

The adverse effect profile of oral azathioprine in pediatric atopic dermatitis, and recommendations for monitoring

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Background: Azathioprine is efficacious in the treatment of severe childhood atopic dermatitis; however, robust data on adverse effects in this population are lacking.

Objective: We sought to assess adverse effects of azathioprine treatment in a pediatric atopic dermatitis cohort, and make recommendations for monitoring based on these data.

Methods: Blood test results for all 82 children prescribed oral azathioprine for atopic dermatitis in our department between 2010 and 2012 were collated prospectively, and clinical notes were reviewed retrospectively.

Results: Mean age at commencing azathioprine was 8.3 years (SEM 0.4). Mean maximum doses were 2.4 mg/kg (SEM 0.1) and 1.5 mg/kg (SEM 0.1) for normal and reduced serum thiopurine-S-methyltransferase levels, respectively. Adverse effects on blood indices occurred in 34 of 82 patients (41%), with pronounced effects in 18 of 82 (22%) after a median time of 0.4 years. Two patients stopped therapy as a result of abnormal blood indices. Clinical adverse effects occurred in 16 of 82 (20%), two resulting in cessation of therapy. Incidence of adverse effects was unaffected by age, sex, thiopurine-S-methyltransferase level, and drug dose on multivariate regression.

Limitations: Comparison with other studies is limited by varying definitions of adverse effects.

Conclusion: Oral azathioprine was associated with few pronounced adverse effects for the duration of use and dosage in this cohort. Recommendations for monitoring are made. (J Am Acad Dermatol 2015;72:108-14.)

Key words: atopic dermatitis; azathioprine; child; eczema; guidelines; monitoring; pediatric; safety; systemic; therapy.

Benefit from systemic treatment of atopic dermatitis (AD) with azathioprine (AZT) has been demonstrated with randomized, placebo-controlled trials in adults showing a 17% to 23% improvement in the Six Area Six Sign AD

Abbreviations used:

AD: atopic dermatitis
CBC: complete blood cell count
TPMT: thiopurine-S-methyltransferase

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score.^{1,2} A randomized comparison with methotrexate showed comparable efficacy.³ Nonrandomized studies of 48⁴ and 24⁵ pediatric patients reported significant improvement in 88% and 61% of cases, respectively. A series of 12 children treated with azathioprine for recalcitrant AD reported improvement in 92% of cases.⁶

Prospective studies in adults have found a low incidence of adverse effects requiring cessation of AD treatment, all of which were reversible after reduction or cessation of therapy.^{1-3,7} Similar findings are reported in pediatric AD studies.⁴⁻⁶

Azathioprine is metabolized by the enzyme thiopurine-S-methyltransferase (TPMT) and causes immunosuppression via inhibition of the lymphocyte cell cycle.⁸ Serum levels of TPMT activity vary due to DNA sequence polymorphisms, with normal levels in 80%, low in 10%, high in 9%, and undetectable in 0.5%⁹ of the population. Patients with lower TPMT levels are routinely commenced on a lower dose of azathioprine to reduce the risk of adverse effects.^{4,10-12}

Known adverse effects of azathioprine include gastrointestinal symptoms, nausea, fatigue and malaise, along with myelosuppression, lymphopenia,¹¹ neutropenia,^{12,13} and hepatotoxicity.¹⁴ Guidelines for adults recommend monitoring of liver enzymes and complete blood cell count (CBC), "at least 3-monthly once on a stable dose, and more frequently before stabilization."¹⁴ There are no published guidelines for monitoring azathioprine use in pediatric AD.

The aims of this study were to document the timing and nature of adverse effects during azathioprine treatment in a cohort of pediatric patients with AD, and to suggest recommendations for monitoring.

METHODS

Hospital pharmacy records were accessed to ascertain the total number of children prescribed azathioprine for AD during the period 2006 to 2012. Adverse effects were studied in detail in all children prescribed oral azathioprine between January 2010 and December 2012. This subset was selected as all blood results from our department, and primary and secondary care facilities

involved in azathioprine monitoring, were collated prospectively into a database from January 2010 onwards. Criteria for commencing azathioprine were: (1) severe eczema affecting growth, quality of life, or both; (2) failure of first- and second-line therapies; and (3) biochemical evidence of normal or carrier status TPMT level.

Oral AZT was the first-line systemic therapy for the cohort studied because of successful clinical experience of this drug for pediatric AD in our department. The dosage was 2.0 to 3.5 mg/kg/d for those with a normal TPMT level. The lowest effective dose was used, only increasing within this range if clinical response was suboptimal and there were no adverse effects. Because of delay in the onset of action of azathioprine a 4- to 6-week bridging course of oral prednisolone was routinely administered.

Clinic notes were reviewed retrospectively to record clinical adverse effects interfering with normal activities, and to review management of all adverse effects. Adverse effects in blood indices were defined as hepatic transaminase levels greater than 50 U/L, leukocyte count less than $4 \times 10^9/L$, lymphocytes less than $1 \times 10^9/L$, and neutrophils less than $1.5 \times 10^9/L$. "Pronounced adverse effects" were defined as hepatic transaminase levels greater than 50 U/L, lymphocytes less than or equal to $0.5 \times 10^9/L$, and neutrophils less than $1.0 \times 10^9/L$. As this study included only children who were prescribed azathioprine, we do not have data on whether there were patients who did not begin therapy as a result of abnormal pretreatment blood tests.

Outcome measures were adverse effects, pronounced adverse effects, and clinical adverse effects requiring alteration of therapy. Drug-related variables were starting dose, maximum dose, and time since commencing or increasing the dose of azathioprine. Patient demographics collected were age at commencing treatment, sex, and TPMT level (normal or carrier). The interaction of drug-related variables and patient demographics on outcome measures was modeled using multiple logistic regression, and a Bonferroni correction applied for multiple testing.

CAPSULE SUMMARY

- There are no published guidelines for monitoring adverse effects of azathioprine treatment in pediatric atopic dermatitis
- Azathioprine was associated with frequent mild and infrequent pronounced adverse effects in this cohort of 82 children with severe atopic dermatitis
- Recommendations for laboratory monitoring of azathioprine therapy are offered based on our experience

RESULTS

Study population

In all, 186 children (112 male) were prescribed azathioprine for AD during the period 2006 to 2012 with a mean age at starting therapy of 9.40 years. The mean duration of use was 2.14 years (780 days) with 4 patients lost to follow-up. There were no irreversible or fatal adverse effects documented due to azathioprine. In the detailed study period (2010-2012), 82 children (54 male) were prescribed azathioprine for AD. The mean age at commencing treatment was 8.3 years (SEM 0.4). Eleven children (13%) had low levels of TPMT, consistent with carrier status for TPMT polymorphisms. Detailed phenotypic information is shown in [Table I](#).

Abnormal laboratory results

Adverse effects on blood indices were seen in 33 of 82 patients (40%), 24 involving CBC, 11 involving liver transaminases, and 2 involving both. Pronounced effects on blood indices were seen in 18 of 82 ([Table II](#)). Of these, 9 of 18 required no change in treatment other than a repeated blood test, 5 of 18 had brief cessation of therapy and a repeated test before continuing treatment unchanged, 2 of 18 required a reduction in dose, and 2 of 18 ceased therapy. The mean time to a pronounced adverse effect after either commencing azathioprine or increasing the dose was 0.46 years (SEM 0.11), median 0.38 years (range 0.00-1.72 years).

Eight patients (10%) had a pronounced adverse effect on CBC: 7 neutropenia and 1 lymphopenia. In 5 patients no action was required other than continued monitoring, 2 required a brief cessation of therapy and 1 required a reduction in dose. In 1 case, azathioprine was discontinued because of recurrent neutropenia. Eleven patients (13%) had abnormal liver transaminase levels. In 5 of 11, these resolved spontaneously with no change in treatment other than repeated blood testing, 4 of 11 had a brief cessation of therapy before continuing, and 1 of 11 had a reduction in dose. In 1 patient therapy was withdrawn because of recurrent elevation in transaminase levels.

Clinical adverse effects

Clinical adverse effects were seen in 16 of 82 (20%) and were generally mild. Most common were cutaneous viral infections (molluscum contagiosum and viral warts) in 12%, with single cases of nausea, lethargy, indigestion, asthma exacerbation, unconfirmed possible myopathy (subsequently lost to follow-up), headache, and recurrent chest infections. Three patients ceased therapy after

Table I. Clinical phenotype of the detailed atopic dermatitis study cohort

Demographic	N (%)
Males	54/82 (66)
Low TPMT	11/82 (13)
Diagnosis of asthma	31/82 (38)
Diagnosis of allergy	70/82 (85)
History of anaphylaxis	13/82 (16)
Raised total IgE	35/82 (43)
Family history of atopy	50/82 (61)

TPMT, Thiopurine-S-methyltransferase.

Table II. Details of 2 subgroups of adverse effects; pronounced adverse effects on blood indices, and clinical adverse effects possibly attributable to azathioprine administration

Adverse effect	N (%)
Abnormal complete blood cell count parameters	8 (10)
Elevated hepatic transaminases	11 (13)
Abnormal complete blood cell count and liver enzymes	1 (1)
Cutaneous viral infection	10 (12)
Nausea	1 (1)
Lethargy	1 (1)
Indigestion	1 (1)
Possible myopathy (unconfirmed and lost to follow-up)	1 (1)
Headache	1 (1)
Chest infection	1 (1)

clinical adverse effects. The first experienced headaches two weeks after a dose increase, which resolved when azathioprine was stopped. The second had recurrent chest infections after the second year of therapy (one occasion requiring admission to hospital). The third had recurrent herpes labialis.

Cessation of azathioprine due to adverse effects

In total, 5 patients (6%) discontinued azathioprine because of adverse effects: recurrent neutropenia (1); persistently raised alanine aminotransferase (1); headaches (1: stopped by parents); recurrent chest infections (1); and recurrent herpes labialis (1).

Statistical analysis

On multiple logistic regression with Bonferroni correction the odds ratio of having an adverse effect on blood indices was unaffected by age, sex, TPMT carrier status and the maximum dose reached, along with any drug-related or patient demographic

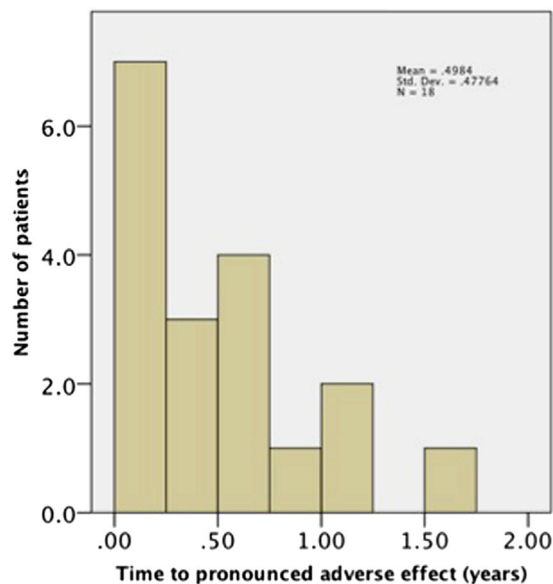


Fig 1. Time to pronounced adverse effects that could be attributable to azathioprine therapy, measured from the start of azathioprine (if no change in dose since commencing) or from the date of the most recent increase in dose. Note the clustering of effects in the first 9 months.

variable. The timing of the adverse effects in blood indices was skewed towards the start of treatment or after a dosage increase (Fig 1).

DISCUSSION

In this cohort of pediatric patients with AD, azathioprine treatment was associated with frequent mild adverse effects and infrequent pronounced adverse effects in blood indices. The majority required little or no treatment alteration, although they were monitored closely. The high number of self-resolving abnormal results was likely a result of unrelated intercurrent infections. Physician assessment is important. Irreversible or fatal adverse effects were not encountered in 186 children prescribed azathioprine for AD in our department in the last 8 years. However, such events have rarely been reported.¹³

The overall pattern of adverse effects is comparable with other studies of azathioprine treatment of AD. In a recent randomized controlled trial comparing azathioprine with methotrexate, 36% and 77% of 22 adult patients receiving azathioprine had abnormal liver transaminase levels and CBC, respectively, but only 9% required withdrawal of treatment and 9% necessitated a dose adjustment.³ Detailed comparison of hepatic transaminase levels with other studies is hampered by varying definitions of abnormality but the numbers reported are of a similar order. We found pronounced hepatic transaminase abnormalities (defined as >50 IU/L) in 13%

of 82 prospectively collected patients, which is similar to other pediatric AD studies (8%-21%⁴⁻⁶); adult AD studies report 10% to 36%¹⁻³ (Table III). It has been suggested that adults with a normal to high TPMT activity are at greater risk of azathioprine-induced liver injury because of increased production of toxic methylated thiopurine metabolites,¹¹ but we did not find any such association in this pediatric cohort.

Neutropenia and lymphopenia were relatively common. In pediatric AD studies rates of lymphopenia vary from 1% to 43%,^{1,2} and neutropenia 5%; a recent systematic review recorded an abnormal CBC in 77% of patients.¹⁴ In a study of 52 adults with inflammatory bowel disease, lymphopenia was significantly associated with concurrent steroid treatment at the start of azathioprine use.¹⁵ As our patients were on systemic steroid treatment for the initial weeks of azathioprine therapy, this potentially contributed to the rate of mild lymphopenia.

Clinical adverse effects were cutaneous viral infections (12%), nausea, lethargy, indigestion, deterioration in asthma, unconfirmed possible myopathy, headache, and recurrent chest infections. Migraines and headaches have occurred in 4% to 12% of adult patients with AD on azathioprine.^{1,2} Respiratory tract infections have been reported in 10% to 13% of cases. Dermatologic manifestations have included folliculitis in 5% and impetigo in 3%.^{1,2} In one pediatric population the rate of cutaneous infection was significantly higher (57%).⁵ Nausea is a well-recognized adverse effect in adult populations, occurring in 51% of patients in one study.² We encountered only a single case of nausea (1%) after one year of treatment and this was successfully managed with a small reduction in dose.

It is interesting that in our subset of children for whom detailed records were available twice as many boys as girls received azathioprine for treatment of AD. In a recent epidemiologic study of pediatric AD in the United Kingdom, girls were more commonly affected than boys but boys were less likely to apply emollients.¹⁶ It may be that the sex difference observed in our study is not a true difference in severity, but related to difficulty implementing first- and second-line therapies. There were no differences in adverse effects between the sexes.

Our current practice for monitoring azathioprine therapy is as follows (Fig 2):

- Pretreatment: Blood tests as per Fig 2. Advice on sun avoidance and sun protection. The presence of any cutaneous viral infections is recorded. If the TPMT level is undetectable, azathioprine is not prescribed. If a polymorphism carrier level is detected an appropriate reduction in dosage

Table III. Comparison of previous publications of azathioprine safety in treatment of atopic dermatitis

Reference	Population	n	Hepatic transaminase AEs	CBC AEs	Clinical AEs	Patients withdrawn because of AEs
Murphy and Atherton, ⁴ 2002	Pediatric	48	5 (10.4%)	Macrocytosis – 3 (6.3%) Transient lymphopenia – 15 (31%) Transient thrombocytopenia – 1 (2.1%)	GI upset – 1 (2.1%) Eczema herpeticum – 1 (2.1%) Hypersensitivity – 1 (2.1%)	Nil
Berth-Jones et al, ¹ 2002	Adult	37	8 (10.4%)	Lymphopenia – 1 (1.3%) Lymphopenia and mild neutropenia – 1 (1.3%)	GI upset – 14 (18%) URTI – 5 (6.5%) Folliculitis – 2 (2.6%)	4 (10.8%)
Murphy and Atherton, ¹⁰ 2003	Pediatric	2				Nil
Meggitt et al, ² 2006	Adult	41	ALT >15% ULN – 4 (10%) ALT >50% ULN – 2 (5%)	>1 Episode neutropenia – 2 (5%) >1 Episode mild lymphopenia (1-1.5 × 10 ⁹ /L) – 18 (43%) >1 Episode moderate lymphopenia (0.5-1 × 10 ⁹ /L) – 10 (24%)	Nausea – 21 (51%) Headache – 5 (12%) Abdominal pain – 4 (10%) Lightheadedness – 3 (7%) Cellulitis – 3 (7%) LRTI – 2 (5%) URTI – 2 (5%) Malaise – 1 (2%)	6 (14.6%)
Waxweiler et al, ⁵ 2011	Pediatric	28	6 (21%)		Cutaneous infection – 16 (57%) GI effect – 8 (29%)	
Schram et al, ³ 2011	Adult	22	8 (36%)	17 (77%)	Infections – 14 (64%) GI effects – 13 (59%) AD exacerbation – 2 (9%)	9%
Caufield and Tom, ⁶ 2013	Pediatric	12	1 (8.3%)	1 (8.3%)		Nil

AD, Atopic dermatitis; AE, adverse event; ALT, alanine aminotransferase; CBC, complete blood cell count; GI, gastrointestinal; LRTI, lower respiratory tract infection; ULN, upper limit of normal; URTI, upper respiratory tract infection.

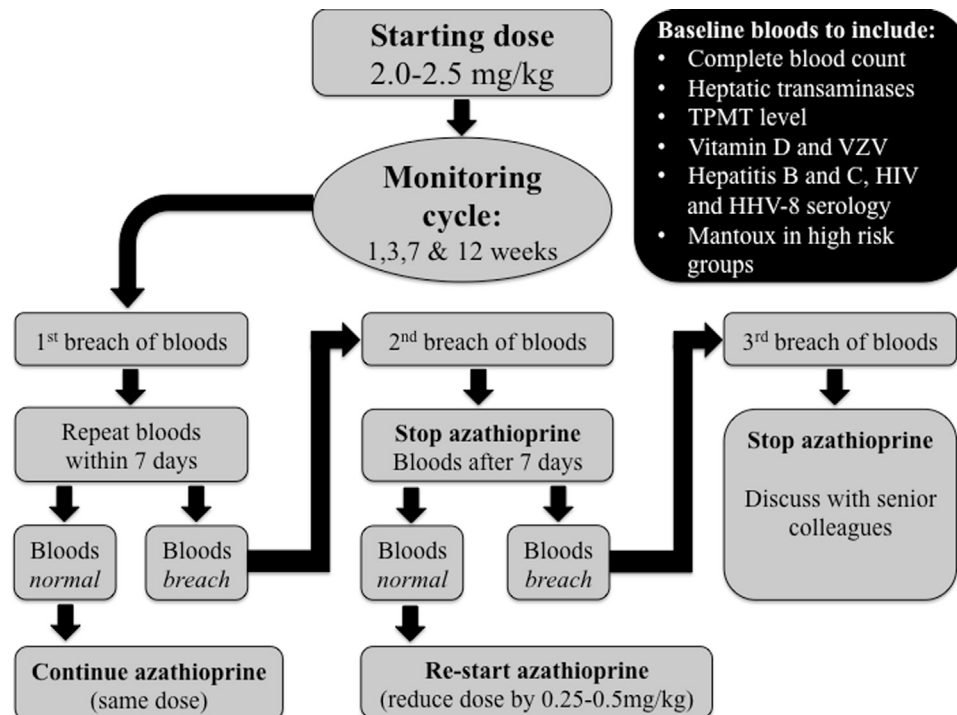


Fig 2. Recommendations for monitoring of blood indices during azathioprine use for atopic dermatitis in children. *HHV*, Human herpesvirus; *TPMT*, thiopurine-S-methyltransferase; *VZV*, varicella zoster virus.

is implemented, commencing at 1 to 1.5 mg/kg/d. Local guidelines for varicella exposure are followed.

- Standard blood monitoring of CBC and hepatic transaminases at weeks 1, 3, and 7 after commencing azathioprine, and every 3 months thereafter, unless there is a breach of blood parameters.
- A breach of blood parameters is defined as neutrophil count less than 1.0, lymphocyte count less than or equal to 0.5, or alanine aminotransferase greater than twice the upper limit of the normal range for age. The latter we consider more appropriate than an absolute value.
- For either a first breach in blood parameters, or a new breach after regular blood tests (every 3 months) have been established, we recommend maintaining the same dose of azathioprine and repeating blood tests after 1 week. If repeated investigations reveal normal findings, treatment is continued unchanged.
- For a second breach of parameters, either in the repeat blood tests after a first breach, or before the regular bloods (every 3 months) are established, azathioprine is withheld for a week and then blood tests are repeated. If the repeated results are normal, azathioprine is recommenced but at a lower dose (reduced by 0.25 mg/kg if

normal level of TPMT, reduced by 0.25-0.5 mg/kg if low level of TPMT).

- For a third breach of parameters, either immediately after a second breach, or before the regular blood tests (every 3 months) are established, the senior clinician decides whether to discontinue azathioprine.
- Whenever a dose adjustment is made or a breach of parameters has occurred, the standard monitoring cycle of blood tests is recommenced.

Assessment of posttreatment effects of azathioprine therapy for pediatric AD is outside the scope of our study. The long-term safety profile is unknown, and this fact should be discussed with families before starting azathioprine. Azathioprine use is associated with a range of hematologic, hepatotoxic, clinical, and long-term carcinogenic adverse effects including nonmelanoma skin cancer. As with any systemic therapy, concerns have to be balanced against the need to treat refractory eczema with its attendant effects on longitudinal growth¹⁷⁻²⁰ and neurodevelopment.²¹

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