ORIGINAL ARTICLE

Utility of azathioprine, methotrexate and cyclosporine as steroid-sparing agents in chronic alopecia areata: a retrospective study of continuation rates in 138 patients

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Abstract

Background The management of chronic alopecia areata (CAA) is challenging. There is currently no therapy that produces consistent successful hair regrowth. Systemic therapies, including prednisolone and steroid-sparing agents (SSA), are often tried in patients with CAA. As there are no head-to-head clinical trials that compare efficacy of one SSA over another, retrospective studies of treatment in clinical practice may help guide clinical practice.

Objective To investigate the utility of SSAs in the treatment of AA.

Methods An electronic medical records search identified patients with AA and those prescribed azathioprine, cyclosporine or methotrexate between 2002 and 2019. Type of AA, treatment duration, reason for cessation, use of concurrent prednisolone, dose of prednisolone and duration of prednisolone use were recorded. The primary outcome was SSA continuation rate at 6 and 12 months.

Results A total of 852 AA patients were identified, among whom 138 patients had been treated with azathioprine, methotrexate or cyclosporine. Of these 138 patients treated with a SSA, 92 (66.7%) continued treatment for at least 12 months: 75.3% (55/73) of azathioprine users, 50% (11/22) of methotrexate users and 60.5% (26/43) of cyclosporine users. At 12 months, 67.3% of azathioprine users required concurrent prednisolone at a mean dose of 5.6 mg daily, 63.6% of methotrexate users required prednisolone at a mean dose of 5 mg daily and 57.7% of cyclosporine users required prednisolone at a mean dose of 8.7 mg daily. The SSA was ceased due to an adverse event in 15.9% of patients and a lack of efficacy in 17.4%.

Conclusion The most well-utilized SSA for CAA patients at our clinic was azathioprine. This study highlights that most CAA patients who commence treatment with azathioprine, methotrexate or cyclosporine continue that treatment for at least 12 months and most require concurrent low-dose prednisolone to maintain remission or promote continued hair regrowth.

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Conflicts of interest

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Introduction

Alopecia areata (AA) is a relapsing, remitting non-scarring T-cell-mediated hair loss condition with a prevalence of 2.11%.[1] There are several subtypes, dependent on the extent or distribution of hair loss, including alopecia totalis (AT) where there is complete loss of hair on the scalp and alopecia universalis (AU) where there is complete loss of scalp and body hair. There is significant impact on health-related quality of life in patients with AA; the mean health utility for patients with AA is 0.748.[2]

The management of AA has been particularly controversial, given a large number of affected individuals, and that 67% experience acute AA – a self-limiting disorder where patches spontaneously self-regrow without any treatment within 6–12 months.[3] Acute AA can be managed conservatively or with local measures, including topical corticosteroids, intralesional steroids, topical minoxidil, topical tofacitinib and topical diphenylcyclopropenone (DPCP).[4] However, 33% of individuals experience chronic AA (CAA), where patches persist beyond

12 months and may be refractory to local measures. Individuals with CAA have a 30% risk of developing alopecia totalis (AT) and a 15% risk of developing alopecia universalis (AU).[3] It is in this cohort of persistent CAA patients where systemic treatments, including prednisolone and steroid-sparing agents (SSAs), such as azathioprine, methotrexate and cyclosporine are utilized in attempt to reverse hair loss. These CAA patients often have moderate to severe disease, generally described as at least 25–30% scalp hair loss.[5] Patient age, disease progression and patient distress also affect use of systemic treatment in AA.

Corticosteroids are often prescribed as a first-line systemic agent to rapidly halt disease progression and are effective in up to 80% of patients.[6] However, many steroid-responsive patients relapse on dose reduction and require maintenance therapy to maintain remission. In these steroid-dependent patients, SSAs may be used to further taper systemic steroid dose.

However, there is a paucity of research into the relative efficacy of these SSAs, both in terms of efficacy as monotherapy to treat initial outbreak of AA, as well as use as combination therapy during a wean of corticosteroid. A recent systematic review of all randomized controlled trials (RCTs) investigating systemic treatments for AA concluded that there is currently no reliably effective systemic treatment that was supported by multiple robust RCTs.[7]

A recent expert consensus statement on the treatment of CAA highlighted that overall utility and order of preference of SSA use vary widely among dermatologists sub-specializing in AA.[3,5] Selection of one agent over another is difficult given the lack of level A evidence. This is a consequence of the high expense and impracticality of conducting randomized controlled head-to-head trials for each and every SSA for CAA.

To our knowledge, there has only been a single randomized, placebo-controlled study investigating a SSA for use as monotherapy treatment in AA.[8] In the absence of data from RCTs, this study aims to elucidate the efficacy of SSAs through a retrospective analysis of continuation rates at one large Melbourne clinic, thus providing comparative data to guide SSA choice.

For retrospective analysis of efficacy, the continuation rate of a medication functions as a crude proxy for response, predicated on the basis that only patients who tolerate, are satisfied and respond to treatment continue buying and consuming the medication. This is a previously established proxy that has been used in rheumatological studies investigating similar systemic agents.[9–12]

We conducted a retrospective analysis of 138 CAA patients who have been prescribed SSAs in a single Melbourne clinic to evaluate the utility of these agents through continuation rates.

Methods

A retrospective analysis of CAA patients at a single large Melbourne hair loss clinic was conducted. Inclusion criteria were patients with AA, AT or AU who had been treated with azathioprine, cyclosporine, methotrexate or sulfasalazine. Electronic medical records were searched to identify patients and record type of AA (patchy, totalis or universalis), systemic agent used, dose of treatment, concurrent use of prednisolone, dose of concurrent prednisolone, duration of treatment and whether cessation was due to remission, relapse or adverse effects. The primary outcome was SSA continuation rate at 6 and 12 months. Continuation rate was defined as percentage of total users who had commenced SSA treatment continuing on the same SSA at 6 and 12 months. Patients who temporarily ceased SSA but then recommenced the same SSA during the course of treatment were counted as users if they continued treatment at 6 and 12 months, as this represented utility of treatment to sustain or promote hair regrowth. Secondary outcomes were as follows: rates of concurrent prednisolone use at 6 and 12 months, dose of prednisolone use and rate of adverse events causing cessation of SSA. Results were tabulated and presented as number of cases and percentage.

Results

Demographic details

Demographic details are displayed in Table 1. A total of 852 AA patients were identified at our clinic, of which 82.9% had patchy AA, 11.3% had AT and 5.9% had AU. 56.9% were female patients, and the mean age was 38.0 years. A total of 138 patients with CAA were identified in our clinic who had been treated with azathioprine, cyclosporine or methotrexate. The remaining 714 AA patients had not been treated with the defined SSAs, having either opted for conservative management or responded to other treatment, including systemic prednisolone, intralesional prednisolone, minoxidil, spironolactone and tofacitinib. Across CAA patients who had been treated with azathioprine, methotrexate and cyclosporine, pattern of scalp hair loss was most commonly patchy AA (86.30%, 72.73% and 81.40%, respectively), followed by AT (6.85%, 18.18% and 30.23%, respectively) and finally AU (6.85%, 9.09% and 2.33%, respectively).

Continuation rates

Continuation rates of SSA use (azathioprine, cyclosporine or methotrexate) are presented in Table 2. The average duration of treatment with SSA was 24.5 months (standard deviation 25.7 months, median 13.5 months, minimum 0 months and maximum 85 months). The average weekly dose of methotrexate was 9.8 mg. The average daily doses of azathioprine and cyclosporine were 74.7 and 118.7 mg, respectively. The average duration of treatment with concurrent prednisolone was 38.2 months (standard deviation 28.2 months).

Overall, 78.3% (108/138) of patients prescribed a SSA continued treatment for at least 6 months and 66.7% (92/138) of

Table 1 Demographic details of study cohort

Characteristic	All AA patients	Azathioprine users	Methotrexate users	Cyclosporine users
Number	852	73	22	43
Mean age, year (SD)	37.99 (17.32)	38.21 (14.92)	35.54 (19.20)	35.73 (14.71)
Female sex, *n* (%)	485 (56.92%)	47 (64.38%)	17 (77.27%)	30 (69.77%)
Pattern of scalp hair loss, *n* (%)				
Patchy AA	706 (82.86%)	63 (86.30%)	16 (72.73%)	35 (81.40%)
AT	96 (11.27%)	5 (6.85%)	4 (18.18%)	13 (30.23%)
AU	50 (5.87%)	5 (6.85%)	2 (9.09%)	1 (2.33%)

Table 2 Continuation rates of steroid-sparing agent use at 6 and 12 months

Agent	Number of patients who have ceased SSA†	Number of patients who continue SSA†	Number of patients continuing SSA as monotherapy only‡	Number of patients continuing SSA with concurrent prednisolone use‡	Average daily dose of prednisolone in patients requiring concurrent prednisolone (mg)
Azathioprine					
6 months (*n* = 73)	14 (19.2%)	59 (80.8%)	13 (22.0%)	46 (78.0%)	8.65
12 months (*n* = 73)	18 (24.7%)	55 (75.3%)	18 (32.7%)	37 (67.3%)	5.62
Methotrexate					
6 months (*n* = 22)	6 (27.3%)	16 (72.7%)	6 (37.5%)	10 (62.5%)	6.53
12 months (*n* = 22)	11 (50.0%)	11 (50%)	4 (36.4%)	7 (63.6%)	5.00
Cyclosporine					
6 months (*n* = 43)	10 (23.3%)	33 (76.7%)	8 (24.2%)	25 (75.8%)	6.01
12 months (*n* = 43)	17 (39.5%)	26 (60.5%)	11 (42.3%)	15 (57.7%)	8.67
Total					
6 months (*n* = 138)	30 (21.7%)	108 (78.3%)	27 (25.0%)	81 (75.0%)	7.57
12 months (*n* = 138)	46 (33.3%)	92 (66.7%)	33 (35.9%)	59 (64.1%)	6.36

SSA, steroid-sparing agent.
†Data are number (percentage out of number of SSA users).
‡Data are number (percentage out of number of patients who continue SSA).

patients continued treatment for at least 12 months. At 6 months, 25% (27/108) of patients taking a SSA ceased prednisolone entirely while 75% (81/108) continued to take prednisolone at an average of 7.57 mg daily. At 12 months, 35.9% (33/92) of patients taking a SSA ceased prednisolone entirely while 64.1% (59/92) continued to take prednisolone at an average of 6.36 mg daily.

A total of 73 patients were prescribed azathioprine and followed for at least 12 months. There was a high continuation rate to azathioprine when used as a SSA. 80.8% (59/73) of patients continued azathioprine treatment for at least 6 months, and 75.3% (55/73) continued azathioprine treatment for at least 12 months. Concurrent prednisolone was required in 78.0% (46/59) of azathioprine users at 6 months at an average dose of 8.65 mg daily and 67.3% (37/55) of azathioprine users at 12 months at an average dose of 5.62 mg daily.

Forty-three patients were prescribed cyclosporine and followed for at least 12 months. 76.7% (33/43) of patients continued cyclosporine for at least 6 months, and 60.5% (26/43) continued cyclosporine for at least 12 months. Concurrent prednisolone was required in 75.8% (25/33) of cyclosporine users at 6 months at an average dose of 6.01 mg daily. 57.7% (15/26) of cyclosporine users at 12 months required prednisolone at an average dose of 8.67 mg daily.

Twenty-two patients were prescribed methotrexate and followed for at least 12 months. 72.7% (16/22) of patients continued methotrexate for at least 6 months, while 50% (11/22) continued methotrexate for at least 12 months. Concurrent prednisolone was required in 62.5% (10/16) of methotrexate users at 6 months at an average dose of 6.53 mg daily. 63.6% (7/11) of methotrexate users at 12 months required prednisolone at an average dose of 5 mg daily.

Adverse events

Number of adverse events causing cessation of SSA is displayed in Table 3. In total, 15.9% of patients using azathioprine, methotrexate or cyclosporine experienced adverse events resulting in cessation of treatment: 17.8%, 22.7% and 9.3%,

Table 3 Number of patients with adverse events causing cessation of SSA

Number of patients with adverse events causing cessation of SSA	Cyclosporine (n = 43)	Methotrexate (n = 22)	Azathioprine (n = 73)
Prior to 6 months†	3 (75%)	2 (40%)	10 (76.9%)
After 6 months†	0 (0%)	1 (20%)	3 (23.1%)
After 12 months†	1 (25%)	2 (40%)	0 (0%)
Total‡	4 (9.3%)	5 (22.7%)	13 (17.8%)

†Data are number (percentage of total number of adverse events for SSA).
‡Data are number (percentage of total SSA users).

respectively. Common side-effects experienced by azathioprine users included nausea and vomiting. One patient using azathioprine developed herpes zoster ophthalmicus, causing cessation of treatment. Cyclosporine users most frequently experienced hirsutism, while methotrexate users most frequently experienced nausea as well.

Discussion

This retrospective study presents an evaluation of the usage of SSAs for CAA in a large Melbourne clinic, highlighting which agents are most popular and have highest rates of continued use. The most commonly used SSAs were azathioprine, cyclosporine and methotrexate. We did not identify any patients in our clinic treated with sulfasalazine. Overall, at 12 months, 66.7% (92/138) of CAA patients commenced on SSA treatment continued to use the same SSA. Approximately, one third of these CAA patients were able to cease systemic corticosteroids entirely at 12 months (35.9%), while approximately two thirds required concomitant prednisolone therapy for disease control at 12 months (64.1%). The mean dose of prednisolone required was 6.36 mg/day.

Continuation rates may be used as a proxy for response rate, predicated on the basis that only patients who receive a treatment response and can tolerate the medication continue to take the SSA.[9–12] Patients who were weaned off treatment due to complete remission were also counted as responders for that particular treatment. Similarly, cessation rates may be a proxy for non-response, as patients are likely to stop treatment if they are unable to tolerate side-effects or if the treatment is not efficacious. In this way, one may roughly infer that approximately 75.3% of azathioprine users, 50% of methotrexate users and 60.5% of cyclosporine users continue to respond or sustain remission to treatment at 12 months, of which 32.7%, 36.4% and 42.3%, respectively, are monotherapy users successfully weaned off prednisolone at 12 months.

A review of the literature identified a total of 14 studies reporting the monotherapy use of azathioprine, cyclosporine, methotrexate or sulfasalazine for treatment of AA, AT or AU: 2 for azathioprine, 5 for cyclosporine, 3 for methotrexate and 4 for sulfasalazine (Table 4). A total of 12 studies were identified reporting combination use of a SSA with a systemic corticosteroid. The mean sample size for the monotherapy studies was 18.8, while the mean sample size of the combination therapy studies was 17.8. The average duration of treatment with monotherapy SSA was 7.6 months, while the average duration of treatment with combination therapy was 5.8 months. It is necessary to note that the average doses used at our clinic of methotrexate, azathioprine and cyclosporine in both mono- and combination therapy are 9.8 mg weekly, 74.7 mg daily and 118.7 mg daily, respectively, which when compared to the monotherapy doses described in current literature is lower; a potential explanation for why a large number of our patients required concurrent prednisolone at 12 months at a low dose. Higher doses of SSA may be more effective at maintaining remission as a monotherapy agent.

Reasons for treatment discontinuation are multifactorial and include intolerable adverse events, ongoing cost, reduction in incremental efficacy with time, relapse or treatment resistance occurring within this period. Cyclosporine, for example, is known to be associated with renal impairment with long-term use, and this side-effect may limit its ongoing use in predisposed patients. Azathioprine and methotrexate are associated with nausea and vomiting which may be intolerable.

The limitation of this study is that the use of continuation rates as a proxy for treatment response is only an estimate of actual treatment response, rather than quantifying response through Severity of Alopecia Tool (SALT) score. In this study, we did not assess or prescribe a particular level of SALT score improvement to define treatment response, and due to the study being retrospective, we could not reliably attain these data for our full cohort. The benefits of using a continuation rate as a proxy, though, are that it allows for a more patient-centred approach to defining response; that is, we assume that if a patient is satisfied with treatment, they will continue to take it and so we include any incremental improvement, regardless of quantity, as a meaningful and worthwhile response for the patient.

Overall, this review demonstrates the real-world utility of azathioprine, methotrexate and cyclosporine as SSAs in the treatment of CAA. Our clinic data highlight that azathioprine is the most well-utilized and efficacious of the SSAs. In an area of practice where comparative studies between commonly used SSAs are lacking, our study provides a useful comparison between

Table 4 Studies investigating steroid-sparing agents: azathioprine, cyclosporine, methotrexate and sulfasalazine

Drug	Study authors	Study design	Sample size	Mean duration of AA (years)	Mean dose	Mean duration of treatment (months)	Response rate
Monotherapy							
Azathioprine	Farshi *et al.*[13]†	Uncontrolled single-arm interventional study	20	2	2 mg/kg/day	6	
	Vano-Galvan *et al.*[14]	Uncontrolled single-arm interventional study	14	2	2.5 mg/kg/day	9.8	6/14 (43%)
Cyclosporine	Acikgoz *et al.*[15]	Case series	22	8.3	4.54 mg/kg/day	4.14	10/22 (45%)
	Ferrando *et al.*[16]	Uncontrolled single-arm interventional study	15	9.8	5 mg/kg/day	9	5/15 (33%)
	Gupta *et al.*[17]	Uncontrolled single-arm interventional study	6	8	6 mg/kg/day	3	3/6 (50%)
	Jang *et al.*[18]	Case series	51	2	3 mg/kg/day	13.2	28/51 (55%)
	Paquet *et al.*[19]	Case report	1	2	6 mg/kg/day	3	0/1 (0%)
Methotrexate	Royer *et al.*[20]	Retrospective review	14	5.7	18.9 mg weekly	14.2	5/13 (38%)
	Hammerschmidt *et al.*[21]	Retrospective review	9	4	17.5 mg weekly	–	4/9 (44.4%)
	Joly *et al.*[22]	Retrospective review	6	11	21.5 mg weekly	–	3/6 (50%)
Sulfasalazine	Rashidi *et al.*[23]	Uncontrolled single-arm interventional study	39	4	3 g/day	6	10/39 (25%)
	Aghaei *et al.*[24]	Uncontrolled single-arm interventional study	26		1 g/day for 1 month, 2 g/day for 1 month, then 3 g/day for 4 months	6	6/22 (27.3%)
	Misery *et al.*[25]	Case report	1	7	1 g/day for 1 month, 2 g/day for 1 month, the 3 g/day	9	1/1 (100%)
	Ellis *et al.*[26]	Retrospective review	39	–	–	–	7/39 (18%)
Combination therapy							
Cyclosporine and prednisolone	Gensure *et al.*[27]	Case report	1	–	4 mg/kg/day cyclosporine; 50 mg/day tapering dose of prednisolone	3	1/1 (100%)
	Kim *et al.*[28]	Uncontrolled single-arm interventional study	43	5	6 mg/kg/day cyclosporine; 30 mg/day tapering dose of prednisolone	3	38/43 (88.4%)
	Lee *et al.*[28]	Uncontrolled single-arm interventional study	34	4	3.75 mg/kg/day cyclosporine; 30 mg/day tapering dose of prednisolone	6	24/34 (77%)
	Shapiro *et al.*[29]	Uncontrolled single-arm interventional study	8	7.5	5 mg/kg/day cyclosporine; 5 mg/day prednisolone	6	2/8 (25%)
	Teshima *et al.*[30]	Uncontrolled single-arm interventional study	6	5.8	2.5 mg/kg/day cyclosporine; 5 mg/day prednisolone	5	6/6 (100%)
Cyclosporine and pulse IV methylprednisolone	Shaheedi-Dadras *et al.*[31]	Uncontrolled single-arm interventional study	18	6.3	2.5 mg/kg/day cyclosporine; monthly pulses of 500 mg IV methylprednisolone	6.5	6/18 (33%)

Table 4 *Continued*

Drug	Study authors	Study design	Sample size	Mean duration of AA (years)	Mean dose	Mean duration of treatment (months)	Response rate
Methotrexate and prednisolone	Anuset *et al.*[32]	Retrospective review	26	6	10 mg methotrexate weekly; 6 mg prednisolone daily		15/26 (57%)
	Hammerschmidt *et al.*[21]	Retrospective review	22	4	17.5 mg methotrexate weekly; 25 mg prednisolone daily	6	17/22 (77.3%)
	Joly *et al.*[22]	Retrospective review	16	11	21.5 mg methotrexate weekly; 19.4 mg prednisolone daily	–	11/16 (69%)
	Landis *et al.*[33]	Case series	14	–	7.3 mg methotrexate weekly; 33 mg tapering dose of prednisolone	–	8/14 (57%)
Methotrexate and pulse IV methylprednisolone	Droitcourt *et al.*[34]	Retrospective review	20	2	18.75 mg methotrexate weekly; 500 mg/day methylprednisolone for 3 days each month for 3 months	12	11/20 (55%)
Sulfasalazine and methylprednisolone	Bakar *et al.*[35]	6 case reports	6	9	3 g sulfasalazine daily; 1 mg/kg/day oral methylprednisolone	5	6/6 (100%)

–, not reported.
†Response rate not reported; however, mean regrowth percentage was 52.3%.

azathioprine, methotrexate and cyclosporine for clinicians to use as a point of reference.

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