Methotrexate for alopecia areata: A systematic review and meta-analysis

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Background: Methotrexate has been used both as monotherapy and as an adjunct to corticosteroids in the treatment of alopecia areata (AA), though there exists a paucity of definitive evidence and guidelines in this setting.

Objectives: To 1) determine the efficacy and risks associated with methotrexate therapy for AA, 2) determine the differences in efficacy of combination (methotrexate plus corticosteroids) versus stand-alone (methotrexate) treatment, and 3) determine the relative efficacy of methotrexate in adult versus pediatric populations.

Methods: A systematic review and meta-analysis was performed according to recommended PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] guidelines.

Results: Methotrexate has reasonable effectiveness in patients with severe AA; adults appear to be more responsive to methotrexate treatment than pediatric patients. Combination treatment results in a higher complete response rate than methotrexate stand-alone treatment. A large proportion of patients had recurrence in the setting of tapering treatment. Complication rates were acceptable and similar between adult and pediatric patients.

Limitations: The studies reviewed were retrospective observational studies with heterogeneity between centers in terms of methotrexate dosages and protocols in use for AA, and there was a lack of data beyond 1 year for the adjunctive treatments.

Conclusion: Methotrexate is an effective monotherapy or adjunct therapy in combination with corticosteroids in the treatment of severe AA. (J Am Acad Dermatol 2019;80:120-7.)

Key words: alopecia; alopecia areata; dermatology; meta-analysis; methotrexate; systematic review.

Alopecia areata (AA) is a common cause of nonscarring alopecia in both pediatric and adult populations. While it poses no threat to mortality, it has the potential to exert a significant impact on morbidity.[1] In most cases, it is a self-limiting disease with approximately half of cases remitting spontaneously within 12 months. Relapse is common however, and for some patients it follows a chronic course. Treatment of AA remains challenging, with <20% of patients obtaining complete long-term hair regrowth.[2-6] This is particularly true in the pediatric population, where tolerability of therapy and need for blood testing pose specific challenges to management. Although there have been a variety of different treatment options studied and used for AA, their efficacy remains variable and there is a lack of high-quality randomized evidence to guide treatment. Standard

Abbreviations used:

AA: alopecia areata
CI: confidence interval

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treatment options include topical and systemic corticosteroids, topical tacrolimus, immunotherapy, and phototherapy, with variable efficacy particularly in severe AA, and some promise had been shown for newer agents, such as the Janus kinase inhibitors tofacitinib and ruxolitinib. Although high-dose pulsed corticosteroids have been shown to have reasonable efficacy in terms of regrowth rates,[7-9] recurrence occurs without maintenance, and long-term steroid therapy is not without sequelae.

Methotrexate has also been proposed in the management of AA. Methotrexate is known to be effective across a range of inflammatory and autoimmune disorders.[10-13] Methotrexate has been used as an adjunct for low-risk maintenance therapy after initiation with corticosteroids, and in some studies, outcomes for methotrexate stand-alone therapy have been reported for AA. Since the initial report by Joly,[14] there have been numerous reports in both adult and pediatric populations with AA in which various dosage protocols (monotherapy or combination with corticosteroids) were used. There remains a lack of clear definitive evidence or guidelines regarding the most effective regimen for use of methotrexate in the management of AA.

The aim of this systematic review and meta-analysis was 1) to determine the efficacy and risks associated with methotrexate therapy for AA, 2) to determine the differences in treatment efficacy of methotrexate stand-alone or combination (combined with corticosteroids) therapy, and 3) to determine the relative efficacy of methotrexate for AA in adult versus pediatric populations.

CAPSULE SUMMARY

- There is lack of synthesized data regarding methotrexate in alopecia areata.
- A good response was observed in 63% of patients and a complete response in 36% of patients. Initial regrowth is observed after 3 months of treatment and takes 6-12 months to achieve complete regrowth. The pooled recurrence rate of alopecia areata was 47.7%.
- Methotrexate is an effective monotherapy and adjunct to corticosteroids and should be considered in the treatment of severe AA in adults and children.

METHODS

Search strategy

The present systematic review and meta-analysis was performed according to recommended PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[15] Electronic searches were performed with Ovid MEDLINE, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ACP Journal Club, and Database of Abstracts of Review of Effectiveness from their dates of inception to May 5, 2018. To achieve the maximum sensitivity of the search strategy, we combined the terms "alopecia areata," "methotrexate," "corticosteroid," and "prednisone," as either key words or medical subject heading terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies and assessed by using the inclusion and exclusion criteria.

Selection criteria

Eligible studies for the present systematic review and meta-analysis included those in which patient cohorts received methotrexate for AA, either in combination with corticosteroids or as monotherapy. Both single-arm and comparative studies were included, as well as case series. Studies that did not include response rates or complications as endpoints were excluded. Reports of all languages were included in the systematic review. Abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded.

Data extraction

All data were extracted from article texts, tables, and figures. Both authors independently reviewed each retrieved article. Discrepancies between the authors were resolved by discussion and consensus. The final results were reviewed by the senior investigator (Dr Sebaratnam).

Statistical analysis

A meta-analysis of proportions was conducted for response rates, recurrences, and complications. To incorporate heterogeneity (anticipated among the included studies), transformed proportions were combined by using DerSimonian-Laird random effects models. Heterogeneity was evaluated by using Cochran Q and I^2 test, with values >50% considered as substantial heterogeneity. I^2 can be calculated by using the formula $I^2 = 100\% \times (Q - df)/Q$, with Q defined as the Cochrane heterogeneity statistic and df as the degrees of freedom. Meta-regression was used for subgroup analysis to compare results in adult versus pediatric cases. For comparative outcomes, odds ratio was used as a summary statistic. All analyses were performed by using the metafor package for R version

Table I. Characteristics of included studies in this systematic review and meta-analysis

First author	Publication year	Study period	Study type	N	Population	Treatment regimen
Landis[17]	2018	2011-2018	R, OS	14	Pediatric AA	Starting on 2.5-5 mg methotrexate in most cases, then advanced to 7.5-15 mg/wk. 12/14 on prednisolone before or during
Lim[18]	2017	2008-2014	R, OS	29	Adult AA	Starting on 10 mg/wk methotrexate, increasing by 2.5 mg every 2 weeks
Chong[19]	2017	2010-2015	R, OS	14	Pediatric AA	3 days IV methylprednisolone 10 mg/kg/d for 3 mo, followed by methotrexate 0.2 mg/kg/d
Alsufyani[20]	2017	NR	R, OS	28	Adult AA	Starting dose methotrexate 10-25 mg/wk, combinations with minoxidil, ILCS, and systemic CS
Alkeraye[21]	2017	2012-2015	P, OS	20	Adult AA	3 days IV methylprednisolone 500 mg/d for 3 d, then monthly for 3 mo, then methotrexate at 10 mg/wk increased to 20 mg/wk for 6 mo
Lucas[22]	2016	2010-2014	R, OS	13	Pediatric AA	Maximum methotrexate 0.38 mg/kg/wk
Batalla[23]	2016	2016	R, OS	3	Pediatric AA	7.5-17.5 mg/wk of methotrexate
Anuset[24]	2016	2006-2012	R, OS	26	Adult AA	Starting at 15-20 mg/wk methotrexate with prednisone (initially 20 mg/d, then tapered)
English[25]	2015	2009-2011	R, OS	31	Adult AA	15-20 mg/wk methotrexate ± 1 mg/kg/d oral prednisolone
Hammerschmidt[26]	2014	NR	R, OS	31	Adult AA	Starting dose 10-25 mg methotrexate ± CS
Firooz[27]	2013	2011-2012	P, OS	10	Adult AA	5-10 mg/wk methotrexate and 0.5 mg/kg/d prednisolone tapered
Droitcourt[28]	2012	2007-2010	R, OS	20	Adult AA	Starting 12.5-25 mg/wk, with 3 d of high-pulse IV 500 mg methylprednisolone
Royer[29]	2011	2005-2009	R, OS	14	Pediatric AA	Starting 15-25 mg/wk, 8 of 14 with CS
Malekzad[30]	2010	2005-2008	R, OS	111	Adult AA	3 cycles of 500 mg/d methylprednisolone for 3 d, at 1-mo intervals, then methotrexate 10 mg/wk with oral prednisolone 15 mg/d for 1 y
Chartaux[31]	2010	2000-2008	R, OS	33	Adult AA	Starting 15-25 mg/wk with oral CS, 19 mixed vs 14 methotrexate alone
Joly[14]	2006	NR	R, OS	22	Adult AA	Starting 15-25 mg/wk (16 combination vs 6 methotrexate only)

AA, Alopecia areata; *CS*, corticosteroid; *ILCS*, intralesional corticosteroid; *IV*, intravenous; *NR*, not reported; *OS*, observational study; *P*, prospective; *R*, retrospective.

3.3. *P* values <.05 were considered statistically significant.

RESULTS

A total of 459 references were identified through electronic database searches. After exclusion of duplicate or irrelevant references, 448 potentially relevant articles were retrieved (Supplemental Fig 1; available at http://www.jaad.org). After detailed evaluation of these articles, 29 studies remained for assessment. Manual search of reference lists yielded 1 new study. After applying selection criteria, 16 studies[14,16-30] were selected for analysis. The study characteristics of these trials are summarized in Table I.

Assessment of efficacy

A complete response was defined as 100% regrowth of hair. Overall, the proportion of complete responses to methotrexate in AA was 35.8% (95% confidence interval [CI] 25.0%-48.3%). From subgroup analysis, the pooled complete response in adult studies was 44.7% (95% CI 32.9%-57.1%) compared with 11.6% (95% CI 5.1%-24.5%) in the pediatric population. There was a significantly higher complete response in adult cases (P = .001; Fig 1).

A good or complete response was defined as 50%-100% regrowth of hair and deemed cosmetically satisfactory. The pooled rate of good and complete responses in patients taking methotrexate for AA was 63.2% (95% CI 54.0%-71.5%). From subgroup analysis, the pooled rate of good and complete responses was 69.3% (95% CI 59.5%-77.7%) in adults and 46.5% (95% CI 34.0%-59.5%) in the pediatric population. This difference was significant (P = .001; Fig 2).

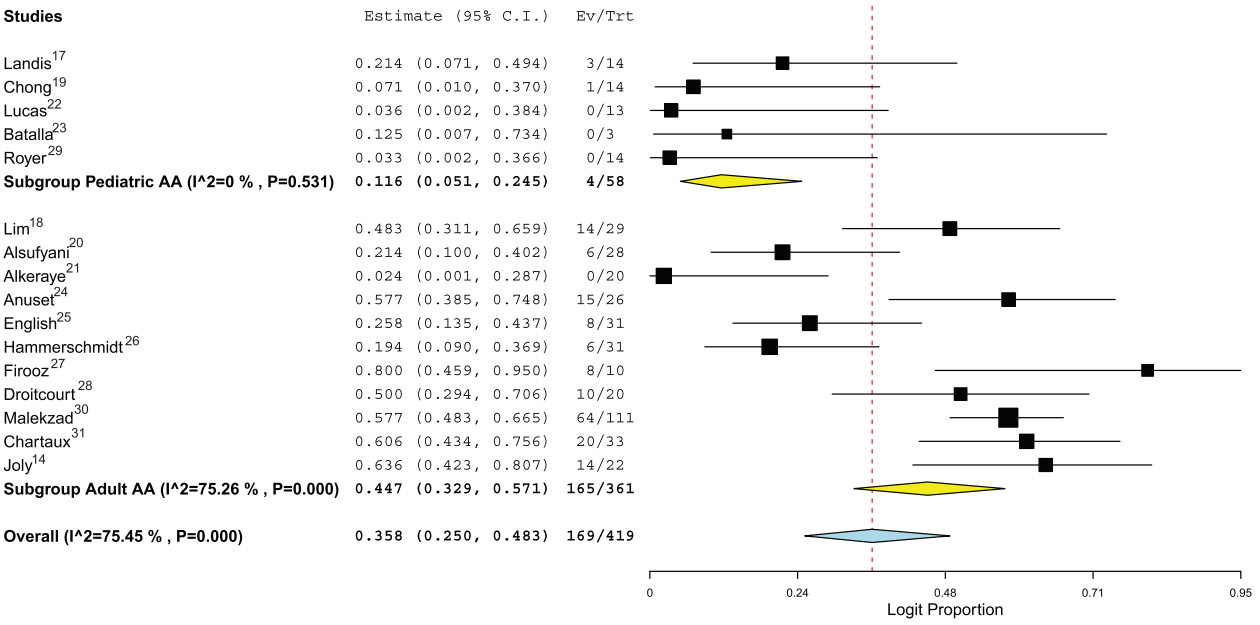

Fig 1. Forest plot comparing the proportion of pediatric and adult AA populations with complete responses on methotrexate treatment. P = .001 for difference between subgroups. *AA*, Alopecia areata; *CI*, confidence interval; *Ev*, event; *Trt*, treated.

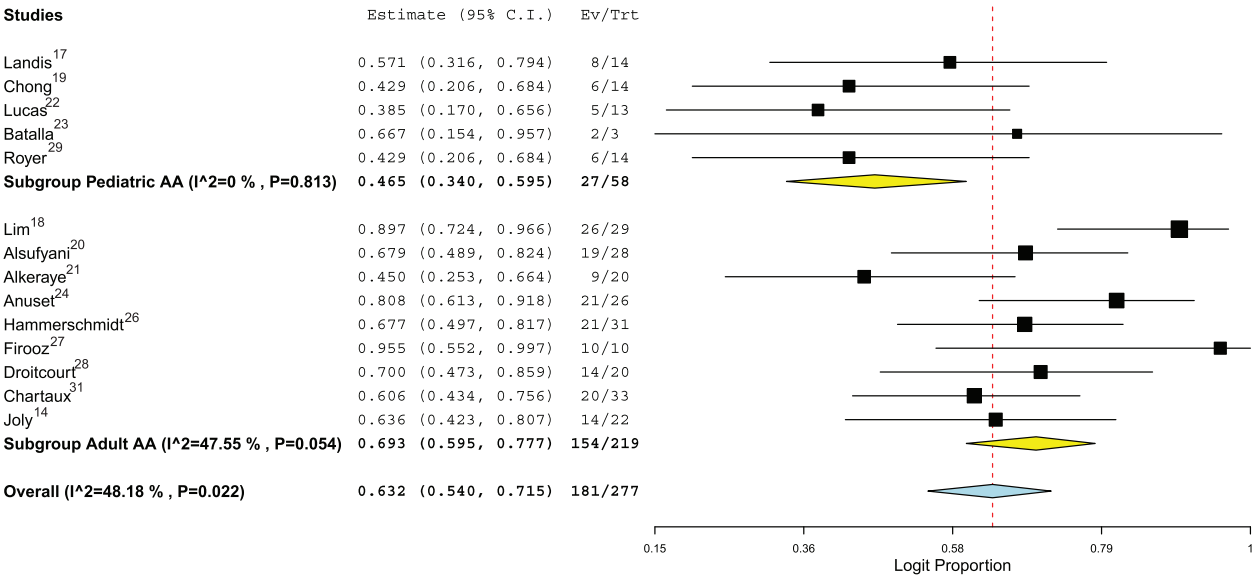

Fig 2. Forest plot comparing the proportion of pediatric and adult AA populations with good and complete responses to methotrexate treatment. P = .001 for difference between subgroups. *AA*, Alopecia areata; *CI*, confidence interval; *Ev*, event; *Trt*, treated.

Assessment of combination versus stand-alone methotrexate

In 4 included studies, patients treated with methotrexate and corticosteroids were compared with those treated with methotrexate monotherapy. Combination therapy had a significantly higher odds of good or complete responses compared with methotrexate monotherapy (odds ratio 2.73, 95% CI 1.19-6.27, I^2 = 0%, P = .018), with minimal heterogeneity in the pooled analysis (Fig 3).

Time course of hair growth

The time delay to beginning diffuse hair regrowth was pooled from the available data from 6 included studies and was found to be 3.125 (95% CI 2.3-4.0) months (Supplemental Fig 2, *A*; available at http://www.jaad.org). By using the data from 2 studies, the pooled time to initial complete regrowth was found to be 9.9 (95% CI 6.0-13.8) months (Supplemental Fig 2, *B*).

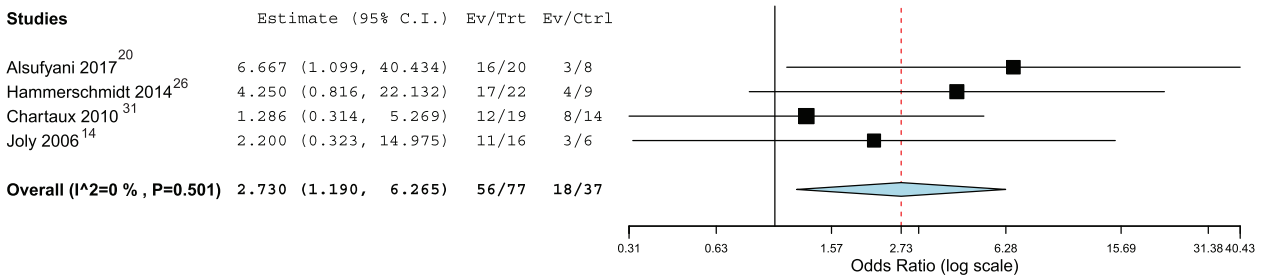

Fig 3. Forest plot comparing the proportion of good and complete responses to methotrexate plus corticosteroid treatment versus methotrexate stand-alone treatment among adults with AA. *P* = .018 for difference between subgroups. *AA*, Alopecia areata; *CI*, confidence interval; *Ctrl*, control; *Ev*, event; *Trt*, treated.

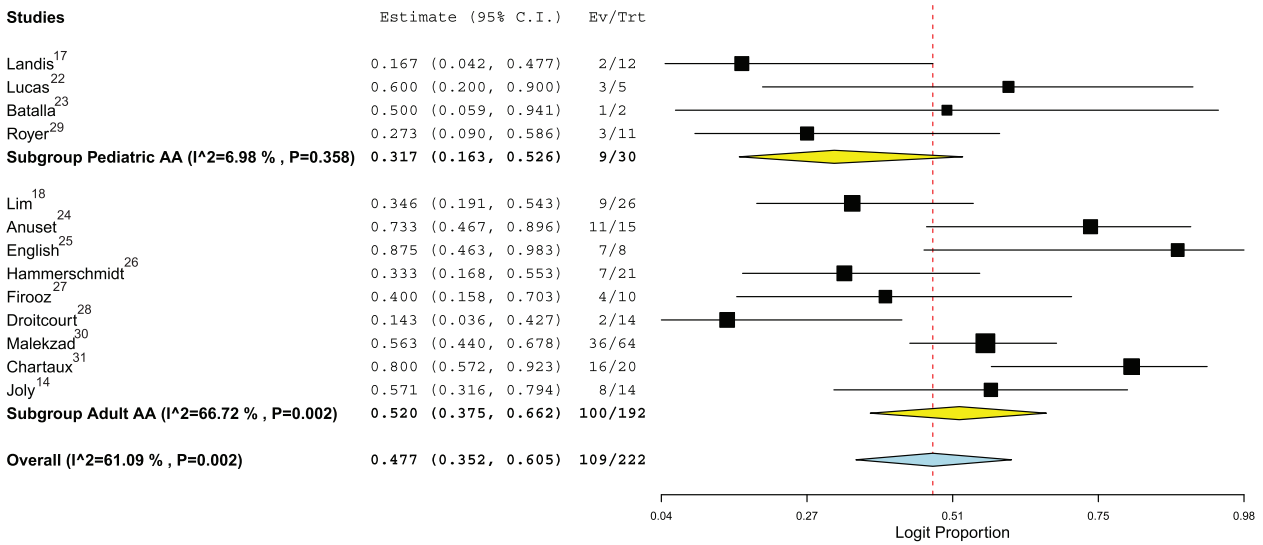

Fig 4. Forest plot comparing the proportion of recurrences after methotrexate treatment for pediatric versus adult AA populations. *P* = .19 for difference between subgroups. *AA*, Alopecia areata; *CI*, confidence interval; *Ev*, event; *Trt*, treated.

Assessment of recurrence

The pooled recurrence rate was 47.7% (95% CI 35.2%-60.5%), with significant heterogeneity (I^2 = 61.09%, *P* = .002). Subgroup analysis demonstrated a pooled recurrence rate of 52.0% (95% CI 37.5%-66.2%) in adult cases and 31.7% (95% CI 16.3%-52.6%) in pediatric cases. There was no significant difference between the subgroups (*P* = .19) (Fig 4). The reasons for recurrence and regrowth are listed in Table II; of particular note, the majority of recurrence was due to stopping or weaning off either the methotrexate or corticosteroid.

Assessment of complications

The total pooled complication rate was 22.1% (95% CI 14.8%-31.7%; Fig 5). A subgroup analysis demonstrated a pooled complication rate of 24.2% (95% CI 15.2%-36.4%) in adults and 14.5% (95% CI 6.6%-28.9%) in the pediatric population. Pooled complication rates were comparable (*P* = .31). The specific complications, which include changes in liver function test enzymes, gastrointestinal symptoms, hematologic changes, and nausea, are listed in Table III.

DISCUSSION

Treatment of severe or recalcitrant AA remains challenging and nonstandardized. Given that AA is associated with a detrimental impact on quality of life, particularly in pediatric cases, there is a need for effective therapeutic options, especially if the disease is refractory to first-line treatments. Methotrexate has been proposed as a potential treatment option for severe AA in adults and, to a lesser extent, AA in children. Our systematic review and meta-analysis of the current evidence demonstrates that methotrexate has reasonable effectiveness in patients with severe AA and that adults appear to be more responsive to methotrexate treatment than children. Second, we show that methotrexate taken in conjunction with corticosteroids results in higher good and complete

Table II. Recurrence rates reported in included studies, with reason for relapse

First author	Recurrence	Proposed reason for recurrence
Landis[17]	2/12	1 case secondary to stress, 1 case after steroid taper
Lim[18]	9/26	Not stated
Chong[19]	NR	NR
Alsufyani[20]	NR	NR
Alkeraye[21]	NR	NR
Lucas[22]	3/5	Due to methotrexate stopped or tapered
Batalla[23]	1/2	Not stated
Anuset[24]	11/15	3 cases occurred when treatment stopped
English[25]	7/8	6 cases occurred due to methotrexate being stopped or tapered
Hammerschmidt[26]	7/21	1 case during treatment, 3 at time of treatment withdrawal, and 3 cases after methotrexate discontinuation
Firooz[27]	4/10	All cases due to tapering of doses; 3 cases reversed with steroids, 1 case when methotrexate dosage restored
Droitcourt[28]	2/14	Both occurred when methotrexate use stopped
Royer[29]	3/11	2 cases during treatment, 1 case after methotrexate was stopped
Malekzad[30]	36/64	Occurred during tapering of CS or within 1 year of therapy discontinuation
Chartaux[31]	16/20	Occurred when CS was reduced or tapered; 14 reversed when CS was given
Joly[14]	8/14	Occurred when methotrexate was tapered or stopped, reversible

CS, Corticosteroid; *NR*, not reported.

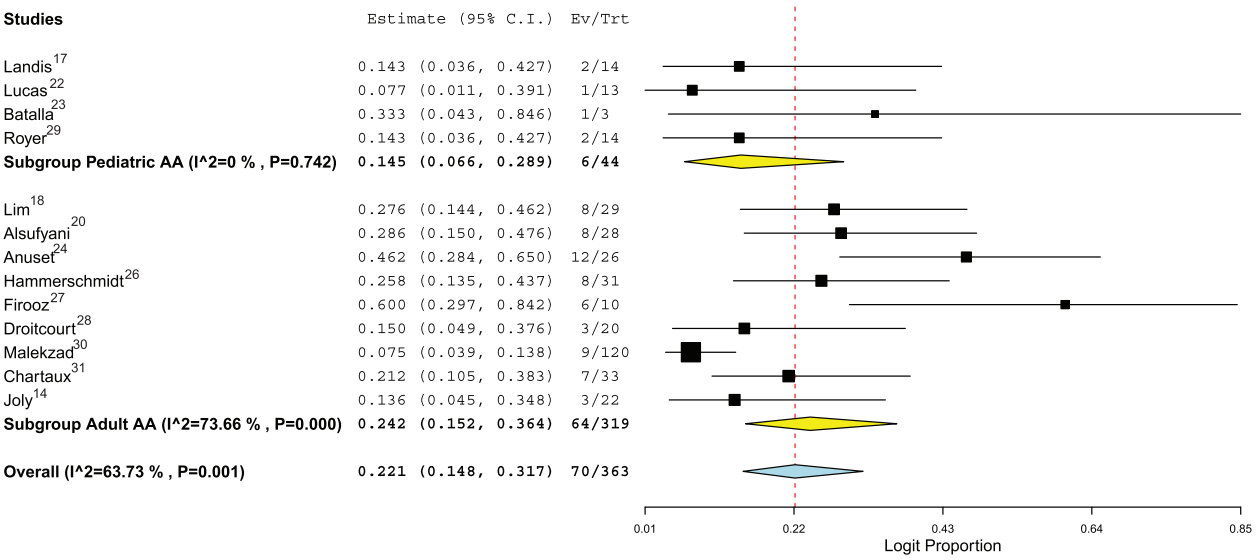

Fig 5. Forest plot comparing total complications after methotrexate treatment for pediatric versus adult AA populations. $P = .31$ for difference between subgroups. *AA*, Alopecia areata; *CI*, confidence interval; *Ev*, event; *Trt*, treated.

response rates than methotrexate taken alone. Third, we found that a large proportion of recurrences occurred in the setting of tapering treatment, which highlights the refractory nature of AA in patients with chronic disease. Complication rates of methotrexate were acceptable and similar between adults and pediatric cases.

The results of our systematic review and meta-analysis is consistent with several prior studies. Joly[14] and Droitcourt et al[28] reported satisfactory regrowth in 64% and 70% of adult cases, respectively, compared with pooled good and complete responses in 68.6% of adults in the present meta-analysis. Factors contributing to satisfactory response were studied by Hammerschmidt et al[26] in their retrospective study of 31 patients with AA. They found response to be associated with male sex, age >40 years, systematic corticosteroid therapy, and a cumulative methotrexate dose of 1000-1500 mg. Likewise in the present study, we found the pooled response rate of adults to be higher than that of the pediatric population and that

Table III. Complications reported by the included studies

First author	Total complications	LFT changes	Gastrointestinal symptoms	Hematologic	Pulmonary TB	Nausea	Other
Landis[17]	1/14	NR	NR	NR	NR	0/14	1 unclear, 1 tooth sensitivity and leg weakness
Lim[18]	8/29	3/29	3/29	1/29	1/29	0/29	NR
Chong[19]	NR	NR	NR	NR	NR	NR	NR
Alsufyani[20]	8/28	2/28	3/28	3/28	0/28	0/28	NR
Alkeraye[21]	NR	NR	NR	NR	NR	NR	NR
Lucas[22]	1/13	0/13	0/13	0/13	0/13	1/13	NR
Batalla[23]	1/3	1/3	0/3	0/3	0/3	0/3	NR
Anuset[24]	12/26	4/26	0/26	0/26	0/26	0/26	2 acne, 4 weight gain, 1 steroid-induced cataract, 1 pneumocystis pneumonia
English[25]	NR	NR	NR	NR	NR	NR	NR
Hammerschmidt[26]	8/31	2/31	3/31	3/31	0/31	0/31	NR
Firooz[27]	6/10	0/10	0/10	1/10	0/10	0/10	2 acne, 2 muscle cramp, 1 herpes simplex, 1 hypertension, 1 weight gain, 1 amenorrhea
Droitcourt[28]	3/20	0/20	0/20	1/20	0/20	2/20	NR
Royer[29]	2/14	0/14	0/14	0/14	0/14	1/14	1 herpes simplex
Malekzad[30]	9/120	2/120	4/120	0/120	0/120	1/120	2 weight gain
Chartaux[31]	7/33	4/33	2/33	1/33	0/33	0/33	NR
Joly[14]	3/22	2/22	0/22	0/22	0/22	1/22	NR

LFT, Liver function tests; *NR*, not reported; *TB*, tuberculosis.

combined methotrexate and corticosteroid treatment offered higher response rates than methotrexate treatment alone.

The most common adverse effects of methotrexate found in our review were hematologic and hepatic. The relative risk for these adverse effects was low but highlights the importance for regular monitoring. In the pediatric setting specifically, the benefit-harm ratio must be considered judiciously.

The optimal duration of methotrexate treatment has yet to be determined. Studies by Joly,[14] Chartaux and Joly,[31] and Royer et al[29] suggest responders should continue to take methotrexate for 18-24 months then taper. However, the results of this systematic review demonstrate that tapering of methotrexate treatment is associated with recurrence, and therefore, treating clinicians should consider a longer period of methotrexate treatment if therapy is well tolerated. It is also possible that the patients who showed early responses to methotrexate were maintained on the drug, receiving a greater cumulative dose and longer treatment course. However, a longer treatment course might not necessarily reflect a greater therapeutic benefit but rather selection bias. Our analysis of the time course for recovery found that the start of initial regrowth occurs after an average of ~3 months of treatment and might take 6-12 months for complete regrowth to occur. Our systematic review did not demonstrate any significant difference in complications or rates in adults versus pediatric AA.

The present study was limited by several constraints. First, most of the available evidence to date are retrospective observational studies; prospective controlled trials evaluating the effectiveness and risks of methotrexate for the treatment of AA are lacking. Second, there was heterogeneity between the centers in terms of dosages and protocols used for methotrexate and adjunctive treatment of AA. Methotrexate could have been introduced before or after corticosteroids or used as a stand-alone therapy after steroid failure. We addressed this variation by performing a subgroup analysis comparing methotrexate and corticosteroid therapy with methotrexate monotherapy for AA. A subgroup analysis could not be performed to compare outcomes among methotrexate-treated patients with alopecia totalis or alopecia universalis, given the limitations in the available evidence. There was also a shortage of long-term data beyond 1 year, and thus, more long-term data are required. The impact

of methotrexate on quality of life in patients with AA requires further evaluation in future trials.

In summary, we provide a summary of the available evidence on the use of methotrexate in adult and pediatric AA populations. We found that methotrexate is another effective option for AA, with better response rates when used concomitantly with corticosteroids. Higher rates of good or complete response appear to be obtained in adult patients compared with pediatric patients, with a similar risk profile. Relapse often occurs in the setting of treatment tapering, highlighting the refractory nature of severe AA. Our study supports the use of methotrexate as an effective monotherapy or adjunct to corticosteroids in the treatment of severe AA.

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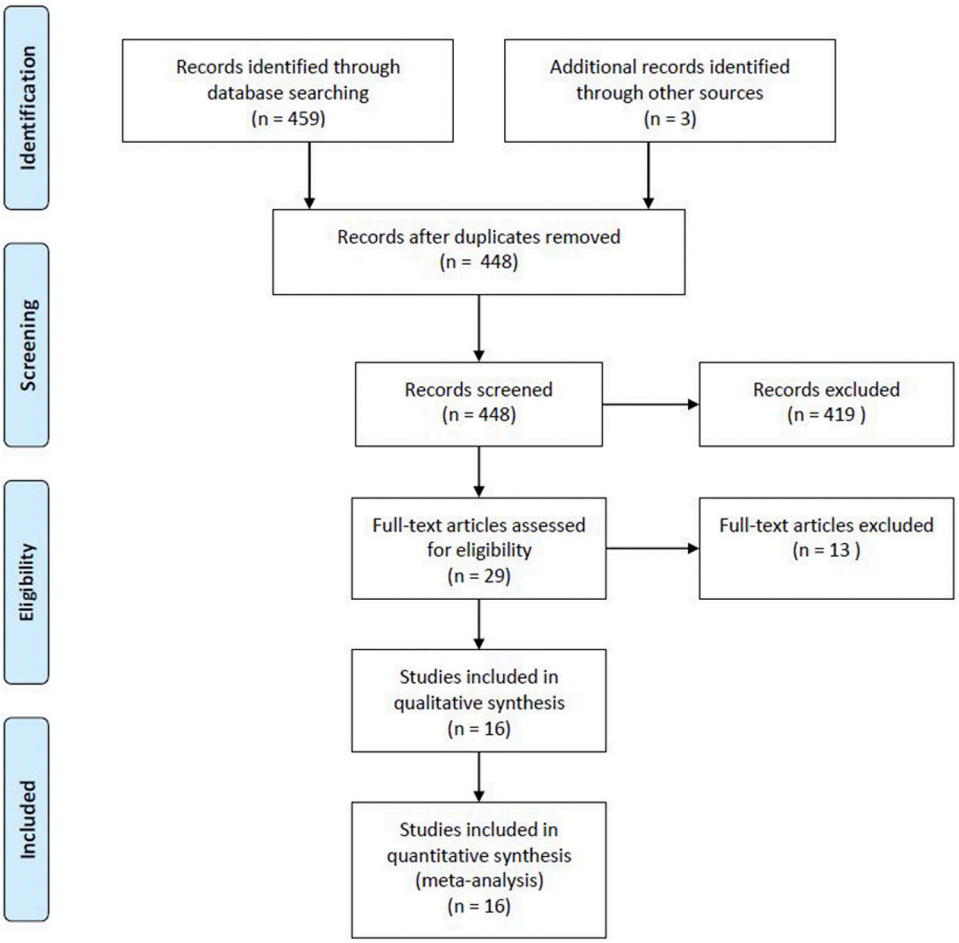
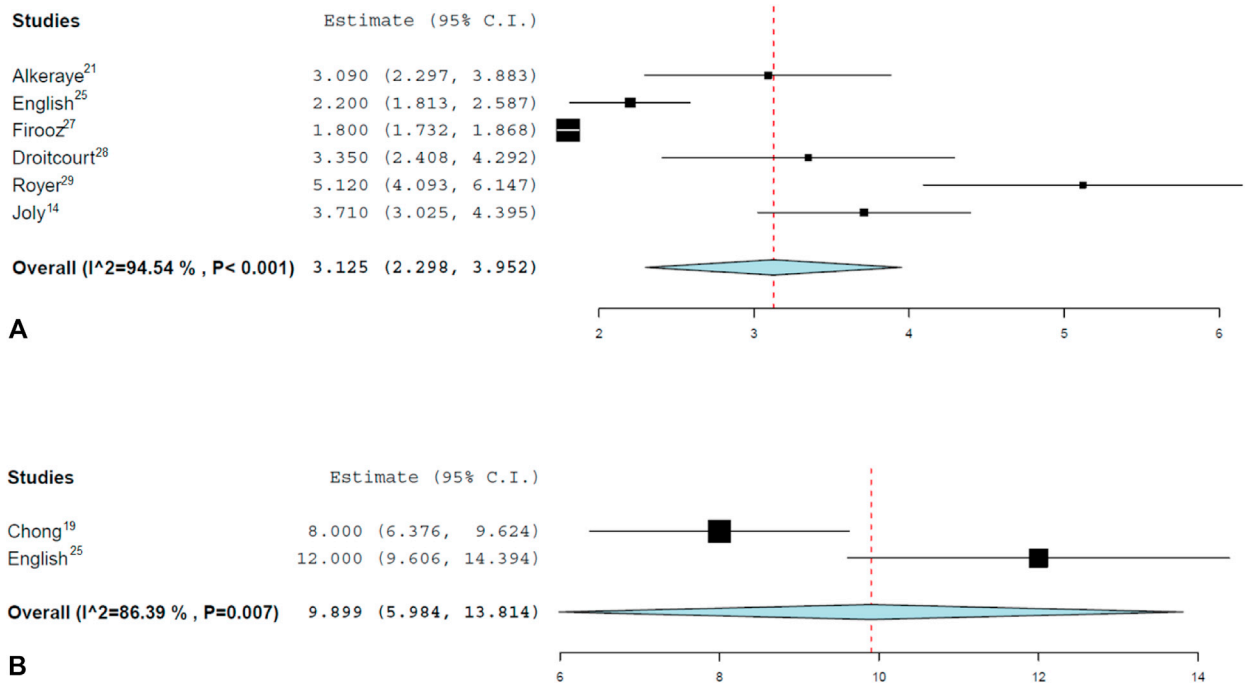


Supplemental Fig 1. PRISMA flow chart of search strategy for present systematic review. *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



Supplemental Fig 2. Forest plot of pooled meta-analyses showing delay to the beginning of regrowth in months (**A**) and time to initial complete regrowth (**B**). *CI*, Confidence interval.