Cyclosporine for moderate-to-severe alopecia areata: A double-blind, randomized, placebo-controlled clinical trial of efficacy and safety

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Background: Despite widespread use of steroid-sparing agents, particularly cyclosporine, for treatment of alopecia areata (AA), there are no clinical trials investigating the efficacy of these agents.

Objective: To evaluate the efficacy of cyclosporine compared with placebo at 3 months in patients aged 18 to 65 years with moderate-to-severe AA.

Methods: A double-blind, randomized, placebo-controlled trial was conducted. Adults aged 18 to 65 years of age with moderate-to-severe AA were randomized in a 1:1 ratio to receive 3 months of cyclosporine (4 mg/kg/d) or matching placebo. Blinded assessments included physical examination, blood biochemistry, photography, quality of life measurements, and efficacy evaluation using Severity of Alopecia Tool score and eyelash and eyebrow assessment scales.

Results: The results obtained for 32 participants (16 who received cyclosporine and 16 who received placebo) were analyzed. Compared with the placebo group, the cyclosporine group had a greater proportion of participants achieving at least a 50% reduction in Severity of Alopecia Tool score (31.3% vs 6.3% [$P = .07$]) and greater proportion of participants achieving a 1-grade improvement in eyelash (18.8% vs 0% [$P = .07$]) and eyebrow (31.3% vs 0% [$P = .02$]) scale score.

Limitations: Small sample size and single-institution trial may limit interpretation and generalizability of these results.

Conclusion: Response approached but did not reach a statistically significant difference between cyclosporine and placebo. (J Am Acad Dermatol 2019;81:694-701.)

Key words: alopecia; alopecia areata; clinical trial; cyclosporine; immunosuppressive agents; randomized controlled trial.

Alopecia areata (AA) is the most common autoimmune disease in humans[1] and the third most prevalent hair loss condition, following androgenetic and diffuse alopecia,[2] with a lifetime incidence of 1.7%.[3] As a T-cell–mediated autoimmune disease of the hair follicle, AA results in acute or chronic patches of nonscarring hair loss, ranging from a single patch to multifocal patches to total scalp hair loss (alopecia totalis [AT]) or total scalp and body hair loss (alopecia universalis [AU]). The etiology remains unknown, though genetic, environmental, and immune elements are involved.

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Current management of AA is suboptimal. Initial therapy includes topical and intralesional corticosteroids. In extensive refractory cases, systemic agents are trialed.[4] However, the literature is deficient in high-quality studies evaluating systemic agents. Our systematic review found only 8 placebo-controlled trials evaluating systemic agents,[5] including no trials evaluating any steroid-sparing agents, such as cyclosporine, methotrexate, and azathioprine, despite common clinical use.

Specifically, cyclosporine, is a popular steroid-sparing agent used to arrest disease progression and induce hair regrowth as a second-line agent in steroid-responsive but steroid-dependent patients. A number of case series have suggested a favorable response rate.[6-9] However, the evidence from these studies is critiqued for small sample sizes, a lack of control, vague definitions of treatment success, and combination with corticosteroids.

Currently, cyclosporine is used for a number of other dermatologic conditions, including eczema and psoriasis. Doses of up to 6 mg/kg/d have been studied in patients with AA. The current literature estimates response rates of cyclosporine to be between 33% to 55%[6-9]; however, this has not been evaluated in randomized controlled trials.

We report what to our knowledge is the first randomized placebo-controlled trial for evaluating the efficacy of cyclosporine in moderate-to-severe AA.

CAPSULE SUMMARY

- Monotherapy cyclosporine is moderately effective at inducing remission in patients with moderate-to-severe alopecia areata.
- These results will guide clinicians in their choice of second-line agent for patients with alopecia areata who are steroid responsive but steroid dependent.

METHODS

Trial design

This was a single-center, double-blind, randomized, placebo-controlled, parallel group study conducted in Melbourne, Australia. The study was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) before enrollment of the first patient (registration no. ACTRN12618001084279).

Participants

Eligible participants were all adults aged 18 to 65 years of age with moderate-to-severe AA. The exclusion criteria were pregnancy and lactation; history of any lymphoproliferative disorder, HIV, hepatitis B, or hepatitis C; hypersensitivity to any ingredient of the medication; use of any hair regrowth treatments before the study without an adequate washout period (generally 5 half-lives); inability to adhere to study procedures and visits; and any acute or chronic medical or laboratory abnormality that may increase the risk of study participation (ie, clinically significant, severe, progressive, and uncontrolled diseases).

Interventions, blinding, and randomization

Participants were randomized in a 1:1 ratio to receive 3 months of either cyclosporine (4 mg/kg/d) or matching placebo. The trial medication was in capsule form, supplied in bottles for twice-daily oral administration, and prepared for each participant's weight. The placebo was identical to the active medication in shape (oblong, bisect caplet), size (capsule size 1), color (white), and taste (gelatin). Participants, study researchers, and all outcome assessors were blinded to the allocation sequence through an independent pharmacy who randomized participants according to a computer-generated randomization list and had no clinical involvement in the trial.

Study protocol

For each participant, the study took place over a maximum of 21 weeks with 6 visits. At screening, inclusion and exclusion criteria were reviewed and written informed consent obtained. Participant demographics, AA disease history, relevant medical history, and prior medication were recorded. Eligible participants were randomized and attended monthly clinical reviews. All visits included the following assessments: physical examination, vital signs, blood biochemistry (full blood examination, electrolytes, liver function tests, cyclosporine trough levels, and lipid levels at baseline and 1 month), urine pregnancy test for females of childbearing potential, and recording of adverse events and concomitant medications. Medication compliance was checked at each visit. The Severity of Alopecia Tool (SALT) score was used to measure efficacy. The SALT score is a summation of the weighted percentage of hair loss across 4 views of the scalp (left, right, back, and superior); it was assessed by the same investigator for all participants at each visit. Additionally, eyelash and eyebrow assessment scales were used; the scales rated quantity of eyelashes and eyebrows categorically from 0 (none) to 3 (normal). Extensive photography of the scalp, including both 2-dimensional and

Abbreviations used:

AA: alopecia areata
AT: alopecia totalis
AU: alopecia universalis
QOL: quality of life
SALT: Severity of Alopecia Tool

3-dimensional photography was performed at each visit to record hair loss. The numbers of nonvellus hairs were counted on macrophotography at baseline (visit 2) and at the end of treatment (visit 5). Participants self-completed 2 quality of life (QOL) questionnaires at each visit (the disease-specific instrument Alopecia Areata Symptom Impact Scale[10] and the generic instrument Assessment of Quality of Life-8D).[11]

Sample size

Sample size was calculated from the estimated proportions attaining response in each group, defined as a 50% reduction in SALT score at 3 months compared with at baseline. Previous case series suggest that the proportion of participants receiving cyclosporine who respond is approximately 50%,[9] and the proportion receiving placebo is 5%.[12] For a 2-sided 5% significance level and a power of 80%, a sample size of 16 participants per group was required.

Outcomes

The primary objective of this study was to evaluate the efficacy of cyclosporine compared with placebo at week 12 in patients aged 18 to 65 years with moderate-to-severe AA. Efficacy end points at week 12 included the proportions of participants achieving a 30%, 50%, 75%, and 100% reduction in SALT, the change from baseline in SALT score, the change from baseline in nonvellus hair counts by macrophotography, and the proportion of participants achieving at least a 1-grade improvement in eyelash and eyebrow assessment scale scores. Response was defined as at least a 50% reduction in SALT score at week 12 compared with at baseline. Two secondary objectives were defined: to evaluate the effect of cyclosporine compared with placebo on QOL at week 12 (measured through a change from baseline in Assessment of Quality of Life-8D and Alopecia Areata Symptom Impact Scale scores) and to evaluate the safety and tolerability of cyclosporine over time (measured through incidence of treatment-emergent adverse events and clinical laboratory abnormalities).

Statistical analysis

All statistical analyses were performed by using Stata software (version 12, StataCorp, College Station, TX).[13] A per protocol analysis was performed. Descriptive statistics were summarized by using means and standard deviations, as there were no significant outliers. Independent *t* tests for normally distributed continuous data and Mann-Whitney U tests for non-normally distributed continuous data were performed to compare groups. Chi-square tests were performed for categoric data. Statistical significance was defined as a *P* value less than .05.

Ethical approval

Ethical approval for this study was received from the Bellberry Human Research Ethics Committee, Committee E (Bellberry Human Research Ethics Committee code, EC00450).

RESULTS

Participant recruitment

Participants were recruited from May 2018 to July 2018. A total of 42 patients were screened; 36 met the inclusion criteria and were randomized (Fig 1).

Participant demographics

The participants were mostly similar across both groups (Table I). Their mean age was 41.0 years, and their mean age at onset of first episode of AA was 24.5 years. The cohort consisted of 80.6% females. The duration of the current episode of AA was on average 6.5 years, and this duration was slightly longer for the cyclosporine group (mean, 7.4) than for the placebo group (mean, 5.7) (P = .75). The mean percentage of scalp hair loss by SALT score at baseline was 79.4%. About half of the participants in each group had AT/AU (in the cyclosporine group, 55.5%; in the placebo group, 61.1%; [P = .92]), and 72.2% of all participants had a history of AT/AU at any time. Having another autoimmune disease was reported in 8.3% of participants, and having a family history of AA was reported in 4% of participants. Around half of the participants had no eyelashes (50.0%) or eyebrows (52.8%) at baseline.

Proportions of participants achieving a 30%, 50%, 75%, or 100% reduction in SALT score

Table II summarizes the results for the main objectives of this trial. Overall, 5 participants (31.3%) in the cyclosporine group achieved at least a 50% reduction at the end of 3 months, compared with 1 participant (6.3%) in the placebo

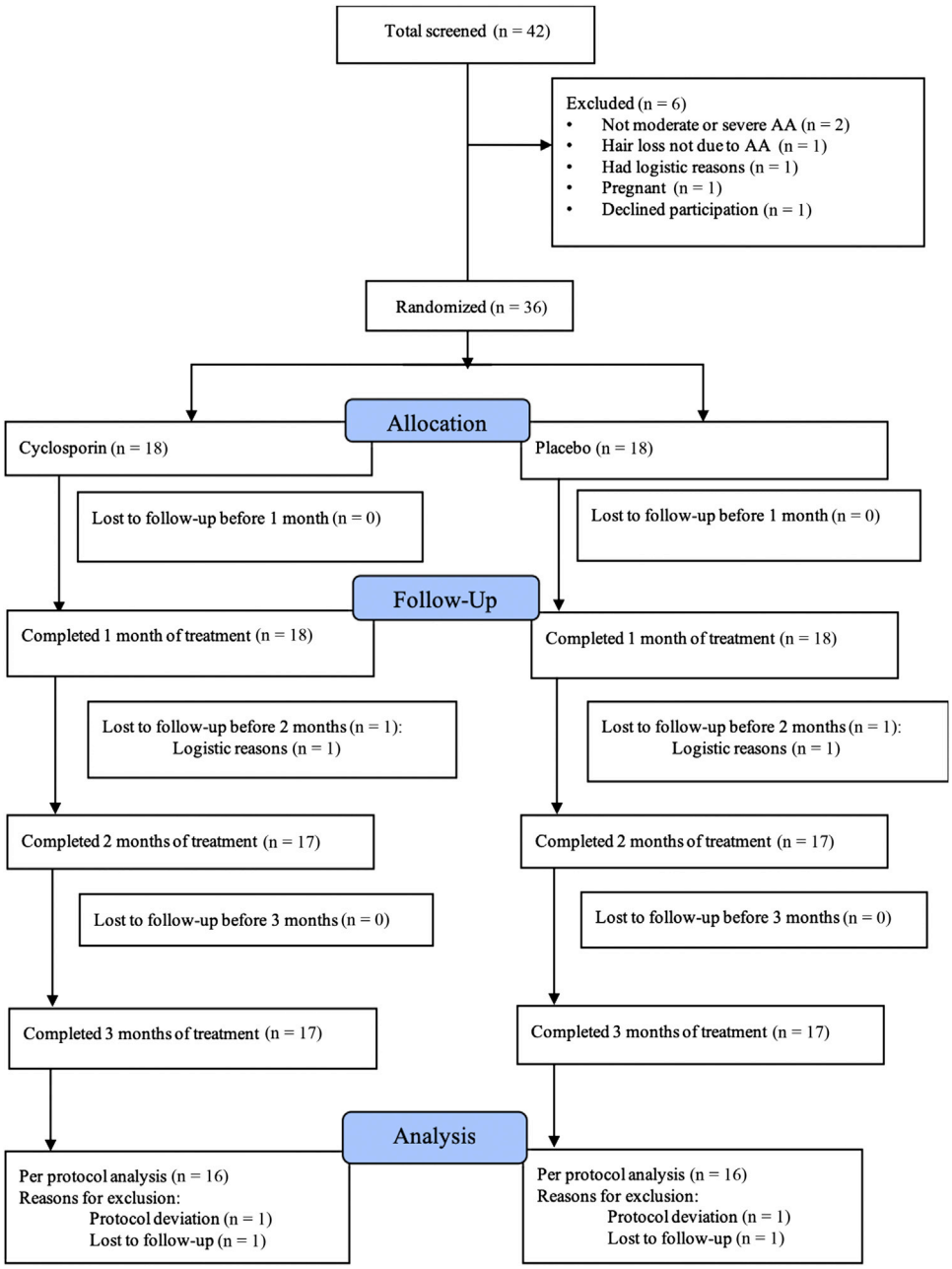

Fig 1. Flow diagram of allocation, follow-up, and analysis of participants.

group (P = .07). This response rate approached but did not reach statistical significance. One participant (6.3%) in the cyclosporine group achieved a 100% improvement in SALT score at 3 months, whereas none achieved this in the placebo group (P = .31).

Change in SALT score from baseline

Participants in the cyclosporine group had on average a greater reduction in SALT score over time than did participants in the placebo group (14.8% vs 2.3% [P = .23]) (Fig 2).

Change from baseline in nonvellus hair counts by macrophotography

On average, the nonvellus hair count increased more for the cyclosporine group than for the placebo group after 3 months (19.9 vs 1.8 [P = .07]).

Proportion of participants achieving at least a 1-grade improvement in eyelash and eyebrow assessment scales

A total of 3 participants in the cyclosporine group achieved a 1-grade improvement in eyelash assessment scale at 3 months, compared with none in the

Table I. Baseline demographic and clinical characteristics of all randomized participants

Characteristic	All (n = 36)	Cyclosporine (n = 18)	Placebo (n = 18)	*P* value*
Mean age, y (SD)	41 (14.5)	36.4 (11.3)	45.7 (16.2)	.12
Female sex, n (%)	29 (80.6%)	13 (72.2%)	16 (88.9%)	.21
Mean age at onset of first episode of AA, y (SD)	24.5 (13.9)	19.7 (10.6)	29.3 (15.4)	.06
Mean age at onset of current episode of AA, y (SD)	34.5 (14.3)	28.9 (10.8)	40.1 (15.3)	.04
Mean duration of current episode of AA, y (SD)	6.5 (9.7)	7.4 (11.6)	5.7 (7.5)	.75
Mean scalp hair loss by SALT score at baseline, % (SD)	79.4 (28.3)	77.8 (31.0)	81.1 (26.1)	.56
Pattern of scalp hair loss, n (%)				.92†
AT	9 (25.0%)	4 (22.2%)	5 (27.8%)	
AU	12 (33.3%)	6 (33.3%)	6 (33.3%)	
Patchy	15 (41.7%)	8 (44.4%)	7 (38.9%)	
Body hair loss, n (%)				.31†
100% loss	13 (36.1%)	7 (38.9%)	6 (33.3%)	
No loss	7 (19.4%)	5 (27.8%)	2 (11.1%)	
Some loss	16 (44.4%)	6 (33.3%)	10 (55.6%)	
Nail involvement, n (%)	16 (44.4%)	9 (50.0%)	7 (38.9%)	.50†
History of AT/AU at any time, n (%)	26 (72.2%)	13 (72.2%)	13 (72.2%)	.70†
Duration of AT/AU, n (%)				.23†
≤2 y	11 (42.3%)	7 (53.9%)	4 (30.8%)	
>2 y	15 (57.7%)	6 (46.2%)	9 (69.2%)	
Medical history, n (%)				.24†
Atopy	12 (33.3%)	4 (22.2%)	8 (44.4%)	
Other autoimmune disease	3 (8.3%)	2 (11.1%)	1 (5.6%)	
Endocrine	2 (5.6%)	1 (5.6%)	1 (5.6%)	
Psychologic illness	3 (8.3%)	3 (16.7%)	0	
Family history of AA	4 (11.1%)	3 (16.7%)	1 (5.6%)	
Score of 0 (no eyelashes) on eyelash assessment scale	18 (50.0%)	9 (50.0%)	9 (50.0%)	.57†
Score of 0 (no eyebrows) on eyebrow assessment scale	19 (52.8%)	9 (47.4%)	10 (52.6%)	.88†

AA, Alopecia areata; *AT*, alopecia totalis; *AU*, alopecia universalis.
*Mann-Whitney U test used for all continuous data.
†Chi-square test used.

placebo group (18.8% vs 0.0% [*P* = .07]). Significantly, 5 participants in the cyclosporine group achieved a 1-grade improvement in eyebrow assessment scale at 3 months, compared with none in the placebo group (31.3% vs 0.0% [*P* = .02]).

Effect of cyclosporine compared with placebo on QOL

There were no statistically significant differences between the cyclosporine and placebo groups in change from baseline in QOL measurements at 3 months. Participants receiving cyclosporine had, on average, greater improvement in all QOL measurements. Responders in the cyclosporine group had, on average, a greater improvement in Global Symptom Impact Score at 3 months.

Safety and tolerability

There were no statistically significant differences between the groups in terms of incidence of adverse events (Table III). In all, 83% of participants reported a total of 47 adverse events during the trial. Adverse events spanned a range of systems, with the most frequent complaints being headaches (n = 11) and hirsutism (n = 9). There were no serious adverse events. There were no clinically significant changes in blood biochemistry or blood pressure between the groups. The change in alkaline phosphatase level was statistically but not clinically significant.

DISCUSSION

Key findings

This randomized, double-blind, placebo-controlled, parallel group prospective clinical trial was designed to investigate the efficacy of cyclosporine in participants with moderate-to-severe AA. The efficacy of monotherapy cyclosporine has been difficult to estimate thus far, with the consistency of the literature only in case series, retrospective reviews, and small uncontrolled trials.

In this clinical trial, we found that 31.3% of participants (5 of 16) in the cyclosporine group

Table II. Summary of results for primary and secondary objectives at 3 months

End point	Cyclosporine group (n = 16)	Placebo group (n = 16)	*P* value*
Primary objective: efficacy			
Mean reduction from baseline of SALT score at 3 mo, SD	14.8 (27.4)	2.3 (7.6)	.23
Proportion of participants achieving ≥30% reduction in SALT score at 3 mo, n (%)	5/16 (31.3)	1/16 (6.3)	.07†
Proportion of participants achieving ≥50% reduction in SALT score at 3 mo, n (%)	5/16 (31.3)	1/16 (6.3)	.07†
Proportion of participants achieving ≥75% reduction in SALT score at 3 mo, n (%)	2/16 (12.5)	0/16 (0.0)	.14†
Proportion of participants achieving a 100% reduction in SALT score at 3 mo, n (%)	1/16 (6.3)	0/16 (0.0)	.31†
Change from baseline in nonvellus hair counts by macrophotography at 3 mo, n (%)	19.9 (36.2)	1.8 (25.2)	.07
Proportion of participants achieving ≥1-grade improvement in eyelash assessment scale at 3 mo, n (%)	3/16 (18.8)	0/16 (0.0)	.07†
Proportion of participants achieving ≥1-grade improvement in eyebrow assessment scale at 3 mo, n (%)	5/16 (31.3)	0/16 (0.0)	.02†
Secondary objective: quality of life impact			
Mean change from baseline in Assessment of Quality of Life-8D score at 3 mo (SD)‡	0.064 (0.085)	0.050 (0.095)	.763
Mean change from baseline in Alopecia Areata Symptom Impact Scale score at 3 mo—Global Symptom Impact Score (SD)§	−0.041 (0.121)	0.009 (0.150)	.558
Mean change from baseline in Alopecia Areata Symptom Impact Scale score at 3 mo—Scalp Hair Loss Score (SD)‖	0.063 (1.389)	0.313 (1.537)	.902

SALT, Severity of Alopecia Tool.
*Mann-Whitney U test used for all continuous data.
†Chi-square test used.
‡The Assessment of Quality of Life-8D scale measures quality of life on a scale from 0 (death) to 1 (full health); positive values reflect an improvement in quality of life.
§The Global Symptom Impact Score measures all alopecia areata symptom impact on a scale of 0 (all symptoms not present) to 1 (all symptoms as bad as you can imagine); negative values reflect an improvement in symptom impact.
‖The Scalp Hair Loss Score measures alopecia areata scalp hair loss from 0 (not present) to 10 (as bad as you can imagine); negative values reflect an improvement in scalp hair loss.

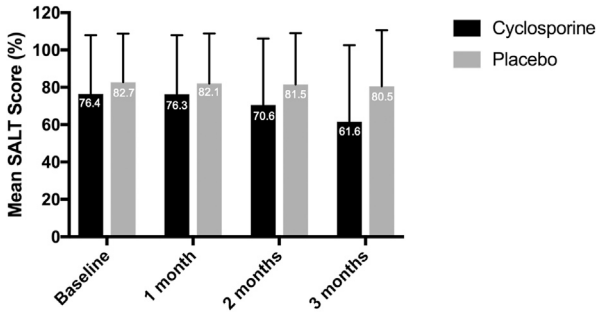

Fig 2. Mean Severity of Alopecia Tool (SALT) score over time. Error bars represent standard deviations.

achieved a response at the end of 3 months, compared with 6.3% (1 of 16) in the placebo group ($P = .07$). This response rate approached but did not achieve statistical significance.

Similar trends existed in terms of all other efficacy measures: the cyclosporine group achieved a greater mean reduction from baseline in SALT score at 3 months, greater increase from baseline in nonvellus hairs, and a greater proportion of participants achieving at least a 1-grade improvement in eyelash and eyebrow scale scores. In all, 31.3% of participants in the cyclosporine group (5 of 16) compared with 0% of participants in the placebo group achieved a 1-grade improvement in eyebrow assessment scales, and this result was statistically significant ($P = .02$). Controlling for potential covariates did not significantly change the results.

Interpretation of findings

Patients with severe, long-standing disease, including AT and AU, are more resistant to treatment than those with limited, patchy disease with a short duration of onset.[14] Many participants in our trial had treatment-resistant, long-standing, extensive disease. On average, the mean duration of the current episode of AA was 6.5 years and the mean percentage scalp hair loss at baseline was 79.4%. The

Table III. Incidence of adverse events

Complaint	Cyclosporine (n = 18)	Placebo (n = 18)	Total (n = 36)	*P* value
Participants with AEs	15 (83%), 25	15 (83%), 22	30 (83%), 47	1.00
Nervous system disorders				
Headaches	4 (22.2%), 4	4 (22.2%), 7	8 (22.2%), 11	1.00
Paraesthesia	1 (5.6%), 1	2 (11.1%), 3	3 (8.3%), 4	.55
Gastrointestinal disorders				
Abdominal pain	2 (11.1%), 3	2 (11.1%), 2	4 (11.1%), 5	1.00
Nausea	0 (0%), 0	2 (11.1%), 2	2 (5.6%), 2	.15
Increased appetite	1 (5.6%), 1	0 (0%), 0	1 (2.8%), 1	.31
Infections				
Urinary tract infection	1 (5.6%), 1	0 (0%), 0	1 (2.8%), 1	.31
MSK	3 (16.7%), 3	2 (11.1%), 3	5 (13.9%), 6	.63
Respiratory disorders	3 (16.7%), 4	0 (0%), 0	3 (2.8%), 4	.07
Dermatologic disorders				
Pruritus	1 (5.6%), 2	1 (5.6%), 1	2 (5.6%), 3	1.00
Hirsutism	5 (27.8%), 5	4 (22.2%), 4	9 (25%), 9	.70
Ophthalmologic disorders	1 (5.6%), 1	0 (0%), 0	1 (2.8%), 1	.31

Data are number of participants (%), cumulative incidence of adverse events from 1 month to 3 months of treatment. *P* values are reported for number of participants (%) in each group.
AE, Adverse event; *MSK*, musculoskeletal.

severity of disease in this cohort should be considered in the interpretation of these response rates.

Relationship with similar literature

Case series suggest response rates to cyclosporine ranging from 33% to 55%.[6-9] In comparison, our study included a cohort with severe disease, a lower dose of cyclosporine, and a shorter treatment period compared with the mean treatment period of these case series.[6-9]

This is, to our knowledge, the first study to use a control arm of participants with similar baseline disease. No previous studies had suitable controls by which to compare treatment response. Particularly in patchy AA, it may be challenging to distinguish the effect of a treatment from spontaneous remission of a patch.

In examining randomized controlled trials of other systemic agents, oral prednisolone pulse therapy had a response rate of 40% within 3 months.[5] A recent trial of the Janus kinase inhibitors PF-06651600 and PF-06700841 reported a 30% and 42% mean reduction in SALT score at 3 months, respectively, and 48% and 60% of participants achieved a 30% improvement in SALT score at 6 months, respectively.[15] Comparatively, cyclosporine resulted in a 14.8% mean reduction in SALT score, with 31.3% of treated participants achieving a 30% improvement in SALT score in this trial, suggesting that cyclosporine is an inferior agent to corticosteroids and new treatments, including Janus kinase inhibitors.

Study strengths and limitations

Our study has a number of strengths and limitations. To answer our research question regarding the efficacy of cyclosporine, we used a suitable study design: a double-blind, randomized, placebo-controlled clinical trial. This study design resolves some key barriers to estimating the true efficacy rate found in the current literature: lack of control, combination with other therapies, changing doses, and selection bias. We achieved a double blind through use of an identical placebo and a third-party pharmacy that performed all randomization and concealed the allocation sequence. Outcome assessments for all participants were graded by the same investigator to ensure consistency. We selected a therapeutic dose and maintained this dose throughout the study, with near-perfect compliance from trial participants. This is also the only clinical trial for AA to use both disease-specific and generic QOL instruments to measure the psychosocial efficacy of pharmacotherapy.

However, our study has a number of limitations. The sample size was powered for a prediction that approximately 50% of those treated with 4 mg/kg/d of cyclosporine would achieve a treatment response (ie, a 50% reduction in SALT score) at the end of 3 months, and so we were unable to significantly detect lower response rates. A longer treatment duration may detect a greater response, given the delay in onset of action with all agents for treatment of AA and the trend of continued improvement seen in this trial.

Clinical implications

This new efficacy data will aid clinicians in deciding a second-line treatment. This is pertinent in patients who fail to respond to systemic corticosteroids or are corticosteroid responsive but corticosteroid dependent and must wean corticosteroid treatment because of cumulative side effects. The use of cyclosporine is a balancing act between the risk of adverse events, particularly nephrotoxicity, hypertension, and hyperlipidemia, and its efficacy. Many clinicians would be hesitant in treating chronic AA with doses higher than 4 mg/kg/d for prolonged periods, as cumulative toxicity would outweigh the potential benefits. This study suggests that 4 mg/kg/d of cyclosporine monotherapy for 3 months is moderately effective at inducing remission of AA. Combination of cyclosporine with glucocorticosteroids may further increase response rates.

CONCLUSION

This is, to our knowledge, the first randomized, placebo-controlled, prospective clinical trial investigating the effectiveness of 4 mg/kg/d of cyclosporine monotherapy in the treatment of moderate-to-severe AA for 3 months. Cyclosporine achieved a 31.3% response rate compared with 6.3% in the placebo group. This result approached but did not reach statistical significance ($P = .07$), most likely because of sample size and treatment duration. These results may be interpreted for patients with moderate-to-severe, long-standing AA and will guide clinicians in their choice of second-line agents for this patient cohort.

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