A randomized trial of methotrexate versus azathioprine for severe atopic eczema

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

Objectives: We sought to compare the efficacy and safety of methotrexate versus azathioprine in adults with severe atopic eczema.

Methods: Patients with severe atopic eczema 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/d) for 12 weeks, followed by a 12-week follow-up period. Primary outcome was the mean change in the severity scoring of atopic dermatitis 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 severity scoring of atopic dermatitis index of 42% (SD, 18%) compared with 39% (SD, 25%) in the azathioprine group ($P = .52$). 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 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 atopic eczema. (J Allergy Clin Immunol 2011;128:353-9.)

Key words: *Atopic eczema, atopic dermatitis, azathioprine, methotrexate, off-label, trial*

Abbreviations used

EASI: Eczema area and intensity index
IGA: Investigator global assessment
PGA: Patient global assessment
POEM: Patient-oriented eczema measurement
SCORAD: Severity scoring of atopic dermatitis
TARC: Thymus and activation-regulated chemokine
TPMT: Thiopurine methyltransferase
VAS: Visual analog scale

Atopic eczema is a chronic inflammatory skin disorder that affects approximately 3% to 5% of the adult population in the western world.[1] Atopic eczema 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.[2] Patients with severe atopic eczema require prolonged treatment with large amounts of highly potent topical corticosteroids, systemic treatment, or both. Frequently used options for systemic treatment of atopic eczema include cyclosporine and systemic corticosteroids. Although proved effective,[3] a proportion of patients have a contraindication for cyclosporine or discontinue treatment because of ineffectiveness or side effects. Moreover, long-term use of cyclosporine raises concerns over (nephro)toxicity.[4] Systemic corticosteroids are used frequently to suppress exacerbations, although high-level evidence is lacking.[5] A recent randomized controlled trial comparing short-term cyclosporine versus prednisolone was interrupted because of an unsuspected high proportion of severe rebound in the prednisolone group.[6] Medium- to long-term treatment with prednisolone is relatively contraindicated because of the cumulative effect of the side effects.[5] This illustrates the need for novel medium- to long-term treatment options for patients with severe atopic eczema. 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 atopic eczema. 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,[7-10] there have been no randomized controlled trials supporting a role for methotrexate in the management of atopic eczema. The role of azathioprine in atopic eczema was established by 2 randomized controlled trials in which azathioprine was significantly superior to placebo,

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with mean improvements of 26% and 37% on clinical outcome scales after 3 months.[11,12] Numerous uncontrolled studies on azathioprine in adult and juvenile patients showed similar results.[13] 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 atopic eczema evaluating efficacy, safety, and effect on quality of life.

METHODS

Design

This study was an investigator-initiated, single-blind, parallel-group (ratio 1:1), randomized controlled trial 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 inpatient and outpatient clinics of the Academic Medical Center of Amsterdam (referral center for severe atopic eczema) or were referred by regional dermatologists. Patients with atopic eczema (with and without the presence of allergen-specific IgE) defined according to the Millennium Criteria and the UK Working Party criteria[14] were eligible if they were 18 years or older; the severity grading by the Rajka and Langeland criteria was severe[15]; the patients were unresponsive, contraindicated, or intolerant to cyclosporine 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.[16] Azathioprine was initiated at 1.5 mg/kg/d in a single dose, and the dosage could be escalated at each visit with 0.5 mg/kg/d until a maximum of 2.5 mg/kg/d 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 (20-20-15-15-10-10-5 mg).

Outcomes

Efficacy. The primary efficacy outcome parameter was the mean relative and absolute change in the severity of atopic eczema at week 12 assessed by means of the severity scoring for atopic dermatitis (SCORAD) score.[17] 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.[18]

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 thymus and activation-regulated chemokine (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).[19] The POEM includes 7 questions regarding skin symptoms (range, 0-28).[20] Change in quality of life was assessed by the use of the Dutch version of the Skindex-17.[21] Scores range from 0 to 85 points, with higher scores indicating more significantly impaired quality of life. Clinical outcome parameters and quality of life were assessed at each visit. Furthermore, at baseline and week 12, serum TARC levels were measured.[22,23]

Safety. The number and severity of adverse events were assessed at each visit by the safety assessor to address safety. 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.