. 3 consecutive days every 3 weeks for 24 weeks
Strober et al	2009	RCT	America	-	45	18-65 years	AA with at least a 50% to 95% patchy scalp hair loss of at least 6 months' duration aged 18 to 65 years	1. Alefacept 15mg weekly IM administration for 12 weeks 2. Placebo weekly IM administration for 12 weeks
Tosti et al	1991	RCT	Italy	Every month	26	16-48 years	AT or AU non-responsive to sensitizing therapy for at least 1 year	1. Intravenous thymopentin (50mg) three times a week for 3 weeks, every 3 months, for 9 months 2. Topical 10% cyclosporine in oily solution (2mL) applied daily for 9 months 3. Photochemotherapy (PUVA) three times a week for 9 months.
Yang et al	2013	RCT	China	Every month	117	2-14 years	AA with severity ≥S3 (50% to 75% hair loss), aged 2-24 years	1. Oral TGPC 300mg, 3 times per day and Oral CGT 25mg, 3 times per day for 12 months 2. Oral CGT 25mg, 3 times per day for 12 months
Yang et al	2012	RCT	China	Every month	86	18-65 years	AA with severity less than S3 (50% to 75% hair loss), aged 18 to 65 years	1. Oral TGPC three times daily and 600 mg per time for 3 months 2. Oral CGT three times daily and 50 mg per time for 3 months

'-': not reported

Table 2. Outcome Measures for Treatment Effect

Berth-Jones et al, 1990	1990	-	• (1) Good response: a response of cosmetic value, between 20 and 100% terminal scalp hair regrowth, (2) Poor response: a response of no cosmetic value, less than 20% terminal scalp hair regrowth, (3) No response
Cipriani et al, 2001	2001	-	• Complete response, partial response or no response
Dehghan et al, 2013	2013	-	• Percentage categories of improvement in scalp hair: (1) less than 30% improvement, (2) 30-60% improvement, (3) 60-99% improvement.
Ead et al, 1981	1981	-	• Response or no response
Galbraith et al, 1986	1986	• Mean length of scalp hair	• Response or no response
Georgala et al, 2006	2006	-	• (1) Complete response: total hair regrowth, (2) Partial response: at least 50% hair regrowth, (3) No response: less than 50% hair regrowth.
Kar et al, 2005	2005	-	• (1) Marked: more than 60% regrowth, (2) Moderate: 31-60% regrowth, (3) Poor: regrowth less than 30%. • Significant regrowth (moderate to marked regrowth) or no significant regrowth
Kurosawa et al, 2005	2005	-	• Response or no response: Response defined as more than 40% regrowth of cosmetically acceptable terminal hair. The ability to abandon a wig or hat was part of this definition.
Mehta et al, 2012	2012	-	• Grades of improvement 1-4
Perini et al, 1994	1994	-	• Full regrowth, terminal hair, vellus hair or no regrowth
Price et al, 2008	2008	• Percentage hair regrowth measured by SALT score • Participant assessment of disease with 100-mm visual analog scale: 0 representing no hair loss and 100 indicating total hair loss	• Percentage categories of improvement in scalp hair: (1) at least 75% hair regrowth, (2) 50-74% hair regrowth, (3) 25-49% hair regrowth • Response or no response: Response defined as at least 50% hair regrowth
Saif et al, 2012	2012	-	• (1) Adequate response: >75% regrowth of terminal hair, (2) Inadequate response: 25-74% regrowth of terminal hair, (3) Poor response: <25% regrowth of terminal hair.
Strober et al, 2009	2009	• Percentage of hair regrowth measured by SALT score	• Response or no response: Response defined as 50% or greater reduction in SALT score • Participant assessment of disease using 7-point qualitative scale: none, trace, mild, mild to moderate, moderate, moderate to severe, severe
Tosti et al, 1991	1991	-	• Cosmetic clinical improvement or no cosmetic clinical improvement • Regrowth of terminal hair or no regrowth of terminal hair
Yang et al, 2012	2012	-	• (1) Cured: hairs all grew out again, normal in density of distribution, color and luster, and negative in pulling hair test; (2) Markedly effective: 70% of hairs grew out again, almost normal in density of distribution, color and luster; (3) Effective: 30% of hairs grew out again, including fine hair and white hair, with no hair loss after treatment; (4) Failed: after a treatment of more than 3 months, new hairs

			grew out less than 30% or with continued hair loss
Yang et al, 2013	2013	• Change in score of alopecia areata severity: Where no hair loss was 0, <25% hair loss was 1, 25% to 49% hair loss was 2, 50% to 74% hair loss was 3, 75% to 99% hair loss was 4, 100% was 5, AT was 6, AT with partial body hair loss was 7, AU was 8.	• (1) Cured: all hairs grew out again, normal in density of distribution, color and luster, and negative in pulling hair test; (2) markedly effective: 50% of hairs grew out again, almost normal in density of distribution, color and luster, with many fine hair turning into hair, and negative in pulling hair test; (3) effective: 10% of hairs grew out again (including fine hair) but grew slowly, and negative or positive in pulling hair test; (4) ineffective: after a treatment of more than 3 months, no new hairs grew out or new hairs just less than 10% or continued with hair loss

'-': not reported

Table 3. Adverse Events

Berth-Jones et al, 1990	1. Oral inosiplex: Nil clinically significant adverse reactions. 2. Diphencyprone 1% solution: occasional severe eczematous rash, cervical adenopathy, vitiligo. 3. Both oral inosine pranobex and diphencyprone: not reported.
Cipriani et al, 2001	-
Dehghan et al, 2013	1. Oral prednisolone PT: 5 patients developed acne, 4 heartburn, 4 striae. 45% of patients developed side effects. 2. Intravenous methylprednisolone PT: 7 patients developed acne, 5 heartburn, 6 striae. 55% of patients developed side effects. The difference in adverse reactions was not statistically significant.
Ead et al, 1981	-
Galbraith et al, 1986	1. Oral inosiplex: Nil clinically significant adverse reactions. 2. Placebo: -
Georgala et al, 2006	1. Oral inosiplex: Nil clinically significant adverse reactions. 2. Placebo: -
Kar et al, 2005	1. Oral prednisolone PT: 11 (55%) patients developed side effects, most commonly general weakness. Other side effects included: acneiform eruption, weight gain, gastrointestinal upset, facial mooning, and oligomenorrhea. All the side effects gradually subsided in the 3-month follow-up period. 2. Placebo: -
Kurosawa et al, 2005	1. Oral prednisolone PT: 3/29 patients (10%) developed side effects, including dysmenorrhea and abdominal discomfort. 2. Intramuscular triamcinolone: 23/56 patients (41%) developed side effects, including abdominal discomfort, worsening acne, dysmenorrhea. 3. Oral dexamethasone: 6/20 patients (30%) developed side effects, including weight gain, abdominal discomfort, weakness, mooning.

Mehta et al, 2012	Only 2 side effects were noted: secondary infection and hypopigmentation in 1 patient each. It was not noted in which treatment arms these patients were from.
Perini et al, 1994	1. Imipramine: Nil clinically significant adverse reactions. 2. Placebo: -
Price et al, 2008	1. Efalizumab: Generally, well tolerated. 2. Placebo: - No statistically significant difference in frequency of adverse events between the efalizumab and placebo treatment groups. Adverse reactions for both groups include: headache, fever, infection, nausea, rash, myalgia, and pharyngitis.
Saif et al, 2012	40 (95%) patients reported 186 adverse events, most commonly fatigue (n=27, 64%), weight gain (n=19, 45%), steroid induced acne (n=15, 35.7%), and sleep disturbances (n=14, 33%). It was not noted in which treatment arms these patients were from.
Strober et al, 2009	3. Alefacept: Generally, well tolerated. 4. Placebo: - The most frequently reported AEs in both treatment groups were upper respiratory infections, headaches, and nasal congestion.
Tosti et al, 1991	-
Yang et al, 2012	1. Oral TGPC: 6 cases of adverse reactions which were mild and resolved after decreasing medication. Reaction not specified. 2. Oral CGT: 7 cases of adverse reactions which were mild and resolved after decreasing medication. Reaction not specified. No statistical difference (P=0.695) in adverse reactions between groups.
Yang et al, 2013	1. Oral TGPC and CGT: 7 cases of adverse events, most frequently abdominal pain and loose stools. 2. Oral CGT: 6 cases of adverse events, most frequently oedema, rash and weight gain. All events were mild and resolved after decreasing medication. No statistical difference in incidence of adverse events between the two groups.

'-': not reported

Table 4. Studies Reporting Relapse Rate

Galbraith et al, 1986	7/11 (64%) of oral inosiplex patients	-	Within 2-11 months
Kar et al, 2005	2/8 (25%) of oral prednisolone PT patients	> 20% hair loss compared with baseline	By 3 months
Kurosawa et al, 2005	10/29 (33%) of oral prednisolone PT patients, 20/43 (46%) of intramuscular triamcinolone patients, 14/19 (75%) of oral dexamethasone patients 6 months post-treatment. The relapse rate was significantly different only	Appearance of new bald patches or abnormal increase of hair fall.	At least 3 months

	between the dexamethasone group and the prednisolone group. In subgroup analyses of AT/AU patients, the relapse rate was 49% in oral prednisolone PT patients, 71% in intramuscular triamcinolone patients, and 100% in the oral dexamethasone group. There was a significant difference in the relapse rate between the oral dexamethasone group and the prednisolone group.		
Saif et al, 2012	Reported for all groups: 13/34 (38.2%) patients relapsed, 5 (14.7%) patients developed moderate hair fall, 3 (8.8%) patients developed mild hair fall, 7 (20.1%) patients maintained their hair regrowth and 6 (17.6%) patients were lost to follow up.	Recurrence or worsening of alopecia from its original severity.	Between 1 to 4 years

'-': not reported

Table 5. Response Rate

Berth-Jones et al, 1990	Oral inosine pranobex: 0/10 (0%)	Diphencyprone 1% solution: 1/11 (9%)	Oral inosine pranobex and diphencyprone: 1/11 (9%)
Cipriani et al, 2001	Oral paroxetine: 2/8 (25%)	Placebo: 1/5 (20%)	N/A
Dehghan et al, 2013[1]	Oral prednisolone PT: 5/18 (27.8%)	Intravenous methylprednisolone PT: 13/17 (76%)	N/A
Ead et al, 1981	Oral zinc sulphate: -	Placebo: -	N/A
Galbraith et al, 1986	Oral inosiplex: 8/17 (47%)	Placebo: -	N/A
Georgala et al, 2006[2]	Oral inosiplex: 5/15 (33.3%)	Placebo: 0/14 (0%)	N/A
Kar et al, 2005	Oral prednisolone PT: 8/20 (40%)	Placebo: 0/16 (0%)	N/A
Kurosawa et al, 2005	Oral prednisolone PT: 19/29 (66%)	Intramuscular triamcinolone: 32/43 (74%)	Oral dexamethasone: 7/19 (37%)
Mehta et al, 2012[3]	Liquid phenol (20%) and oral betamethasone minipulse therapy: 15/17 (88.23%)	Liquid phenol (20%) with topical minoxidil (2%): 9/17 (52.94%)	Liquid phenol (20%): 8/17 (47.06%)
Perini et al, 1994[4]	Imipramine: 1/7 (14%)	Placebo: 0/6 (0%)	N/A
Price et al, 2008	Subcutaneous efalizumab: 2/37 (5%)	Placebo: 0/25 (0%)	N/A

Saif et al, 2012	Oral methylprednisolone PT, 3 consecutive days once every 2 weeks for 24 weeks: 3/6 (50%)	Oral methylprednisolone PT, 2 consecutive daily pulses every 3 weeks for 24 weeks: 3/9 (33%)	Oral methylprednisolone PT, 3 consecutive daily pulses every 3 weeks for 24 weeks: 6/27 (22%)
Strober et al, 2009	Oral alefacept: 2/23 (9%)	Placebo: 2/22 (9%)	N/A
Tosti et al, 1991	Intravenous thymopentin: 0/10 (0%)	Topical 10% cyclosporine in oily solution: 0/8 (0%)	Photochemotherapy: 0/8 (0%)
Yang et al, 2012[5]	Oral TGPC: 30/44 (68%)	Oral CGT: 30/42 (71%)	N/A
Yang et al, 2013[5]	Oral TGPC and Oral CGT: 49/60 (82%)	Oral CGT: 31/57 (54%)	N/A

Treatment response as defined by each RCT. Figures represent number who respond / total number of participants of treatment arm.

[1] At least 60% hair regrowth reported.

[2] 'Complete' response reported.

[3] Grade 4 improvement reported.

[4] Full response reported.

[5] 'Cured' and 'markedly effective' rate reported.

'-': not reported