Atopic dermatitis: epidemiology & off-label therapy
Schram, M.E.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
ME Schram
E Roekevisch
MMG Leeflang
JD Bos
J Schmitt
Phl Spuls

A randomized trial of methotrexate and azathioprine for severe atopic eczema.

*Journal of Allergy and Clinical Immunology* 2011, in press
5.1 A RANDOMIZED TRIAL OF METHOTREXATE AND AZATHIOPRINE FOR SEVERE ATOPIC DERMATITIS
SUMMARY

Rationale: Patients with severe atopic dermatitis/eczema (AD) frequently require systemic treatment to control their disease. Methotrexate and azathioprine are proposed as off-label treatment options, but direct comparisons are lacking.

Objective: We sought to compare the efficacy and safety of methotrexate versus azathioprine in adults with severe AD.

Methods: Patients with severe AD were randomly assigned in a 1:1 ratio to receive either methotrexate (dosage, 10-22.5 mg/wk) or azathioprine (dosage, 1.5-2.5 mg/kg/day) for 12 weeks, followed by a 12-week follow-up period. Primary outcome was the mean change in the severity scoring of atopic dermatitis (SCORAD) index after 12 weeks. Efficacy assessors blinded for allocation of treatment were used to perform clinical outcome assessment. Analyses were done on an intention-to-treat basis.

Results: Of the 45 patients screened, 42 were included. At week 12, patients in the methotrexate group had a mean relative reduction in the SCORAD index of 42% (SD 18%) compared with 39% (SD 25%) in the azathioprine group (P= 0.52). Proportions of patients achieving at least mild disease and reductions on impact of quality of life, symptoms, and levels of thymus and activation regulated chemokine (TARC) were similar in both groups at weeks 12 and 24. No statistically significant differences were found in the number and severity of adverse events. Abnormalities in blood count were more common in the azathioprine group. No serious adverse events occurred.

Conclusion: Both treatments achieved clinically relevant improvement and were safe in the short-term. Methotrexate and azathioprine are appropriate options for the treatment of severe AD.
INTRODUCTION

Atopic dermatitis/eczema (AD) is a chronic inflammatory skin disorder that affects approximately 3% to 5% of the adult population in the western world. AD can result in impairment of skin function, poor sleep, and social stigma over a long period of time. Patients often have to bear the burden of considerable psychological comorbidity. Patients with severe AD require prolonged treatment with large amounts of highly potent topical corticosteroids, systemic treatment, or both. Frequently used options for systemic treatment of AD include cyclosporin and systemic corticosteroids. Although proved effective, a proportion of patients have a contraindication for cyclosporin or discontinue treatment because of ineffectiveness or side effects. Moreover, long-term use of cyclosporin raises concerns over (nephro)toxicity. Systemic corticosteroids are used frequently to suppress exacerbations, although high-level evidence is lacking. A recent randomized controlled trial (RCT) comparing short-term cyclosporin versus prednisolone was interrupted because of an unsuspected high proportion of severe rebound in the prednisolone group. Medium- to long-term treatment with prednisolone is relatively contraindicated because of the cumulative effect of the side effects. This illustrates the need for novel medium- to long-term treatment options for patients with severe AD. However, commercial interest for research in eczema is low, and thus investigator-initiated studies are needed.

As health care costs are increasing, dermatologists are looking for cheaper alternatives. Long-existing and relatively cheap disease-modifying antirheumatic drugs seem to be beneficial for AD. Two of those drugs are methotrexate and azathioprine. Azathioprine, a purine synthesis inhibitor that inhibits the proliferation of leukocytes, and methotrexate, a folic acid antagonist that targets several key T-cell activities, are currently used off-label in some (referral) centers. Despite several case series and open-label studies for methotrexate, there have been no RCTs supporting a role for methotrexate in the management of AD. The role of azathioprine in AD was established by 2 RCTs in which azathioprine was significantly superior to placebo, with mean improvements of 26% and 37% on clinical outcome scales after three months. Numerous uncontrolled studies on azathioprine in adult and juvenile patients showed similar results.

To our knowledge, no comparison of methotrexate with azathioprine in a randomized controlled fashion has been performed. With the present study, we conducted a randomized comparison of methotrexate with azathioprine for the treatment of severe AD evaluating efficacy, safety and effect on quality of life.
METHODS

Design

This study was an investigator-initiated, single-blind, parallel-group (ratio 1:1), RCT evaluating efficacy, safety and quality of life with methotrexate versus azathioprine over a 12-week period. The trial was conducted between July 2009 and December 2010 at the Department of Dermatology of the Academic Medical Center in Amsterdam, The Netherlands. Patients were evaluated every 2 weeks in the first month and monthly thereafter. The follow-up phase consisted of another 12 weeks in which study drugs could be continued, stopped or switched, reflecting normal clinical practice.

The study protocol was reviewed and approved by the local medical ethics committee (institutional review board) and was performed in accordance with the Good Clinical Practice Guidelines of the International Conference of Harmonisation, Declaration of Helsinki. The trial was registered in the Dutch Trial Register (NTR1916). Written informed consent was obtained from all patients before study-related procedures were commenced.

Patients

Patients were recruited from the in- and outpatient clinic of the Academic Medical Center of Amsterdam (referral center for severe AD) or were referred by regional dermatologists. Patients with AD (with and without the presence of allergen-specific IgE) defined according to the Millennium Criteria and the UK Working Party criteria\textsuperscript{14} were eligible if they were 18 years or older; the severity grading by the Rajka and Langeland criteria was severe\textsuperscript{15}; the patients were unresponsive, contraindicated, or intolerant to cyclosporin treatment; and the patients had not previously been treated with azathioprine or methotrexate.

Excluded were patients who were pregnant, breast-feeding, or planning pregnancy (men and women) until 3 months after discontinuation; those with a history of cancer, alcohol abuse, organ transplantation, chronic or recurrent infectious diseases, or any severe and uncontrolled disease; those with a history of herpes zoster infection within 2 months of baseline or current bacterial skin infection; and those who had received phototherapy, any systemic medication or a potent topical medication within the last 2 weeks.

Because thiopurine methyltransferase (TPMT) is a key enzyme in the purine metabolism and genetic variation in the gene that transcribes TPMT is linked to interpersonal differences in toxicity of azathioprine, patients randomized to the azathioprine group were tested for TPMT activity. When TPMT activity was
low or absent (<21 nmol/g/hour), indicating homozygous TPMT mutations and a subsequent risk for life-threatening myelotoxicity, patients were excluded.

Patients randomized to receive methotrexate were excluded if abnormal laboratory results were discovered after they had taken a test dose of 5 mg of methotrexate.

At every study visit (weeks 0, 2, 4, 8, 12 and 24), laboratory tests were done, including a full blood count and kidney and liver function measurement. Women of childbearing potential underwent a serum pregnancy test at every visit.

**Treatment regimens**

Treatment with methotrexate was initiated at 10 mg/wk and administered as a single oral dose. Dose escalation with 2.5 to 5 mg per scheduled visit was allowed until 22.5 mg/wk was reached. Because folate supplementation reduces the risk for hepatotoxicity in patients with rheumatoid arthritis, each patient randomized to methotrexate received 5 mg of folate 1 day after methotrexate intake. Azathioprine was initiated at 1.5 mg/kg/day in a single dose, and the dosage could be escalated at each visit with 0.5 mg/kg/day until a maximum of 2.5 mg/kg/day was reached.

Dosage was escalated if patients did not achieve at least a 25% reduction in disease activity at a study visit. The dosage could be decreased according to protocol in case of abnormal findings on physical examination, laboratory markers, and/or adverse events. After the first 12 weeks, dosages in responders were reduced to find the optimum dosage.

Patients were allowed to continue or start with concomitant topical triamcinolone acetonide ointment (body), hydrocortisone ointment (face) and oral antihistamines. In case of an exacerbation or postponed treatment effect in the first 8 weeks of treatment, patients were allowed to receive a maximum of 2 courses of rescue medication: 30 mg/d oral prednisolone for 1 week and a 1 week reduction schedule (20-20-15-15-10-10-5mg).

**Outcomes**

_Efficacy_. The primary efficacy outcome parameter was the mean relative and absolute change in the severity of AD at week 12 assessed by means of the SCORAD. The SCORAD score combines both objective items as affected area and intensity of the lesions (erythema, edema/induration, excoriation, oozing/crusting, lichenification, and dryness) and subjective items as extent of pruritus and sleep loss on a visual analog scale (VAS). Scores range from 0 to 108 points.

Secondary outcome parameters included the number of patients with a SCORAD score reduction of 50% or more (SCORAD50) and the number of
patients achieving mild disease (defined as mild, minimal, or no disease activity on investigator global assessment (IGA)), IGA and patient global assessment (PGA), mean change in the eczema area and intensity index (EASI), patient-oriented eczema measurement (POEM), itch and sleeplessness on a VAS, Skindex-17, levels of TARC, amount of concomitant topical corticosteroids and number of courses of rescue medication used.

The IGA and PGA were assessed by using a 6-point Likert scale: 0, clear; 1, almost clear; 2, mild disease; 3, moderate disease; 4, severe disease; and 5, very severe disease. The EASI is based on the extent of the eczematous involvement of the body surface area, as well as the intensity of the lesions (range, 0-72). The POEM includes 7 questions regarding skin symptoms (range, 0-28). Change in quality of life was assessed by the use of the Dutch version of the Skindex-17. Scores range from 0 to 85 points, with higher scores indicating more significantly impaired quality of life. Clinical outcome measures and quality of life were assessed at each visit. Furthermore, at baseline and week 12, serum TARC levels were measured.

Safety. The number and severity of adverse events were assessed at each visit by the safety assessor. Adverse events that were transient and easily tolerated by the patient were considered mild. Moderate adverse events were defined as causing discomfort and interrupting the subject’s usual activities. Adverse events were severe if the event caused considerable interference with the subject’s usual activities and could be incapacitating or life-threatening. Serious adverse events were defined as life-threatening events, death, prolonged or initial hospitalization, disability or permanent damage. The safety assessor defined adverse events as not, possible, probably or definitely related to treatment.

Blinding
Concealment of allocation was achieved by using a computerized program (see the Statistical analysis section). Clinical outcome measurements were assessed by trained efficacy assessors, who were blinded for allocation. Statistical analysis was performed by the third author, who was also blinded for allocation. Patients and safety assessors were not blinded.

Statistical analysis
In the primary analysis the difference in mean SCORAD scores between the treatment groups at week 12 was analyzed by using intention-to-treat analysis. The criterion for including patients in the intention-to-treat analysis was receiving at least 1 dose of study medication.
Randomization was performed in a 1:1 ratio by using a computerized program (TENALEA Clinical Trial Data Management System) with the (nondeterministic) minimization method described by Pocock and Simon. Patient factors (strata) did not influence the allocation scheme. If a patient missed a visit, we used the score from the previous visit for the intention-to-treat analysis.

Without the availability of a formally calculated minimal clinically important difference, we deemed it appropriate to use an 8-point difference in SCORAD scores between groups as the nonequivalence limit. Assuming an SD of 10 points in both groups, the power analysis showed that 42 participants were needed for a study with 80% power and 5% significance.

No interim analysis was performed. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Specific statistical tests used are indicated in the legends of the tables. SPSS 18.0 for Windows (SPSS, Inc, Chicago, Ill) was used to perform data analysis.

RESULTS

Patients’ characteristics

Between September 2009 and May 2010, 45 patients were screened for enrollment, 43 of whom were randomized (Figure 1). Twenty patients were assigned to the methotrexate group and 23 patients were assigned to the azathioprine group. One patient randomized to the azathioprine group withdrew informed consent before the initiation of study medication and was not included in the analyses. Baseline characteristics of included patients are shown in Table 1. Fifty-two percent of the patients were male, the mean age was 40 years, and the mean duration of eczema was 36 years over the 2 groups. The mean SCORAD score was 58 points at baseline. The mean Skindex-17 score was 51 points.

Mean dosage of methotrexate was 20 mg/wk at week 12 and 17.5 mg/wk at week 24. Mean dosage of azathioprine was 2.2 mg/kg/d at week 12 and 2.1 mg/kg/d at week 24.

During the study, 1 patient in the methotrexate group dropped out after 4 weeks because of nausea and fatigue. Three patients withdrew in the azathioprine group: 1 patient because of lymphocytopenia, increased liver enzyme values, and worsening of preexisting mild anemia at week 4; 1 patient because of nausea and vomiting at week 5; and 1 patient because of failure to adhere to the study protocol at week 2. No patients were lost to follow-up.
45 patients were screened for eligibility

2 did not meet inclusion criteria

43 patients underwent randomization

1 Did not receive study medication

20 patients received methotrexate and were included in intention to treat analysis

1 Did not complete study
1 Discontinued due to AE

19 patients completed the study and were included in per-protocol*

At week 12:
18 Patients continued treatment
1 Patient discontinued treatment

22 patients received azathioprine and were included in intention to treat analysis

3 Did not complete study
1 Did not adhere to study protocol
2 Discontinued due to AE

19 patients completed the study and were included in per-protocol*

At week 12:
16 Patients continued treatment
2 Patients discontinued treatment
1 Patient switched

0 Loss to follow up at week 24

*Data per-protocol analysis not shown. AE; adverse event
Efficacy

At week 12, mean SCORAD scores in the patients in the methotrexate group changed from 57.2 (SD 11.8) to 34.4 (SD 13.0), representing a relative reduction of 42% (P<0.001, Table 2). SCORAD scores in patients randomized to the azathioprine group changed from 58.4 (SD 10.4) to 36.3 (SD 16.9), representing a relative reduction of 39% (P < 0.001). The P value for the absolute difference between the groups is 0.89. Figure 2 shows the mean SCORAD scores during the study period.

Eight (40%) patients in the methotrexate group versus 10 (45%) patients in the azathioprine group achieved a SCORAD50 response (P= 0.76). Fifteen patients in each group (75% in the methotrexate group vs 68% in the azathioprine group) achieved at least mild disease on IGA (P= 0.74). On global assessment, the mean IGA score was reduced to 1.8 (SD 0.7) in the methotrexate group versus 1.4 (SD 0.9) in the azathioprine group (P= 0.20) and the mean PGA score was reduced to 1.3 (SD 0.9) in the methotrexate group versus 1.2 (SD 1.3) in the azathioprine group (P= 0.95). The EASI score was reduced to 17.4 (SD 6.6) points in the methotrexate group compared with 17.2 (SD 14.1) points in the azathioprine group (P= 0.95). Reduction in the mean POEM score was 6.9 (SD 5.7) in the methotrexate group versus 7.9 (SD 7.7) in the azathioprine group (P= 0.65). Clinical improvement was paralleled by a decrease in symptoms. Mean VAS itch scores decreased to 2.5 (SD 2.2) in the methotrexate group versus 2.6
(SD 2.2) in the azathioprine group (P= 0.78). Mean VAS scores for sleeplessness decreased to 2.8 (SD 2.6) in the methotrexate group versus 3.8 (SD 2.8) in the azathioprine group (P= 0.24).

When comparing quality of life, the mean Skindex-17 score was reduced from 50.2 (SD 11.7) at baseline to 37.8 (SD 9.8) at week 12 in the methotrexate group (P < 0.001). In the azathioprine group the mean Skindex-17 score was reduced from 51.7 (SD 8.6) to 41.5 (SD 13.1; P < 0.001). This equals a reduction of 26% versus 20% (P= 0.65).

Median TARC levels decreased to 1215 ng/mL (interquartile range, 302-2496 ng/mL) in the methotrexate group and 885 ng/mL (interquartile range, 122-3107 ng/mL) in the azathioprine group (P= 0.61).

---

**Table 2. Clinical response at week 12 (intention-to-treat analysis)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th>Methotrexate (n=20)</th>
<th>Azathioprine (n=22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in SCORAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute reduction, mean (SD)</td>
<td></td>
<td>22.7 ± 7.9</td>
<td>22.2 ± 16.5</td>
<td>0.89*</td>
</tr>
<tr>
<td>Relative reduction, mean (SD)</td>
<td></td>
<td>42% (18%)</td>
<td>39% (25%)</td>
<td>0.70*</td>
</tr>
<tr>
<td>At least 50% (SCORAD50), no. (%)</td>
<td></td>
<td>8 (40%)</td>
<td>10 (45%)</td>
<td>0.76¥</td>
</tr>
<tr>
<td>Improvement IGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction, mean (SD)</td>
<td></td>
<td>1.8 (0.7)</td>
<td>1.4 (0.9)</td>
<td>0.20*</td>
</tr>
<tr>
<td>Cleared, minimal or mild disease (IGA &lt;2), no.(%)</td>
<td></td>
<td>15 (75%)</td>
<td>15 (68.2%)</td>
<td>0.74¥</td>
</tr>
<tr>
<td>Improvement other outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in PGA, mean (SD)</td>
<td></td>
<td>1.3 (0.9)</td>
<td>1.2 (1.3)</td>
<td>0.95*</td>
</tr>
<tr>
<td>Reduction in EASI, mean (SD)</td>
<td></td>
<td>17.4 (6.6)</td>
<td>17.2 (14.1)</td>
<td>0.95*</td>
</tr>
<tr>
<td>Reduction in POEM, mean (SD)</td>
<td></td>
<td>6.9 (5.7)</td>
<td>7.9 (7.7)</td>
<td>0.65*</td>
</tr>
<tr>
<td>Reduction in VAS itch score, mean (SD)</td>
<td></td>
<td>2.5 (2.2)</td>
<td>2.6 (2.2)</td>
<td>0.78*</td>
</tr>
<tr>
<td>Reduction in VAS sleeplessness score, mean (SD)</td>
<td></td>
<td>2.8 (2.6)</td>
<td>3.8 (2.8)</td>
<td>0.24*</td>
</tr>
<tr>
<td>Reduction in Skindex-17, mean (SD)</td>
<td></td>
<td>12.9 (8.8)</td>
<td>10.3 (12.9)</td>
<td>0.46*</td>
</tr>
<tr>
<td>Reduction in TARC levels, median (IQR)</td>
<td></td>
<td>1215 (302 to 2496)</td>
<td>885 (122 to 3107)</td>
<td>0.61**</td>
</tr>
<tr>
<td>Use of concomitant topical steroids(g), median (IQR)</td>
<td></td>
<td>115.2 (45 to 173)</td>
<td>79.1 (22 to 121)</td>
<td>0.16§</td>
</tr>
<tr>
<td>No. of rescue medication, no. (%)</td>
<td></td>
<td>2 (10%)</td>
<td>4 (18%)</td>
<td>0.67¥</td>
</tr>
</tbody>
</table>

IQR; interquartile range
* T-test for independent groups;
§ Mann-Whitney U test for independent groups;
¥ Fisher’s exact test
** based on ln_TARC.
Patients in the methotrexate group used a median of 115.2 g of concomitant topical corticosteroids versus 79.1 g in the azathioprine group. Two (10%) patients in the methotrexate group required a course of rescue medication at weeks 1 and 2, respectively, and 4 (18%) patients in the azathioprine group required a course at weeks 1, 2, 4 and 5 respectively (P= 0.67).

Safety

Table 3 shows an overview of the safety results. Abnormalities in blood count (mostly lymphocytopenia) were statistically significantly more frequent in the azathioprine group (P= 0.002). Infections, gastrointestinal adverse events, and increased liver enzyme levels occurred in equal proportion in both groups. Fourteen patients in each group experienced infections, mainly upper airway infections, common colds, and mild skin infections. Skin infections occurred in 5 (25%) patients in the methotrexate group and 7 (32%) patients in the azathioprine group; all were mild. Five infections in the methotrexate group and
8 in the azathioprine group were considered moderate of intensity. Three (15%) patients in the methotrexate group had an exacerbation of their eczema during the study compared with 2 (9%) patients in the azathioprine group. No severe and serious adverse events occurred.

### Follow-up

After 12 weeks, 18 (95%) patients in the methotrexate group continued their treatment, and 1 patient discontinued after induction of remission. In the azathioprine group 16 (84%) patients continued, 1 switched to methotrexate because of lack of efficacy, and 2 discontinued because of induction of remission. At week 24, the mean SCORAD score on intention-to-treat analysis was 30.4 (SD 14.3) in the methotrexate group and 33.7 (SD 16.9) in the azathioprine group.

### Table 3: Adverse events and other key safety data through week 24 Treatment group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Total no. of patients with adverse events, no. (%)</td>
<td>20 (100%)</td>
<td>22 (100%)</td>
</tr>
<tr>
<td>Serious and severe adverse events**</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adverse events, total events**</td>
<td>113</td>
<td>121</td>
</tr>
<tr>
<td>Adverse events leading to withdrawal</td>
<td>1 (5%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Adverse event requiring dose adjustment, no. of patients (%)</td>
<td>2 (10%)*****</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Treatment-related adverse events§, no. of patients (%)</td>
<td>14 (70%)</td>
<td>12 (64%)</td>
</tr>
<tr>
<td>Categorized adverse events, no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>14 (70%)</td>
<td>14 (64%)</td>
</tr>
<tr>
<td>Gastro-intestinal adverse events</td>
<td>11 (55%)</td>
<td>13 (59%)</td>
</tr>
<tr>
<td>Exacerbation of atopic eczema</td>
<td>3 (15%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Abnormalities in blood count</td>
<td>6 (30%)</td>
<td>17 (77%)</td>
</tr>
<tr>
<td>Increased liver enzymes</td>
<td>7 (35%)</td>
<td>8 (36%)</td>
</tr>
</tbody>
</table>

*P Values were calculated using Chi-square test or Fisher's exact test.

**Adverse events were classified as serious and severe according to pre-defined definition (see methods section).

**Total number of adverse events: all patients displayed adverse events, the number of events per patient ranging from 1 to 14 (median 5, interquartile range 3.25 to 8). If a patient presented twice with the same adverse effect (e.g. twice migraine), then this was counted as 1 adverse event. This was the case in 17 out of the 42 patients; 2 patients presented a certain symptom 3 times (which was also counted as 1 time).

***One patient required two dose lowerings

§Treatment-related adverse events are those classified as possibly, probably or definitely related to the study drug by the safety assessor.
After 24 weeks of treatment, there was no statistically significant difference between the 2 groups in all outcome measures.

**DISCUSSION**

**General conclusion**

Disease-modifying antirheumatic drugs, such as methotrexate, azathioprine and mycophenolate, offer a range of off-label therapeutic options for patients with severe AD. In the present RCT methotrexate and azathioprine were compared. Patients in the methotrexate group experienced a statistically significant overall improvement of 42% in mean SCORAD score at week 12. Patients in the azathioprine group showed a statistically significant overall improvement of 39% in mean SCORAD score.

In addition, intensity of symptoms and TARC levels were reduced in a similar fashion in both groups. Effect on quality of life reduced by 26% in the methotrexate group versus 20% in the azathioprine group. Overall, there was no statistical difference between both therapies in any primary or secondary efficacy outcome measures assessed at weeks 12 and 24.

In this study the number and severity of adverse events, including laboratory abnormalities, appeared to be generally similar in short-term treatment, with the exception of mild myelosuppression in the azathioprine group. No severe or serious adverse events occurred.

Because of the relatively slow onset of action of both treatments, it is common in some clinical practices to give patients concomitant oral corticosteroids to support them in the first weeks of treatment. In our study both treatments were given as single systemic therapy with the possibility of adjuvant rescue medication. This was needed in 6 of the 42 patients treated. This might indicate that routine administration of concomitant oral corticosteroids is not necessary.

Our results are in concordance with the previous results of 2 placebo-controlled studies regarding azathioprine, in which improvements of 26% and 37% on the 6-area, 6-sign atopic dermatitis score at 12 weeks were found. Similar results were found for the effect of methotrexate in cohort studies, although in some the effect was more pronounced: 52% at week 24 in one study and a greater than 70% reduction in outcome parameters in 65% of the patients at week 12 in another. Studies on cyclosporin, which is the first-choice systemic treatment, showed a more marked response. A systematic
review showed that relative improvements were consistently greater than 50% at 6 to 8 weeks.³

In conclusion, methotrexate and azathioprine can be considered equally effective for the treatment of severe AD in adults. Overall, this study is limited to conclude about the safety for medium- to long-term use. Nevertheless, because both drugs have been available for more than 50 years, they have a well-known toxicity profile, and dermatologists are familiar with the use of these drugs in the treatment of psoriasis or bullous diseases. Patients treated with azathioprine should be monitored for myelosuppression, and preferably, TPMT levels should be measured before the initiation. Patients receiving methotrexate should be monitored for hepatic and pulmonary toxicity and myelosuppression. Individual treatment decisions should be based on patients’ preferences and comorbidity.

Strengths and limitations

Important strengths of our trial include that our study is the first head-to-head comparison of methotrexate versus azathioprine in patients with severe AD. Thereby, the study was investigator-initiated, with the investigators having no conflict of interest; the study included patients naïve for methotrexate or azathioprine; and validated outcome measures were used.

Our trial had certain limitations. Power analysis was based on the SCORAD score. Because the minimal clinically important difference of the SCORAD score is unknown, we decided that a difference of at least 8 points would represent a clinical meaningful difference. This was based on other studies and on personal experience with the scale. Nevertheless, it could have been possible that a smaller SCORAD score difference was clinically meaningful. In that case our sample size would not have been sufficient to detect a meaningful difference between the therapies.

In our study the washout period for systemic treatment was relatively short. This might have resulted in a lower baseline SCORAD score and in a smaller difference between baseline and week 12 efficacy outcomes. At baseline, patients were allowed to start or increase the amount of topical steroids. This could have influenced the treatment effect. However, considering the low total amount and low potency of the topical steroids used during the trial, the effect on efficacy outcomes will be minimal. Continuing with a stable dose or implementation of a stabilization period would have been more methodologically sound.

Ideally, patients should be blinded for allocation of treatment to avoid a performance bias. Because each patient received active treatment in this study, this effect will be less pronounced than in a placebo-controlled design. Concerning the non-blinded safety assessors, patient management could have
been biased. However, it should be noted that safety assessors did not have personal preferences or conflicts of interest. A patient-blinded design could not be performed because of a lack of funding and other financial resources.

In the absence of international guidelines for these treatments, our dosing schedule was based on earlier performed studies and experience with the drugs in other indications. Therefore it could be argued that the interventions were not similar.

Currently, there is an international initiative to harmonize outcome assessment in AD: the Harmonizing Outcome Measurement in Eczema initiative. During a Delphi round on core outcome domains, it was shown that symptoms, physician assessed clinical signs, and measurement for long-term control were of particular interest. Symptoms were addressed by means of VASs on itch and sleeplessness and by means of the POEM. Physician-assessed clinical signs were addressed by using the SCORAD and EASI. Both were sufficiently validated according to a recently published systematic review on the validity of clinical outcome measures. Although we have performed a 3-month follow-up period to indicate long-term control, we could not totally comply with the measurement for long-term control because of the design of the study. An observational follow-up study, which is currently being conducted, is directed at that particular outcome domain.

**Generalisability**

This study was performed in adults (18-75 years of age) with severe AD who were unresponsive or contraindicated for cyclosporin treatment. Sex was equally distributed. Because the included patients were 40 years old and had a mean duration of disease of 36 years, we can conclude it concerned a very chronic population. In some cases included patients were very severely affected and had frequent hospitalizations for disease management in the past. All except 1 of the patients showed the presence of allergen-specific IgE on a Phadiatop test (Pharmacia, Uppsala, Sweden). We believe that our data are applicable to all adults with difficult-to-treat chronic AD, depending on their comorbidity and preferences. Studies in children should be performed to establish the role of these treatments in children.

**Clinical research implications**

We have demonstrated that both methotrexate and azathioprine are effective and short-term safe treatment options for adults with severe AD. We believe that the results from this study justify treatment with these drugs when regular treatment is insufficient. Furthermore, the results from this study can be used to
update or formulate clinical practice guidelines for the treatment of severe AD. In light of the rules and regulations concerning off-label treatment, it is important to generate evidence-based guidelines for its use. Future studies should be performed to confirm the long-term safety profile of both methotrexate and azathioprine, to confirm their role in children, and to compare both treatments with other therapies, such as cyclosporin and oral corticosteroids.

AKNOWLEDGEMENTS

We thank all the patients who participated in this study, B. Arents of the patient association of atopic dermatitis (VMCE), and all our fellow dermatologists for referring patients (in particular F. Wu, M. Nahuys, M. D. Njoo and B. Nanninga). We also thank G. A. Appel and A. C. Q. de Vries for being the blinded efficacy assessors, M. Bonnerjee for monitoring the study, E. M. Kemper for being the involved pharmacologist, A. B. P. van Kuilenberg for assessing the TPMT levels, and K. Szegedi and P. Res for assessing TARC levels.

REFERENCES


8. Zoller L, Ramon M, Bergman R. Low dose methotrexate therapy is effective in late-onset atopic dermatitis and


24. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled


