

Azathioprine treatment and drug survival in patients with chronic hand eczema – results from daily practice

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Azathioprine is an off-label treatment for chronic hand eczema. A few small studies have found a positive effect of azathioprine on this disease, with few side-effects (1–3). More data are needed in order to optimize treatment strategies. Therefore, our aim is to present our experience with azathioprine in the treatment of hand eczema in daily practice.

Methods

We retrospectively reviewed patient records between January 2000 and 16 December 2015 (data lock). Patients were identified according to the International Classification of Disease (10th edition) diagnoses L20, L23–25, and L30. We included adult patients with severe chronic hand eczema who were treated with azathioprine. Patients with concomitant mild atopic dermatitis on other body areas were also included.

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Many of our patients had recurrent vesicular hand eczema. Because of the treatment-refractory nature of this subtype, these patients had often been treated with cyclosporine (20/26, 76.9%). If this failed, azathioprine was used as a third-line alternative. Most patients were thus not immunosuppressant-naïve. Only first episodes of azathioprine treatment were included in the analyses.

Results

Table 1 shows individual patient data. For effectiveness, a Physician Global Assessment (PGA) after 3 months of treatment was estimated retrospectively from patient records. Patients were scored as follows: good improvement (PGA1); moderate improvement (PGA2); and no change or worsening (PGA3) (4). Seventeen of 30 patients discontinued treatment prior to the 3-month assessment: 15 because of adverse effects, and 2 because they were lost to follow-up before this time. Five of the remaining 13 patients discontinued treatment at some point following the 3-month assessment, because of insufficient responsiveness or non-responsiveness. Three patients were lost to follow-up, and 2 patients discontinued treatment because they were worried about possible long-term adverse effects of immunosuppressive therapy. These patients all had moderate to good improvement of their

Table 1. Individual data of patients treated with azathioprine

Patient no.	Sex	Age at start of therapy (years)	HE morphological subtype	History of AD	Immunosuppressant/immunomodulator-naïve	Polysensitized ^a	Duration of therapy (months)	Aza dose at start (mg/day)	Aza dose at discontinuation (mg/day)	Concomitant OCs. Fraction of Aza treatment duration (OC starting dose)	PGA at 3 months ^b (OC dose at 3 months)	Event(s) leading to discontinuation ^c
1	M	48	Recurrent vesicular	No	No (CsA)	No	0.46	50	50	1.0 (10 mg)	NA	AE: GI, flu-like symptoms, arthralgia
2	F	63	Recurrent vesicular	Yes	No (CsA, AcI)	Yes	0.59	50	50	–	NA	AE: flu-like symptoms
3	M	56	Recurrent vesicular	Yes	No (CsA)	Yes	0.69	50	50	–	NA	AE: headache, arthralgia
4	F	55	Recurrent vesicular	No	No (CsA)	No	0.69	50	50	–	NA	LTFU
5	F	80	Hyperkeratotic	No	No (AcI)	No	0.72	50	50	–	NA	AE: increased liver enzymes
6	F	56	Recurrent vesicular	No	No (CsA)	No	0.76	50	50	–	NA	AE: GI
7	M	33	Recurrent vesicular	Yes	No (CsA)	No	0.89	50	100	1.0 (30 mg)	NA	AE: GI, increased liver enzymes
8	F	55	Recurrent vesicular	Yes	Yes	No	0.89	50	100	1.0 (10 mg)	NA	AE: GI, tiredness
9	F	51	Recurrent vesicular	No	No (AlI)	Yes	0.92	125	125	1.0 (20 mg)	NA	AE: GI
10	M	42	Recurrent vesicular	Yes	No (CsA)	Yes	1.02	50	100	1.0 (10 mg)	NA	AE: increased liver enzymes
11	F	58	Recurrent vesicular	No	No (AlI)	Yes	1.15	50	100	–	NA	AE: GI
12	M	66	Recurrent vesicular	Yes	No (MTX)	^d	1.22	50	150	–	NA	AE: GI
13*	M	59	Recurrent vesicular	No	No (CsA)	No	1.22	50	125	–	NA	AE: increased liver enzymes
14	M	46	Pulpsitis	No	No (CsA, AcI)	No	1.58	50	100	0.2 (10 mg)	NA	LTFU
15*	M	64	Recurrent vesicular	Yes	No (CsA)	No	1.84	50	100	0.1 (?)	NA	AE: tiredness, lowered Hb
16	F	60	Recurrent vesicular	Yes	No (CsA)	No	2.14	50	50	–	NA	AE: increased liver enzymes
17	F	33	Pulpsitis	Yes	No (CsA)	No	2.30	100	100	–	NA	AE: not specified
18	M	31	Recurrent vesicular	Yes	No (CsA)	Yes	3.88	50	250	0.8 (30 mg)	2 (20 mg)	Non-responsiveness
19	F	53	Recurrent vesicular	No	Yes	No	4.40	50	100	–	3	Non-responsiveness
20	M	22	Recurrent vesicular	No	No (CsA)	No	4.53	50	100	–	2	Non-responsiveness; AE: GI
21	M	71	Recurrent vesicular	Yes	No (CsA)	No	4.73	50	150	0.8 (30 mg)	2 (5 mg)	Non-responsiveness
22	M	41	Recurrent vesicular	No	No (CsA)	Yes	6.18	50	300	0.7 (10 mg)	2 (10 mg)	Non-responsiveness
23	M	43	Recurrent vesicular	No	No (CsA)	Yes	7.36	50	100	0.2 (10 mg)	1	LTFU
24	F	60	Recurrent vesicular	Yes	No (MTX)	No	11.17	75	50	–	2	LTFU
25*	F	54	Chronic fissured	No	Yes	No	13.60	50	50	–	1	Remission
26	M	32	Recurrent vesicular	No	No (CsA)	No	20.90	50	100	–	1	Personal concern
27	F	54	Recurrent vesicular	Yes	No (CsA)	No	28.12	50	100	–	1	LTFU
28	F	24	Recurrent vesicular	Yes	No (CsA)	No	34.96	50	50	–	1	–
29	F	40	Recurrent vesicular	Yes	No (CsA)	No	60.94	50	125	< 0.01 (5 mg)	1	Personal concern
30	M	34	Recurrent vesicular	Yes	No (CsA)	Yes	70.18	50	125	0.1 (10 mg)	1 (10 mg)	–
		50.0 ± 14.2					1.98 (7.43)	50 (0)	100 (75)			

AcI, acitretin; AD, atopic dermatitis; AE, adverse effect; AlI, alitretinoin; Aza, azathioprine; CsA, cyclosporine A; F, female; Hb, haemoglobin; HE, hand eczema; GI, gastrointestinal; LTFU, lost to follow-up; M, male; MTX, methotrexate; NA, not applicable; OC, oral corticosteroid; PGA, Physician Global Assessment; SD, standard deviation.

Mean ± SD or Median (interquartile range). Thiopurine methyltransferase activity was measured in 17 patients. No low activity (or inactivity) was found. The table is arranged according to Aza treatment duration.

^aPolysensitization was defined as three or more positive patch test reactions to allergens in the European baseline series (5).

^bThirteen patients were still being treated at 3 months (43%).

^cSix more patients reported adverse effects that did not lead to discontinuation.

^dNo patch test.

^eThese 3 patients were retreated with Aza. For details, see text.

hand eczema. One patient discontinued treatment with azathioprine because of remission after 13.6 months. Two patients, who had used azathioprine for approximately 3 and 6 years, were still treated at data lock. Their hand eczema was in full remission at that time.

Concomitant treatment with oral corticosteroids at the start of azathioprine treatment was given in 13 of 30 patients (43.3%), to decrease symptoms during the first weeks of treatment. We found no difference between patients with or without oral corticosteroid treatment at the start of azathioprine treatment, and good improvement at 3 months ($p > 0.99$, Fisher's exact test). Also, no difference was found between patients who used oral corticosteroids at the start of treatment and patients who did not regarding the adherence to azathioprine at 3 months (χ^2 ; $p = 0.79$). Finally, in the first 3 months, non-responsiveness was never a reason for discontinuing azathioprine treatment, regardless of whether or not oral corticosteroids were concomitantly given. This means that, regarding the long-term effectiveness and drug survival (the time for which patients remain on a drug) of azathioprine, it might be unnecessary to co-prescribe oral corticosteroids. However, despite these observations, a valid reason for co-prescribing oral corticosteroids at the start of azathioprine treatment could be their rapid onset of action, leading to a decrease in symptoms in the short term. Figure 1 shows the drug survival flow diagram of azathioprine.

No differences were found between patients with or without a history of atopic dermatitis and an outcome of good improvement at 3 months ($p > 0.99$, Fisher's exact test). Furthermore, we did not find a difference between patients with or without polysensitization and good improvement at 3 months: ($p > 0.99$, Fisher's exact test). Polysensitization was defined as having three or more positive patch test reactions to allergens in the European baseline series (5).

Three of the 30 patients (2 males and 1 female; age range 56–64 years) were retreated with azathioprine at a median dose of 100 mg daily. No oral corticosteroids were given at the start of retreatment. One patient discontinued treatment after 2.5 months because of insufficient response; 2 patients continued treatment for 1 year, and discontinued treatment because of remission of their hand eczema. No severe harmful effects occurred in the studied population. Considering first episodes and retreatments, 7 of 15 (46.7%) patients who used azathioprine at 3 months were still being treated at 1 year.

Discussion

Discontinuation of azathioprine treatment was often caused by subjective adverse effects. This occurred mainly

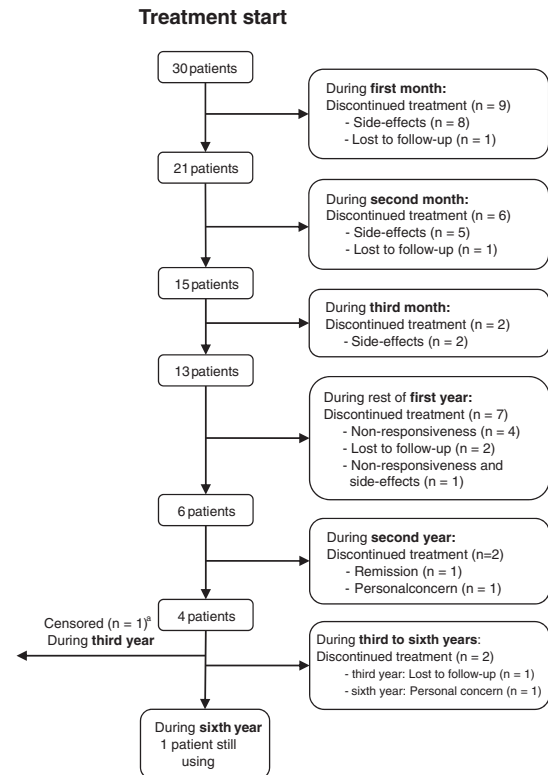


Fig. 1. Azathioprine drug survival flow diagram.

^aThe censored patient was still using azathioprine at data lock, and had full clearance of hand eczema during the third year of treatment.

during the first 3 months. In this timeframe, patients frequently experienced no change or worsening, probably because of the delayed onset of action of azathioprine (8–12 weeks). Treating patients who indicate subjective adverse effects can therefore be difficult, and it is vital to critically weigh subjective adverse effects against the possible benefit of azathioprine in the long term. In several of our cases, treatment might have been discontinued too soon. Physicians should motivate patients with mild subjective adverse effects to continue treatment for at least 8–12 weeks, when the clinical effect of azathioprine becomes apparent.

Limitations of this study were the small sample size, a probably highly treatment-refractory study group, the lack of a controlled design, and the fact that data on effectiveness were collected retrospectively. Unfortunately, the weight of patients was not documented, so dosage could not be calculated in relative terms (mg/kg).

Our data support the notion that azathioprine can be effective in the treatment of hand eczema. On the other hand, a considerable number of patients experienced adverse effects, leading to early discontinuation

of treatment. Prospective studies comparing treatment modalities (especially systemic drugs) in hand eczema

are needed to determine more adequate management strategies.

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