

ORIGINAL ARTICLE

Efficacy and tolerability at 3 and 6 months following use of azathioprine for recalcitrant atopic dermatitis in children and young adults

KAM-LUN E. HON¹, GARY K. W. CHING¹, TING-FAN LEUNG¹, CHUNG-MO CHOW¹, KENNETH K. C. LEE² & PAK-CHEUNG NG¹

¹Department of Paediatrics, and ²School of Pharmacy, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong Special Administrative Region, People's Republic of China

Abstract

Introduction: Recalcitrant childhood atopic dermatitis (AD) causes significant morbidity and may necessitate systemic treatment with immunomodulating agents such as azathioprine. We reviewed the clinical and biochemical effects of this agent in children and adolescents receiving this treatment between November 2005 and December 2007. **Methods:** The clinical efficacy of azathioprine, and its hematological and biochemical effects (serum IgE level, liver and renal function), were assessed at 3 months and 6 months in 17 cases of recalcitrant AD. Disease severity was evaluated with the SCORing Atopic Dermatitis (SCORAD) score which has two components, namely (1) the objective SCORAD which measures the extent (percentage of body surface area involved) and intensity of the lesions, and (2) visual analog scales which measure the subjective symptoms of pruritus and sleep loss. **Results:** There were nine males and eight females with a mean (SD) age of 16.1 (3.9) years. Compared with baseline, significant improvements were observed at 3 months ($n = 17$) and 6 months ($n = 16$) in SCORAD ($p = 0.002$; $p < 0.001$), objective SCORAD ($p = 0.002$; $p = 0.001$), extent ($p = 0.001$; $p < 0.001$), pruritus ($p = 0.004$; $p = 0.001$) and dryness ($p = 0.033$ at 6 months). Compared with males, objective SCORAD was significantly lower in females ($p = 0.009$) at 6 months. Azathioprine was stopped in one female after 4 months due to lack of efficacy. Serum total IgE ($p = 0.006$) was significantly lower at 6 months. The frequency of oral antihistamine usage and *Staphylococcus aureus* carriage were also significantly reduced ($p = 0.031$ and $p = 0.016$, respectively). Mild transient elevation of glutamic-pyruvic transaminase in one patient which became normalized on cessation of the drug, and mild elevation of serum bilirubin in two other patients were observed. **Conclusions:** Azathioprine reduced the disease severity of AD within 3 months of use in these children. Better efficacy was observed in females at 6 months. Adverse hematologic and biochemical effects appeared acceptable but longer-term monitoring is desirable.

Key words: Azathioprine, childhood atopic dermatitis

Introduction

Childhood atopic dermatitis (AD) is a chronic relapsing disease associated with intense itching, sleep disturbance, and impaired quality of life (1,2). The general principle of management includes regular emollient usage and treatment of flare ups. During disease flare up, topical immunomodulating agents such as a topical steroid or calcineurin inhibitor is needed. Severe exacerbation or superimposed bacterial infection by *Staphylococcus aureus* with erythema, crusting or oozing are often empirically treated

with systemic anti-staphylococcal antibiotics such as cloxacillin $\pm$ a brief course of systemic corticosteroid. Corticosteroids, either in topical or systemic form, are the mainstay of treatment but their use might also be associated with deranged metabolism, growth suppression, increased susceptibility to infections and suppression of the hypothalamic-pituitary-adrenal axis (3). Steroid-sparing medications are often considered to avoid excessive or recurrent use of systemic corticosteroids.

There remains a group of children and adolescents with recalcitrant disease despite this management

Correspondence: K. L. E. Hon, Department of Paediatrics, The Chinese University of Hong Kong, 6/F, Clinical Sciences Building, Prince of Wales Hospital, Shatin, Hong Kong Special Administrative Region, People's Republic of China. Fax: 852 2636 0020. E-mail: ehon@cuhk.edu.hk

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strategy, necessitating systemic treatment with immunomodulating agents, which include cyclosporine, azathioprine, and narrow-band UVB (4). Cyclosporine is a very useful drug but limited by its renal and hypertensive toxicity and its cost. The efficacy of cyclophosphamide and MMF has not been extensively studied in pediatrics. There is a potential risk of photocarcinogenesis from chronic narrow-band UVB administration (5). Azathioprine is a standard systemic immunosuppressant used after organ transplantation and in patients with inflammatory bowel disease. The drug is generally very safe and slow in onset of action, but may cause derangement of liver function. Recently, it has been used as systematic monotherapy for severe AD in both adult and pediatric practices (4,6–8). A randomized control study in adult AD patients showed efficacy (8), but no similar randomized trials have been done in children with AD. We reviewed the clinical and biochemical effects in a series of children and adolescents who had received this treatment.

Methods

The clinical course of 17 patients with recalcitrant AD who received azathioprine at a university teaching hospital between November 2005 and December 2007 were reviewed to analyze the clinical efficacy and hematological and biochemical effects at 3 months and 6 months. Patients with impaired hepatic or renal function, myelosuppression, or other chronic infection or malignancy were excluded. Thiopurine methyltransferase (TPMT) measurement was not available in Hong Kong. Patients were generally started with 25–100 mg daily, and complete blood counts and liver function were monitored weekly. The dosage was increased every 1–2 weeks until some therapeutic effects were appreciated or when aberrant hematologic and/or liver function occurred. The target dosage range was 2–5 mg/kg if liver function remained normal. The patients continued with topical corticosteroids and antihistamines as necessary.

Disease severity was evaluated with the SCORing Atopic Dermatitis (SCORAD) score and their complete blood counts, serum total IgE levels, and liver and renal functions were followed. Blood counts and liver functions were initially performed weekly until the target dosage was reached and then performed 4–6 weekly. Adverse events were recorded at each visit with the use of non-leading questions. All clinical and laboratory outcomes followed normal distribution, and were expressed as mean and standard deviation (SD). Paired data on total and objective SCORAD scores, serum total IgE levels, corticosteroid and antihistamine usage as well as skin bacteria growth between baseline

Table I. Baseline characteristics of the patients treated with azathioprine.

Clinical characteristics	Males (<i>n</i> = 9)	Females (<i>n</i> = 8)	<i>p</i>
Eczema onset in infancy: 0–1 years old	4 (44.4%)	2 (25%)	0.429
Mean (SD) age, years	17.2 (3.6)	14.7 (4.3)	0.206
Mean (SD) SCORAD	68.2 (6.8)	65.0 (20.0)	0.679
Positive bronchial challenge test	3	4	0.486
Allergic rhinitis	6	1	0.024
Mean (SD) serum total IgE, kIU/l	21 448 (11 482)	19 389 (9916)	0.707
Mean (SD) eosinophil percentage	12.1 (3.3)	10.1 (7.4)	0.502
Treatment tried			
Topical corticosteroids	9	8	–
Systemic corticosteroids	7	4	0.232
Systemic antibiotics	4	5	0.457
Traditional Chinese herbal medicine	8	4	0.079
Oral antihistamine	8	6	0.453
Topical tacrolimus	9	8	–
Phototherapy	1	1	0.929

SCORAD = SCORing Atopic Dermatitis score, which reflects disease activity and symptomatology of pruritus and sleep loss over the preceding 3 days.

and post-treatment visits were analyzed two-tailed by paired-sample *t*-test or McNemar test. *P*-values less than 0.05 were considered significant. The retrospective review was approved by the local ethics committee.

Results

The clinical course of the 17 patients with recalcitrant AD (nine males and eight females; mean (SD) age 16.1 (3.9) years, median (range) 17.0 (9.3–22.1 years) who received azathioprine between November 2005 and December 2007 were reviewed to analyze the clinical efficacy and hematological and biochemical effects at 3 months and 6 months (Tables I and II). The target dosage was generally achieved within 4–8 weeks. The dosage range at 3 months was 1.2–3.5 mg/kg per day with the median at 2.4 mg/kg (no sex difference). The dosage of azathioprine bore no significant relationship with baseline SCORAD, body swab for *S. aureus*, or steroid or antihistamine usage.

Compared with baseline, significant improvements were observed in SCORAD (*p* = 0.002), objective SCORAD (*p* = 0.002), extent (*p* = 0.001) and pruritus (*p* = 0.004) at 3 months. The improvement in SCORAD

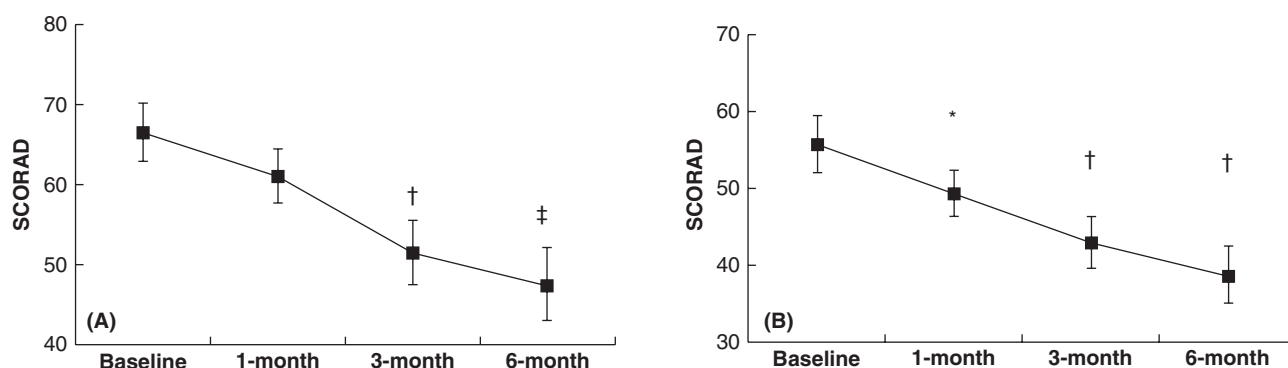


Figure 1. Changes in (A) total SCORAD and (B) objective SCORAD during the 6-month study period. Error bar at each time point represents mean and standard error of mean. Asterisks are significant p -values at each time point following azathioprine as compared with the baseline value. * $p < 0.05$; † $p < 0.005$; ‡ $p < 0.001$.

($p < 0.001$), objective SCORAD ($p = 0.001$), extent ($p < 0.001$), dryness ($p = 0.033$) and pruritus ($p = 0.001$) was sustained at 6 months of azathioprine usage (Figure 1). Azathioprine at average doses of 1.2–3.5 mg/kg per day resulted in 19–83% improvement (median 27%) in the total SCORAD in three-quarters of patients at 6 months in this small series.

Compared with males, the mean objective SCORAD ($p = 0.009$) was significantly lower in females at 6 months (Table II). Obvious improvement was observed in one female patient when her objective SCORAD dropped 83% from 67.4 (severe) at baseline to 11.6 (mild) after prescription of azathioprine for 6 months. She was completely off topical steroids and antihistamines, which she had used 3 days per week and daily at baseline, respectively. In another female patient, the objective SCORAD of 76.3 (severe) dropped to 35.2 (moderate), and her *S. aureus*

carriage dropped from heavy growth to scanty growth. The objective SCORAD of another female dropped from 44.2 (severe) to 18.6 (moderate) with clearance of her *S. aureus* carriage. She stopped her antihistamine medication and her topical steroid usage dropped from daily to not more than three times per week. One male also achieved a reduction in objective SCORAD from 46.4 (severe) to 20.6 (moderate), and *S. aureus* carriage from heavy growth to scanty growth.

Mild derangement in glutamic-pyruvic transaminase (glutamic-pyruvic transaminase (GPT) 68 IU/l, normal < 58) was only observed in one female at 3 months, and the azathioprine was discontinued due to lack of clinical efficacy with normalization of her GPT level. Serum bilirubin levels were mildly elevated in two males. In one patient, the bilirubin level was transiently elevated at 5 months to 23 $\mu\text{mol/l}$ (normal < 15) and this normalized by 12 months without dosage reduction. In another male, a bilirubin level of 37 IU/l was noted at 7 months. All patients tolerated the medication.

Serum total IgE levels decreased significantly at 3 and 6 months following azathioprine treatment (Figure 2). Compliance to treatment was generally good, and no patients suffered from any significant adverse reaction. Compared with baseline, there was a trend of reduced topical steroid usage ($p = 0.063$; Figure 3) and oral antihistamine usage ($p = 0.031$; Figure 4). By 6 months, 7 patients were completely off topical steroids and nine patients were off oral antihistamines. There was also a significant reduction in *S. aureus* carriage ($p = 0.016$; Figure 5).

Table II. Efficacy at 3 and 6 months.

Clinical characteristics	Males ($n = 9$)	Females ($n = 8$)	p
At 3 months			
Mean (SD) objective SCORAD	46.6 (9.8)	39.1 (16.0)	0.415
Mean (SD) serum total IgE, kIU/l	15 038 (10 474)	16 466 (11 342)	0.825
	Males ($n = 9$)	Females ($n = 7$)	
At 6 months			
Mean (SD) objective SCORAD	46.8 (12.2)	28.4 (11.7)	0.009
Mean (SD) serum total IgE, kIU/l	12 211 (9375)	14 322 (13 141)	0.718

In males, a significant reduction of objective SCORAD from baseline was observed at 3 months ($p = 0.002$) and at 6 months ($p = 0.034$). In females, a significant reduction of objective SCORAD was observed at 6 months ($p = 0.009$) but not at 3 months ($p = 0.061$).

Discussion

In this case series of patients with moderate-to-severe recalcitrant AD, azathioprine, at average doses of

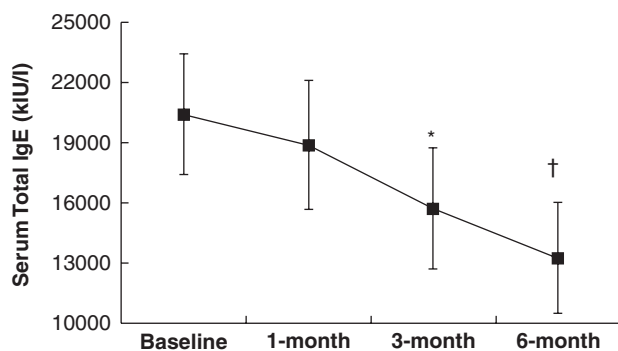


Figure 2. Changes in serum total IgE levels during the 6-month study period. Asterisks are significant p -values at each time point following azathioprine as compared with the baseline value. * $p < 0.05$; † $p < 0.01$.

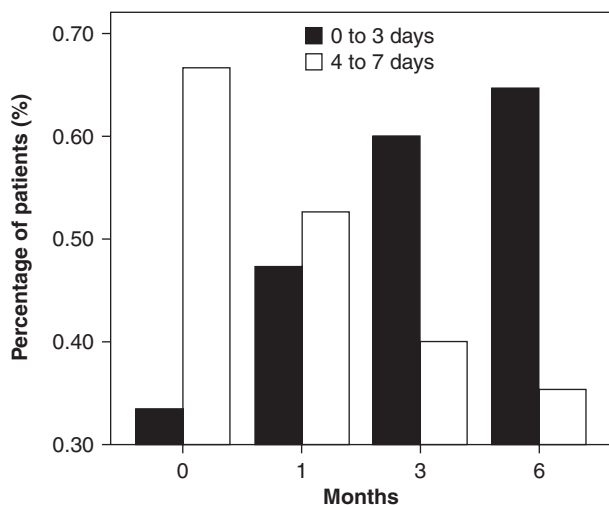


Figure 3. Average usage of topical steroid in days per week reduced after 6 months ($p = 0.063$ by McNemar test).

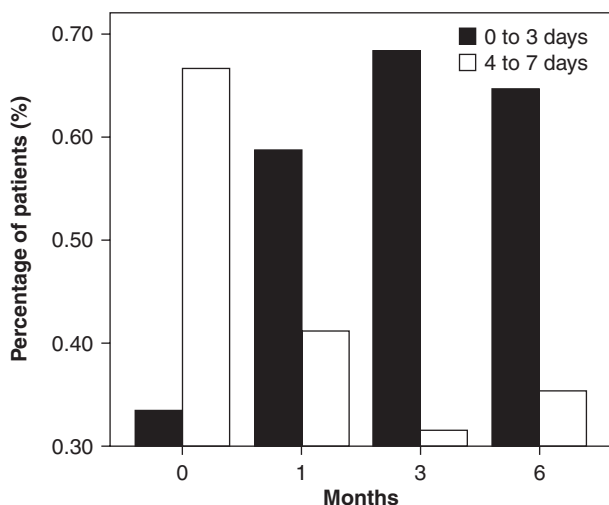


Figure 4. Average usage of oral antihistamine in days per week reduced significantly after 6 months ($p = 0.031$ by McNemar test).

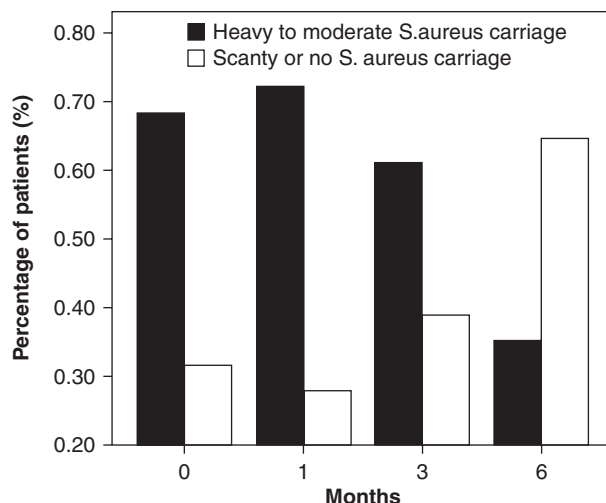


Figure 5. *S. aureus* carriage was reduced at 6 months following use of azathioprine ($p = 0.016$ by McNemar test).

1.2–3.5 mg/kg per day, resulted in a significant reduction in the total SCORAD in three-quarters of patients at 6 months. The intensity of AD also improved significantly after azathioprine usage. Compared with the males, the females had significantly lower mean objective SCORAD scores at 6 months. The reason for this sex difference in efficacy is not clear but TMPT activity in Sprague-Dawley (S-D) rat kidneys has been found to be lower in females, reflecting possible testosterone dependence (9). However, TMPT activity was not significantly influenced by sex and age in other studies (10,11).

Serum total IgE is a marker of allergy and was significantly reduced at 6 months ($p = 0.008$). We previously found age-specific serum IgE levels to be an inexpensive and readily available marker of AD severity (12). The therapeutic effect of azathioprine might be partly mediated by the reduction of this allergic marker.

Side effects were uncommon. Transient elevation of GPT was observed in one female, and her azathioprine was discontinued due to lack of efficacy and her GPT normalized. In our series, there was no severe hypersensitivity reaction, which may include vasculitis, erythema multiforme or erythema. No increased susceptibility to cutaneous viral infections due to the immunosuppression was observed. It is important to measure serum TMPT, which is a major metabolizer of azathioprine but is deficient in 1 out of 300 individuals (4,13). Ideally, the enzyme should be measured prior to commencement of azathioprine treatment to avoid serious derangement of liver function (7), but this enzyme assay was unavailable locally. Thus, a lower starting dose of 0.5–1 mg/kg to the nearest tablet (25 mg/kg tablet) was used and carefully increased to a therapeutic dose of 1.2–3.5 mg/kg per day with frequent checks of

blood counts and liver function. No myelosuppression or hepatotoxicity was observed with this approach in our series. The final dosage was comparable to that used in a large pediatric series (4). The disadvantage of this practice is that it takes about 1 month to achieve the final dosage and frequent blood tests are initially required.

It is suggested that azathioprine can be used in children with minimal risk if usage is limited to 2 years (4). Treatment with this immunosuppressant is more cost-effective than therapy with cyclosporine or tacrolimus (6). In a double-blind, placebo-controlled, crossover trial of 37 severe adult AD patients, azathioprine was also found to be an effective and useful drug, although it was not always well tolerated (8).

The major limitations of this present study were the small sample size, the wide age range and the absence of a control group. Despite these, individual patients may significantly benefit from the use of this medication. This once-daily treatment may be particularly convenient in adolescents whose AD is not controlled or who have experienced side effects with topical corticosteroids. We observed that azathioprine is efficacious in lowering topical corticosteroid usage and disease severity in the majority of patients. A large, randomized, placebo-controlled study is needed to confirm the usefulness of azathioprine in young children and adolescents with AD.

In conclusion, azathioprine appears useful in reducing the severity of AD. The therapeutic effects are generally observed within 3 months of its use. Better efficacy was observed in females. No significant derangements in liver function were observed.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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