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Original Article

Evaluation of clinical efficacy and tolerability of azathioprine in adult Chinese atopic dermatitis patients in Hong Kong with pre-treatment thiopurine methyltransferase assessment

硫唑嘌呤在香港華裔異位性皮膚炎成年患者中的功效及耐受性評估，暨治療前硫嘌呤甲基轉移酶檢測

SM Wong 黃思敏 and KM Ho 何景文

Background: Azathioprine (AZA) has been proposed as an off-label option in treating moderate-to-severe atopic dermatitis. Pre-treatment thiopurine methyltransferase (TPMT) assessment is commonly used in western countries, but TPMT test is not commonly available locally. ***Objective:*** We sought to evaluate the efficacy and tolerability of AZA in adult Chinese atopic dermatitis patients with pre-treatment TPMT assessment. ***Methods:*** Patients with atopic dermatitis seen in all government skin clinics in Hong Kong were screened to receive AZA for 12 weeks. The target dose of AZA was 2.5 mg/kg/day. The primary outcome was the change in disease activity as measured by the Six-area, Six sign Atopic Dermatitis (SASSAD) scores after treatment. ***Result:*** Thirty-six patients were recruited. The data were analysed on an intention-to-treat basis. The mean age was 26.9 years (range 18-63) with a male-to-female ratio of 1.4:1. After a treatment duration of 12 weeks, the disease activity was reduced by 52.1% (95%CI 47.6-52.6%) ($p<0.05$). Twenty-one patients (58.3%) achieved at least 50% reduction in disease activity (SASSAD50). The reduction in disease activity parallelled a significant improvement of symptoms and quality of life. The overall drug tolerability was good. Two patients discontinued AZA due to neutropaenia but both had a normal TPMT level. Other recognised adverse events such as nausea, rash, and raised liver enzymes were also observed. ***Conclusion:*** AZA can be considered as an effective and well-tolerated systemic treatment for patients with moderate-to-severe atopic dermatitis. Close blood monitoring is still warranted despite a normal level of thiopurine methyltransferase.

背景：硫唑嘌呤已被提議爲治療中度至嚴重異位性皮膚炎的一種標籤外的治療選項。治療前的硫嘌呤甲基轉移酶檢測已是西方國家的常規，但在本地卻未普及。**目的**：我們試圖評估華裔異位性皮膚炎成年患者對硫唑嘌呤治療的療效及耐受性，並在治療前進行硫嘌呤甲基轉移酶水平的檢測。**方法**：在香港的所有政府皮膚科門診，對異位性皮膚炎患者進行篩選，參與者其後接受硫唑嘌呤共十二週的療程，目標劑量是服用者每天每公斤體重計爲2.5毫克。主要療效指標定爲治療後由六

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區域六體徵評分法（SASSAD）得分所反映的病情改變。**結果**：本研究共招募三十六例病患，平均年齡爲 26.9 歲（範圍是十八歲至六十三歲），男性與女性的比例爲 1.4:1 。數據基本採用意向治療分析，經過十二週的治療時間，疾病活躍性的減幅爲 52.1%（95%CI 47.6-52.6%）（$p<0.05$）。二十例（58.3%）的疾病活躍性（SASSAD50）達到五成或以上的減幅。此外，疾病活躍性的減少，與生活質量及顯著的症狀改善並行發展。整體藥物的耐受性良好，只有兩名硫嘌呤甲基轉移酶水平正常的患者因爲中性粒細胞減少而須停服硫唑嘌呤，而其他觀察到的不良反應則包括噁心、皮疹和肝酶升高。**結論**：硫唑嘌呤對中度至嚴重病情的異位性皮膚炎患者來說，可視爲有效和耐受性良好的全身治療。服用者即使有著正常水平的硫嘌呤甲基轉移酶，緊密的血液監測仍是不可或缺的。

Keywords: Atopic dermatitis, eczema, azathioprine, thiopurine methyltransferase, TPMT

關鍵詞：異位性皮膚炎，濕疹，硫唑嘌呤，硫嘌呤甲基轉移酶， TPMT

Introduction

Atopic dermatitis (AD; synonym: atopic eczema) is a chronic inflammatory skin disorder which affects 3-5% of the adult population.[1] Atopic dermatitis not only results in skin function impairment, but also causes considerable psychosocial dysfunction. Patients with moderate-to-severe AD often have difficulties in controlling disease by topical treatments alone. Long-term effective and safe treatments are required. Systemic treatment includes corticosteroid, azathioprine (AZA), cyclosporine and methotrexate, but their use is often limited by the potential side-effects.[2]

AZA is widely used in various corticosteroid-responsive diseases as steroid-sparing agents. The role of AZA in atopic dermatitis has been established by two randomised controlled trials that AZA was significantly superior to placebo and could be used as monotherapy for moderate-to-severe AD rather than as a steroid-sparing agent.[3,4] The major drawback is, however, bone marrow suppression.

Thiopurine methyltransferase (TPMT) is one of the major determining enzymes that is involved in the metabolism of AZA.[5] Due to polymorphism of the TPMT gene, persons homozygous for the wild-type alleles have normal TPMT activity; persons homozygous for the variant TPMT alleles have deficient TPMT level and have the highest risk of life-threatening bone marrow suppression; while persons with heterozygous genotype (i.e. one wild-type allele and one variant allele) have intermediate or low TPMT activity and would also suffer from increased risk of bone marrow toxicity if given a standard dose of AZA.[6,7]

Pre-treatment screening for TPMT will identify patients with low TPMT activity who are at increased risk of marrow toxicity on standard doses of AZA but will tolerate a reduced AZA dose. In patients with high TPMT activity, an increased AZA dose may lead to accumulation of inactive metabolites and increased risk of hepatotoxicity.[8,9]

Erythrocyte TPMT activity has been recommended as a pre-treatment test for patients requiring AZA in United Kingdom (UK) dermatological guidelines.[6] However, it is not available locally. In Chinese, the prevalence of TPMT deficiency was low and the usefulness of TPMT screening before AZA in our patients was uncertain.[10-12] To our knowledge, apart from one local retrospective study in children by Hon et al,[13] no prospective study on AZA in treating atopic dermatitis in adult Chinese patients has been performed.

Objectives

In the present study, we sought to 1) evaluate the efficacy and 2) tolerability of AZA in adult Chinese

patients with refractory moderate-to-severe atopic dermatitis, with pre-treatment TPMT assessment in order to exclude patients with deficient level and use a lower AZA dose in patients with low TPMT level.

Methods

Study design

This was a prospective open-label multi-centre study evaluating the efficacy and safety of AZA in Chinese adult patients with moderate-to-severe atopic eczema refractory to topical treatment over a 12-week period. The trial was conducted between January 2011 and August 2012 in all public dermatological clinics under the Department of Health, which were tertiary care-units caring for dermatological patients in Hong Kong.

Subject recruitment

Inclusion criteria

All consecutive patients who attended our clinics aged 18-65 years suffering from moderate-to-severe atopic dermatitis, defined according to the UK modification of Hanifin and Rajka's diagnostic criteria,[2,14] with a Six Area, Six Sign Atopic Dermatitis (SASSAD) score[15] of at least 15 were eligible if their disease was refractory to topical corticosteroid treatment (defined as no satisfactory clinical improvement after continuous application of potent topical corticosteroid for at least six months). The participation was on a voluntary basis.

Exclusion criteria

Patients were excluded if they had mild atopic dermatitis (SASSAD <15), unstable atopic dermatitis or had received treatment with AZA or other immunosuppressants, potent topical corticosteroids (class I-II) and topical calcineurin inhibitors, phototherapy, herbal medicine within three months or systemic corticosteroid within one month. Patients were also excluded if they suffered from infections, blood abnormalities or malignancies; had a history of hypersensitivity to AZA or other thiopurine drugs; were taking medications with possible drug interactions with AZA or had blood transfusion within three months. Hepatitis B carriers, patients who were immunosuppressed as well as those who were pregnant, unable to give consent or non-compliant were also excluded.

Study procedure

Pre-treatment thiopurine methyltransferase enzyme activity measurement

In this study, TPMT activity in whole blood was checked prior to treatment. In view of TPMT phenotype/genotype test is not available locally, and from previous studies, the observed difference in TPMT activity across gender and race was small,[5,12] the tests were performed in an accredited TPMT laboratory in City Hospital, Birmingham, United Kingdom through Doctor's Laboratory, London. The TPMT activity was measured with validated methodology in mU/L.[16] Patients with absent or deficient TPMT level were excluded from the study.

Treatment regime

At baseline (week 0), subjects were recruited for the initial 12-week AZA treatment. AZA was given as single-daily dose according to the TPMT level and body weight, starting from 25 mg for patients with low TPMT level; 50 mg for those with normal TPMT level; and then gradually increased by 0.5 mg/kg/day weekly to the target dose over four weeks in order to decrease the possible gastrointestinal disturbance and continued for 12 weeks. The target dose for patients with normal TPMT level was 2.5 mg/kg/day and for patients with low TPMT level was 1.5 mg/kg/day. This target dose was chosen based on the suggested dose from British Association of Dermatologists' guidelines[6] and local experience.

At week 12, if the reduction of disease activity as measured by SASSAD[15] was less than 50%, patients would continue AZA for another 12 weeks. However, if the SASSAD improved more than 50%

or there was complete resolution, patients would either stop AZA at week 12 or continue AZA with a dose reduction to the minimal effective dose by decreasing 0.5 mg/kg/day per month for three months. If there were adverse events, the dose would be reduced or the drug withdrawn. Patients were then followed-up for another 12 weeks after AZA was stopped.

Patients were allowed to continue their baseline treatments as necessary (1% hydrocortisone cream or equivalent for facial lesions; 0.025% fluocinolone acetonide cream or equivalent for the trunk and limbs; emollients including aqueous cream, emulsifying ointment and white soft paraffin; oral antihistamines including chlorphenamine 4 mg three times daily, hydroxyzine 25 mg nocte). These were not altered during the study period for the convenience of interpretation. Systemic corticosteroid or other immunosuppressants, high potency topical corticosteroids (class I-II potency) or topical calcineurin inhibitors were not allowed during the study. Oral antibiotics and acyclovir were allowed in case of infections.

Besides a detailed history and physical examination, blood investigations including full blood count, total immunoglobulin E (IgE) level, hepatitis B status, liver and renal function tests and chest X-ray were performed before treatment. Urine pregnancy test, date of the last menstrual period and adequate contraception were required for all females of reproductive age.

Outcome measurement

Frequency of assessment

As disease activity can fluctuate widely over short periods, isolated measurements might not indicate the underlying trend. Patients were therefore assessed by the same investigator (Wong) clinically at baseline, bi-weekly in the first month then every 4 weeks subsequently during the 12-week treatment period and in the 12-week post-treatment period.

Primary outcome - SASSAD

The primary efficacy measurement was the change in disease severity at week 12, using SASSAD score and the proportion of patients achieving SASSAD50 (reduction of 50% or more).

Dermatology life quality index (DLQI),[17] SCORAD (SCORing Atopic Dermatitis)[18] and global score were also assessed to give an overall impression of disease activity. Patient-assessed drug tolerability by a five-point scale (1. very poor; 2. poor; 3. fair; 4. good; 5. very good) was assessed at the end of treatment.

Adverse effects reported by the patients were documented regardless of whether it was related to the study drug. In case of adverse events, the dose was reduced or the drug withdrawn.

Further investigations including full blood count, liver and renal function were done weekly for the initial four weeks then every month during the treatment period. All blood tests except TPMT level were done in the Public Health Laboratory Centre, Hong Kong to minimise inter-laboratory discrepancy.

Defaulted patients were traced and assessed at the designated point. Patients were advised to bring the medication pack on follow-up to encourage drug compliance.

Ethical approval

The study protocol was approved by the local ethics committee. Written informed consent was obtained for all patients prior to study-related procedures.

Statistical analysis

Based on previous trials,[3,4] assuming that the standard deviation of the SASSAD change was 19, to detect a size of effect of 12 units in disease activity (SASSAD) reduction after treatment, i.e. 30% relative to baseline value,[10,11] we aimed to recruit at least 30 patients with 80% power, 5% level of significance (SAS v9.13) and drop-out rate

of 25%. The data were included for intention-to-treat analysis if patients had taken at least one dose of AZA. Normal distribution of the continuous data was verified with Shapiro-Wilk test. Wilcoxon signed rank test was used to analyse the mean change in disease activity before and after treatment. Specific statistical tests were indicated in the legend of the tables. Data were analysed using SPSS 17.0 for Window (SPSS Inc. Chicago, Ill).

Results

Baseline patient characteristics

During the study period, 144 moderate-to-severe atopic dermatitis patients were screened; 73 patients improved with topical treatment and 71 were refractory to topical treatment. Twenty-four patients of the latter group refused giving a consent and nine of them did not meet the inclusion criteria. Hence, thirty-eight patients were initially recruited. However, one patient withdrew consent later and one patient used prednisolone prior to AZA and was thus excluded for analysis. Hence, the data of thirty-six patients were analysed. Baseline characteristics of the patients are shown in Table 1. The mean age was 26.9 years (range 18-63) and male-to-female ratio was 1.4:1. Thirty-one (86.1%) patients had a personal history of allergic rhinitis or asthma and 19 (52.8%) had a family history of atopy. The mean duration of eczema was 23.2 years (range 8-47). Twenty-eight percent of patients had received treatment with systemic corticosteroid and 31% with traditional Chinese medicine for eczema in the past. None of the patients had previously used AZA or other immunosuppressive drugs.

Normal distribution of TPMT level was verified with the Shapiro-Wilk test (p=0.943) and Q-Q plot (not shown). The mean and median TPMT activity were 107.3 mU/L (±standard deviation 19.1 mU/L) and 109 mU/L (range 66-155 mU/L) respectively (Table 2). One out of 36 (2.8%) patients was detected with a low level of TPMT (66 mU/L). Thirty-five (97.2%) patients had a normal TPMT level. No patients with deficient TPMT level were detected.

Table 1. Baseline characteristics of the participants (n=36)

	Azathioprine (n=36)
Age, years	26.9 (±8.4)
Male, no. (%)	21 (58.3%)
Body weight, kg	60.9 (±14.1)
Personal history of allergic rhinitis or asthma, no. (%)	31 (86.1%)
Family history of atopy, no. (%)	19 (52.8%)
Raised serum IgE, no. (%)	35 (97.2%)
Duration of follow-up, years	7.2 (±6.4)
Duration of eczema, years	23.2 (±8.8)
Previous use of systemic corticosteroid, no. (%)	10 (27.8%)
Previous use of traditional Chinese medicine, no. (%)	11 (30.6%)
Baseline SASSAD	58.1 (±12.0)
Baseline body area involved (%)	44.6 (±16.3)
Baseline DLQI	18.5 (±6.1)
Use of TCs ≥3 days/week	32 (88.9%)
Use of oral antihistamine ≥3 day/week	28 (77.8%)

Note TCs: topical corticosteroids. Data expressed in mean (SD) or number of patients (%)

Table 2. Thiopurine methyltransferase level and AZA dosage of the participants

	Participants received azathioprine
TPMT level (mU/L), mean (SD)	107.3 (19.1)
Patients with TPMT range, no. (%)	
High (>150 mU/L)	1 (2.8%)
Normal (68-150 mU/L)	34 (94.4%)
Low/intermediate (20-67 mU/L)	1 (2.8%)
Absent/deficient (<20 mU/L)	0 (0%)
Azathioprine	
Dose (mg/kg/day), mean (SD)	
At week 12	2.05 (0.42)
At week 24	1.74 (0.34)
Patients received AZA dosage, no. (%)	
<1.5 mg/kg/day*	2 (5.6%)
1.5-2.0 mg/kg/day	10 (27.8%)
≥2.0-2.5 mg/kg/day	24 (66.7%)

Note: At week 12, patients received AZA n=36; at week 24 patients received AZA, n=15.
*Patients' AZA dosage was limited by adverse events/drug tolerance.

Clinical efficacy

The mean AZA dosage was 2.05 mg/kg/day (median 2.1 mg/kg/day). The median dose of AZA in patients with normal TPMT level was 125 mg (mean 124.2 mg, 95% confidence interval (CI) 113.1-135.2 mg). The disease activity was significantly improved (Figure 1). At week 12, 58.3% (21) patients achieved SASSAD50. The mean SASSAD score was 58.1 points (95% CI 54.1-62.2) at baseline and was reduced to 27.9 points (95% CI 24.8-30.9) ($p<0.01$) at week 12 while the mean reduction was 30.2 points (95%CI 27.0-33.6) and 52.1% (95%CI 47.6-52.6%) (Tables 3 & 4). Clinical improvement in disease activity was also associated with a statistically significant decrease in symptoms, use of topical steroid and oral antihistamine and global score (Figure 2).

Positive correlation of a reduction in SASSAD was found to be significant with the baseline SASSAD score ($p=<0.001$), AZA dose received ($p=0.002$) and a longer treatment duration (24-week compared to 12-week AZA) (Table 5). Patients with higher baseline SASSAD scores and those treated with an optimal dose of AZA and a longer treatment duration experienced greater clinical improvement.

Further improvement in disease activity, symptoms and quality of life was observed in the 12-week post-treatment period in patients receiving 24 weeks of AZA (Figure 3).

Drug tolerability

Overall, 97.2% (35) patients rated the tolerability of AZA as fair to very good. Twenty-eight (77.8%) patients completed 12-week AZA; five patients (13.8%) stopped due to AZA-related adverse events while three patients stopped due to non-compliance. Of the two patients who discontinued AZA due to neutropaenia, both had a normal TPMT level: one female patient's TPMT level was 112 mU/L (normal range

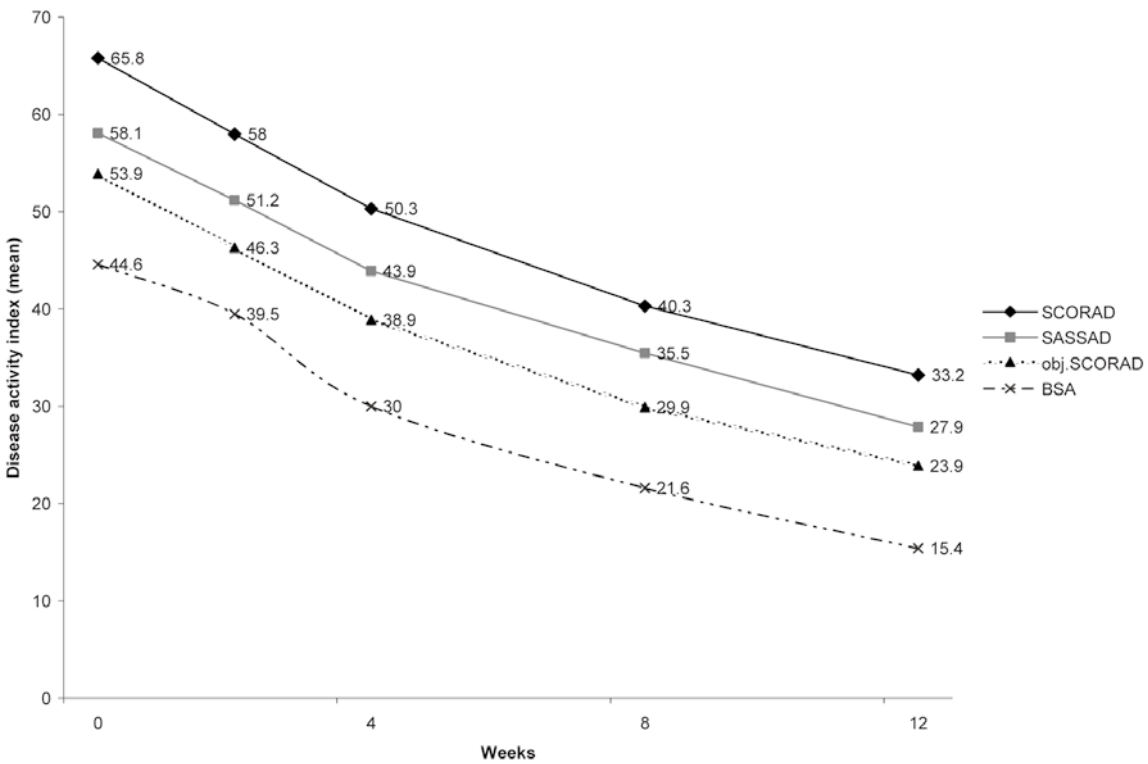

Figure 1. Trend of improvement in disease activity index over 12-week azathioprine treatment period (n=36) (All p values were <0.001 as early as week 2, 4, 8, 12 compared with baseline).

Table 3. Comparison of disease activity, quality of life, symptoms and frequency of medication use in participants at baseline, week 12 (n=36) and week 24 (n=15) of azathioprine

	Baseline Mean (SD)	**Week 12 Mean (SD)**	**p#**	**Week 24 Mean (SD)**	**p#**
Disease activity :					
SASSAD	**58.1** (±12.0)	27.9 (±9.1)	<0.001*	**20.7** (±8.0)	0.001*
SCORAD	**65.8** (±12.7)	33.2 (±9.3)	<0.001*	**25.5** (±10.3)	0.001*
Objective SCORAD	**53.9** (±12.4)	23.9 (±9.4)	<0.001*	**18.1** (±8.4)	0.001*
BSA, %	**44.6** (±16.3)	15.4 (±9.3)	<0.001*	**7.0** (±5.8)	0.001*
Symptoms:					
DLQI	**18.6** (±6.1)	12.5 (±5.7)	<0.001*	10.6 (±5.1)	0.001*
VAS Itch	**6.3** (±2.0)	5.0 (±2.1)	0.006*	3.8 (±2.4)	0.007*
VAS loss-of-sleep	**5.9** (±2.5)	4.2 (±2.2)	<0.001*	3.5 (±2.7)	0.004*
	% (no.)	**% (no.)**	**p^**	**% (no.)**	**P^**
Use of medication:					
Topical corticosteroid ≥3 d/w	**88.9%** (32)	52.8% (19)	0.001*	**40%** (6)	0.025*
Oral antihistamine ≥3 d/w	**77.8%** (28)	55.6% (20)	0.039*	**33.3%** (5)	0.034*

Data were expressed in mean (SD) or no. (%) #Wilcoxon signed rank test used for non parametric continuous data (mean score) before and after treatment at week 12/week 24 and baseline. ^McNemar test used for change of proportions of patients before and after treatment. *Two-tailed p<0.05 was used as statistically significant. Note: no, no. of patients. SASSAD 0-108. DLQI (0-30): 0-1 mild, 2-5 small, 6-10 moderate; 11-20= large; 21-30=extremely large impact on life from skin disease.

Table 4. Reduction in outcome parameters at week12 (n=36) vs week 24 (n=15) azathioprine therapy

	Reduction in disease activity from baseline	
	Week 12 Mean reduction (95% CI)	**Week 24 Mean reduction (95%CI)**
SASSAD		
Absolute	30.2 (27.0-33.6)	36.9 (32.5-42.6)
Relative (%)	**52.1** (47.6-56.5)	**67.8** (54.5-73.5)
Body surface area involved		
Absolute	29.2 (24.6-33.8)	37.4 (28.5-46.2)
Relative (%)	**64.6** (58.1-71.0)	**82.4** (64.3-95.8)

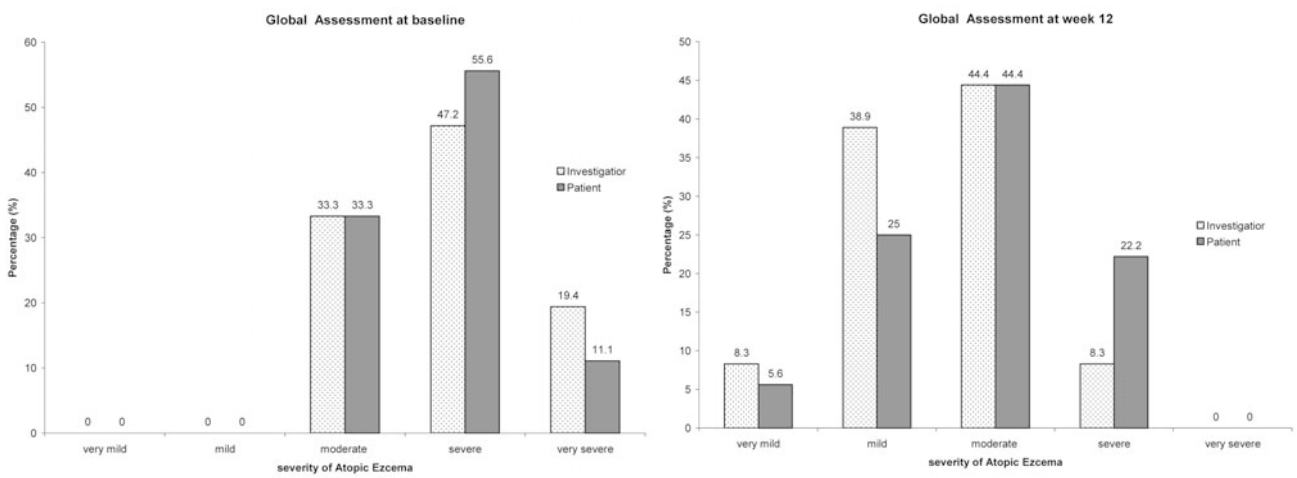

Figure 2. Global assessment (investigator- and patient-assessed) at baseline and week 12. This graph showed that patients shifted from severe to milder disease severity at week 12 (IGA, PGA; p=<0.001, p=0.001 respectively by McNemar test).

68-150 mU/L) and her AZA dose was 2.32 mg/kg/day; another female patient's TPMT level was 75 mU/L and her AZA dose was 2.25 mg/kg/day. Minor abnormalities in blood counts were observed in 50% of the patients, mostly lymphopaenia followed by anaemia, neutropaenia and thrombocytopaenia which were transient and reverted to normal after dose reduction. No significant bone marrow toxicity was observed in the patient with low TPMT level who received a lower dose of AZA. Eight (22.2%) patients reported dyspepsia. Nine (25%) patients experienced transient elevation in liver enzymes. No serious infection requiring systemic antibiotics or hospitalisation was reported.

Table 5. Association of reduction in SASSAD at week 12 with patient's baseline characteristic, disease activity (SASSAD) and azathioprine dose (n=36)

	Correlation coefficient ^	p ^	Correlation coefficient ^ ^	p ^ ^
Age	0.003	0.988	–	–
Gender	0.071	0.682	–	–
Body weight	0.044	0.797	–	–
Baseline serum IgE level	-0.014	0.939	–	–
TPMT activity	-0.192	0.263	–	–
Duration of eczema	0.005	0.976	–	–
Baseline SASSAD score	0.454	0.005*	0.632	<0.001*
Baseline body area involved	0.262	0.123	–	–
Azathioprine dose per body weight (mg/kg/day)	0.369	0.027*	0.518	0.002*
Treatment duration#	0.509/0.414	0.002*/0.012*	0.564/0.441	0.001*/0.01*

^ Spearman's rank (rho) correlation coefficient. ^ ^ partial correlation controlling variables with statistically significance including baseline SASSAD, AZA dose, treatment duration correspondingly as applicable. *Correlation is significant at the 0.05 level (2-tailed). #Correlation was analysed in reduction in disease activity (SASSAD) from baseline comparing patients received 12-week azathioprine vs 24-week azathioprine.

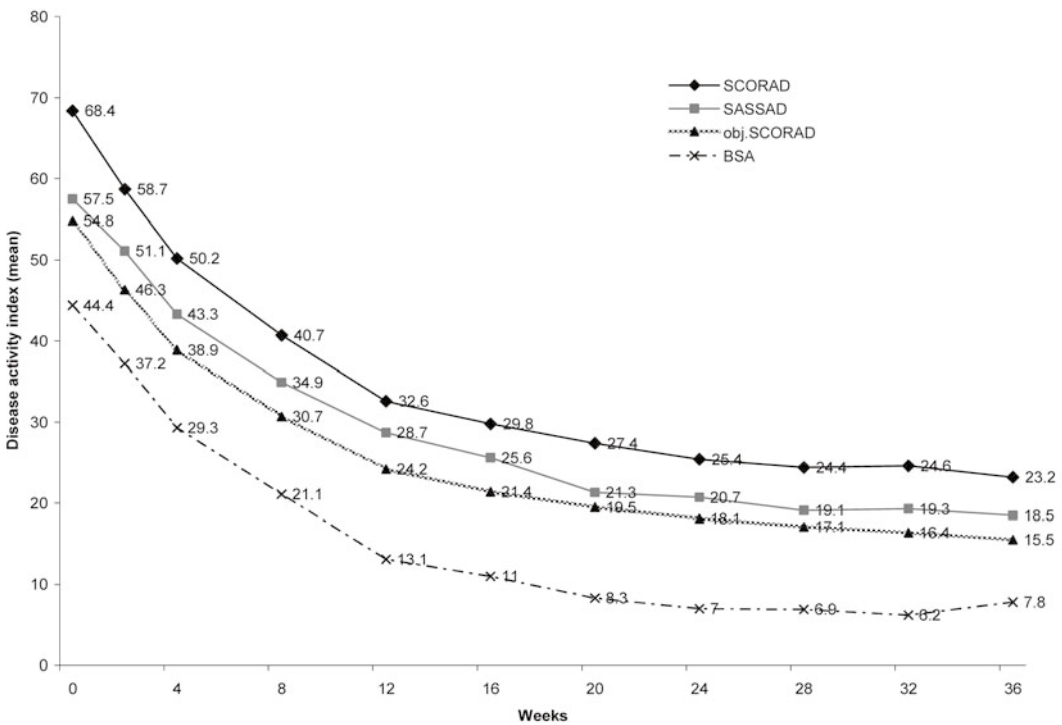

Figure 3. Trend of improvement in disease activity index and body area involved over 24-week azathioprine treatment period and 12-week post-treatment follow-up phase (n=15). (Note all p<0.001 compared to baseline)

Discussion

There have been two recent randomised controlled trials[3,4] showing that AZA could be used as systemic monotherapy in moderate-to-severe atopic dermatitis. In our study, AZA resulted in a statistically significant improvement in disease activity, symptoms and quality of life. Although the improvement in disease activity between 12 and 24 weeks was not robust, it showed that the current AZA dosage used would be adequate in disease control and is comparable to the dosage suggested in the British Association of Dermatologists' guidelines.[6] Moreover, patients continued to show greater disease control after a longer duration of AZA treatment. (Figure 3). It would be explained by the slow onset of action of AZA.[19] Therefore, patients should be counselled about this delay.

Furthermore, disease control could generally be sustained after drug cessation for up to three months (Figure 3). This would be explained by the persistent beneficial effect of AZA.[19] Patients with more severe disease would have a greater improvement with an optimal AZA dosage and longer treatment duration.

Myelotoxicity

A growing number of studies support the association between absent TPMT activity and acute severe neutropaenia in patients receiving conventional dose of AZA.[20-22]

In our study, patients with normal TPMT level were given conventional dose of AZA (maximum dose: up to 2.5 mg/kg/day). Patients with low TPMT activity were given a lower AZA dose (1.5 mg/kg/day). Interestingly, transient neutropaenia which normalised after stopping AZA was in fact observed in patients with normal TPMT activity. Further studies on this are needed. Polymorphism of drug metabolising enzymes other than TPMT might also be important. For example, inosine triphosphate pyrophosphatase polymorphisms are associated with AZA hypersensitivity symptoms[23] and AZA-induced neutropaenia has been reported in patients with low 5-nucleotidase activity.[24]

On the other hand, a lower AZA target dose may not be adequate to prevent myelotoxicity. Apparently, pre-treatment TPMT assessment alone would be inadequate in preventing leucopaenia and cannot substitute close haematological monitoring even if the TPMT is within the normal range.

Limitations

This was a local pilot study in our Chinese adult population. Participants had not received AZA and other immunosuppressants before; and validated outcome parameters were used. Ideally the trial should be performed in a double-blind placebo-controlled setting to avoid placebo-effect and minimise intra-observer bias.

Conclusion

We demonstrated that AZA was an effective and well-tolerated treatment for patients with refractory moderate-to-severe atopic dermatitis. Pre-treatment TPMT level can be considered before the initiation of AZA, although the risk of bone marrow toxicity still cannot be neglected despite the normal TPMT activity and close blood monitoring is warranted. Further randomised controlled trials are needed to establish the optimal dosage and duration of AZA in our population.

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