

ORIGINAL ARTICLE

Low-dose methotrexate treatment for moderate-to-severe atopic dermatitis in adults

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Abstract

Background Atopic dermatitis (AD) is a common inflammatory skin disease. Methotrexate (MTX) was suggested as an effective treatment option in cases of moderate-to-severe atopic dermatitis. This study assessed the efficacy and safety of treatment with low weekly doses of methotrexate for moderate-to-severe AD in adults.

Methods Twenty adult patients with moderate-to-severe AD were included in this retrospective study. Those patients were unresponsive to topical treatments, antihistamines and at least one of the second-line treatments. MTX in low weekly doses of 10–25 mg was administered orally or intramuscularly with folic acid supplementation 5 mg per week for at least 8–12 weeks. The response to treatment was evaluated by change in SCORAD (SCORing Atopic Dermatitis), DLQI (Dermatology Quality of Life Index) and the global assessment of the clinical response score.

Results After 8–12 weeks of treatment, we observed an objective response in most patients. There were 16 responders and 4 non-responders. The mean SCORAD and DLQI decreased by 28.65 units (44.3%) and 10.15 units (43.5%), respectively. The first improvement was observed after a period ranging from 2 weeks to 3 months (mean 9.95 w $\pm$ 3.17). Treatment was more effective in adult onset AD than in childhood onset. Tolerance of treatment was good. However, nausea and an increase of liver enzymes were observed in 5 patients and 3 of them required a transient discontinuation of MTX. One patient developed peripheral neuropathy, which was resolved several weeks after the discontinuation of MTX.

Conclusion MTX seems to be an effective and safe second-line treatment for patients with moderate-to-severe atopic dermatitis. A randomized, controlled study is warranted.

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Keywords

atopic dermatitis (AD), corticosteroids (CS), DLQI (Dermatology Quality of Life Index), methotrexate (MTX), SCORAD (SCORing Atopic Dermatitis) index

Conflicts of interest

None declared.

Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease affecting between 10% and 20% of children and 1% and 3% of adults.^{1,2} It is characterized by dry skin, intense itching, inflammation and exudation. AD causes significant physical, psychological and social distress. The prevalence of AD has increased steadily over the last 30 years.^{1,2} The disease accounts for 10% to 20% of all referrals to dermatologists and about 30% of dermatologic consultations in general practice.³ At present, there is no 100% life-long cure for AD. Management comprises avoidance of trigger factors (irritants, microbes, psychological stress and allergens), skin moisturizers, antihistamines and anti-inflammatory agents. Topical steroids and calcineurin inhibitors are the current standards for topical

anti-inflammatory therapy. However, there are considerable safety concerns associated with long-term use of topical steroids.⁴ The treatment with topical immunomodulators is also limited by the body surface involved.⁴ Patients with moderate-to-severe disease refractory to a combination of topical agents and antihistamines may require second-line treatment such as phototherapy or systemic immunosuppressants. The side-effects profile of systemic steroids over long periods or at high doses is well known. Therefore, there is a need for safe effective therapy for control and maintenance of the disease. This is why over the last 50 years, many steroid-sparing drugs have been assessed, and yet no ideal candidate has been found. MTX has been documented to be effective in adult AD,^{5–8} palmoplantar pompholyx⁹ and eczema in the elderly.¹⁰ Although

MTX is widely used and effective treatment for other inflammatory diseases, there are only a few small retrospective records^{5,7,8} and one open prospective trial⁶ suggesting that it is an effective and well-tolerated treatment in AD. In light of the previous published results and our positive preliminary experience, we carried out the present study to test the efficacy and tolerance of MTX in low weekly doses in patients with moderate-to-severe AD.

Methods

Patients

Patients with moderate-to-severe AD who were treated with MTX between August 2004 and April 2008 at the department of dermatology and the dermatology outpatient clinic, Sheba Medical Center, Tel-Hashomer, Israel, were included in this retrospective study. The study was approved by the institution's review board. All subject patients were over 18 years old and had AD defined according to Hanifin and Rajka's diagnostic criteria.¹¹ The diagnosis was confirmed by skin biopsies in all patients. The patients were divided into subgroups of childhood and adult onset of AD (the cut-off point used was onset before or after 18 years of age). The disease severity was measured before MTX treatment using the SCORAD index (SCORing Atopic Dermatitis).¹² SCORAD was performed in each visit by the same physician. Patients with a SCORAD score of less than 15 were regarded as having a mild disease and were excluded from the study. Those with a SCORAD score between 15 and 40 were considered as having a moderate, and more than 40 as having a severe disease. The Dermatology Quality of Life index (DLQI)¹³ was also assessed in all patients. All participants had a low response to the routine first-line treatment which included topical steroids, emollients and systemic antihistamines. All patients had previously tried at least one form of second-line treatment, such as phototherapy or systemic immunosuppressants, all patients had a 'wash-out' period of at least 2 months from other second-line treatment. It is our policy not to give MTX to patients with other interfering skin diseases, pregnancy, lactation, present hepatic, renal or haematological disease, abnormal liver or renal function test, and previous or current neoplasm. Patients were allowed to continue with their previous topical treatment and systemic antihistamines throughout the study as needed. All other previous systemic treatments were stopped.

Study protocol

Before starting the treatment with MTX, a complete physical examination, chest X-ray and blood tests including complete blood count, blood chemistry and serologic tests for hepatitis B and C were performed on all patients. The initial dose of MTX was 10–25 mg per week given orally or intramuscularly. Intramuscular injections were chosen for patients with previous history of peptic disease or other gastrointestinal problems. In general, the initial dose of MTX was related to the patient's weight: those weighing less than 50 kg were given 10 mg/week, those between 50 kg and

80 kg were given 15 mg/week, and those above 80 kg were given 25 mg/week. If a patient was responding to a given dose with at least mild improvement of SCORAD and DLQI, then no further increases were made. If the patient did not respond to the initial dose for 4-week period, the dose was increased by 2.5 mg every 4 weeks to a maximum of 25 mg. In patients with oral treatment, the weekly dose was divided into three sub-doses in 12-h intervals, in order to lower the risk of gastrointestinal side-effects. In the subgroup treated intramuscularly, the treatment was administered as a single weekly dose. The folic acid supplements were given in a weekly dose of 5 mg, the day after the last dose of MTX. When excellent response was achieved, the weekly dose of MTX was decreased by 2.5 mg every month. In each visit, patients underwent physical examination including dermatological examination and were interviewed regarding possible MTX-induced side-effects. Blood tests including a complete blood count and blood chemistry were performed twice monthly during the first month, and once per month for the rest of the treatment period. Abnormal blood tests were repeated, and, if persistent, the dosage of MTX was either reduced, or the drug was stopped completely, depending on the extent of abnormality and the presence of other side-effects.

Assessment of response and follow-up measurements

Patients were examined once a month at the outpatient clinic. The follow-up included clinical evaluation of efficacy, laboratory tests and assessment of side-effects.

The change in activity of the disease, measured using the SCORAD index and DLQI, was the main end-point of the study. These indexes were assessed both before the beginning of the treatment with MTX and after 8–12 weeks. The timing of 8–12 weeks was chosen because from past experience of timing the MTX effect in other dermatological indications, this time interval is expected to cause significant clinical improvement in responders. If the treatment shows no effect in the patients after 12 weeks, it is unreasonable to continue this treatment.

The global assessment of the clinical response was performed for the SCORAD and DLQI with a score of 0–4: 0, no improvement (0%); 1, mild improvement (1–25%); 2, moderate improvement (26–50%); 3, marked improvement (51–75%); 4, excellent response (76–100%).

The second end-point was to evaluate safety of MTX treatment.

Statistical analysis

Statistical package for the social sciences (SPSS) version 15.0 for Windows software was used for the data entry and analysis. Normally distributed numerical data were summarized by their mean values and standard deviation. All analyses of paired data were performed using paired *T*-test. Confidence intervals were extended to a level of 95%. One-way repeated measures ANOVA (analysis of variance) was used for the statistical comparison between groups. *P* values below 0.05 were accepted as statistically significant.

Table 1 Demographic data, disease onset, severity and previous 2nd line treatment of study participants and route of MTX treatment.
a) childhood-onset atopic dermatitis

N	Age (year)/gender	Severity	Previous second-line treatment	MTX treatment
1	20/male	Severe	Phototherapy, CS, cyclosporin	PO
2	21/female	Moderate	CS	IM
3	25/male	Severe	Phototherapy, CS, cyclosporin	PO
4	29/male	Severe	CS	PO
5	38/female	Severe	Phototherapy, CS, cyclosporin	PO

b) adult-onset atopic dermatitis

N	Age (year)/gender	Severity	Previous second-line treatment	MTX treatment
1	38/female	Severe	CS	PO
2	44/male	Moderate	CS	PO
3	47/female	Moderate	Phototherapy, CS	IM
4	55/male	Severe	Phototherapy	IM
5	56/male	Severe	Phototherapy, CS	IM
6	58/female	Severe	Phototherapy	IM
7	60/male	Moderate	CS	PO
8	60/female	Severe	Phototherapy, CS	IM
9	61/male	Severe	CS	PO
10	64/male	Severe	Phototherapy	PO
11	66/female	Severe	CS	PO
12	67/female	Severe	Phototherapy	PO
13	68/male	Moderate	CS	PO
14	73/male	Moderate	Phototherapy	PO
15	85/male	Severe	CS	PO

CS, systemic corticosteroids; PO, oral treatment; IM, intramuscular.

Results

Patients

Of the 25 patients identified, 5 patients were not included: 3 three withdrew from the treatment due to administrative issues and two did not follow-up. Hence, results in this study refer to those 20 patients whose data are complete. The patients' data are summarized in Table 1. Of the 20 patients enrolled in this study, there were 13 (65%) men and 7 (35%) women. Fifteen (75%) of the patients had adult onset AD and 5 (25%) had AD since childhood. The age ranged from 20 to 85 years [average age 51.75 ± 18.27 (26.6 ± 7.3 in the group childhood onset and 60.1 ± 11.7 in adult onset group)]. The male/female ratios were 1.5 in both subgroups.

Fourteen patients were treated orally and 6 patients by intramuscular injections (Table 1a,b). Four patients received an initial dose of 10 mg MTX/week (patient 4 from the group of childhood onset AD and patients 1,4,14 from the group of adult onset AD) and 2 were started on 25 mg/week (patients 2,6 from the group of adult onset AD). For the remaining 14 patients, the initial dose of MTX was 15 mg/week.

Six of the 20 patients had a moderate disease before the treatment with MTX (SCORAD 15–40) and 14 had a severe disease (SCORAD

more than 40, Fig. 1a,b). The mean SCORAD before the treatment was $63.85 (\pm 18.9)$. The mean SCORAD in the subgroups with adult onset and child onset AD was similar (64.7 ± 20.8 and 61.2 ± 13.2 , Fig. 2a). DLQI before the treatment was between 7 and 30 (mean 23.35 ± 5.8 , Fig. 1c,d). The mean DLQI was slightly higher in the subgroup of childhood onset AD, than in adult onset (26.2 ± 1.3 and 22.4 ± 6.4 , Fig. 2b).

Efficacy

Among the 20 patients, 16 achieved clinical improvement and 4 were non-responders. The time for achieving a marked clinical response to the treatment was between 2 and 12 weeks (mean 9.95 ± 3.2). The mean SCORAD after the 8–12 weeks of MTX treatment was $35.2 (\pm 23.6)$, (Fig. 1a,b). The mean decrease in SCORAD following the treatment was 28.65 ± 23.2 units, (10.6 ± 14.6 in the childhood onset group and 34.7 ± 22.7 in the adult onset group). The difference between the SCORAD before and after treatment was statistically significant ($P < 0.05$). The mean DLQI after the treatment was $13.2 (\pm 10.2)$. The mean decrease in DLQI following treatment was 10.15 ± 8.44 units. The difference between the DLQI before and after treatment was statistically significant ($P < 0.05$). The decrease in DLQI was more significant in the adult

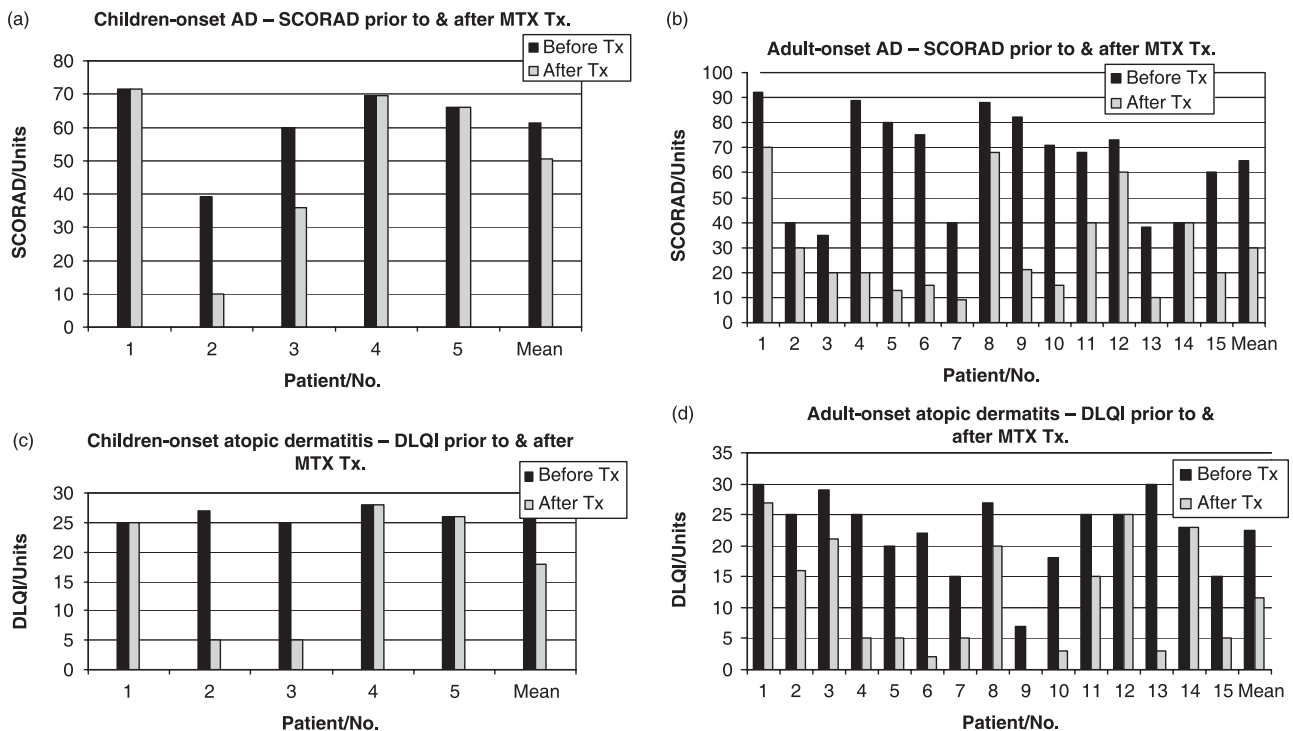


Figure 1 Improvement in disease activity with MTX treatment. (a) SCORAD – individual patient improvement in patients with childhood-onset atopic dermatitis. (b) SCORAD – individual patient improvement in patients with adult-onset atopic dermatitis. (c) DLQI – individual patient improvement in patients with childhood-onset atopic dermatitis. (d) DLQI – individual patient improvement in patients with adult-onset atopic dermatitis.

onset than in the childhood onset group (10.7 ± 7.6 vs. 8.4 ± 11.5 , respectively, Fig. 1c,d). There were no statistically significant differences in efficacy between different age or sex groups, but it appears that the treatment was more effective in the adult onset group than in the child onset group, as reflected by both the SCORAD and the DLQI decrease (Fig. 2a,b). With respect to the mode of treatment, it seems that the intramuscular injections were slightly superior to the oral therapy (patient 2, Fig. 1a; patients 3,4,5,6,8; Fig. 1b). The response was faster and the SCORAD showed a greater decrease, yet, this was not statistically significant. The global assessment of the clinical response in SCORAD showed no improvement in 4 patients (3 patients with severe child onset AD and 1 patient with moderate adult onset AD), mild improvement in 4 patients, moderate improvement in 3 patients, marked improvement in 4 patients, and an excellent response in 5 patients (Fig. 3a). Thus, 5 patients with severe AD were shifted to moderate, 3 other patients with severe AD to mild AD, and 3 patients with moderate AD to mild. Other participants who responded to the treatment, even if remaining in the same group of severity, showed a significantly decreased mean SCORAD. The global assessment of clinical response in DLQI showed no improvement in 5 patients, mild improvement in 1, moderate improvement in 4, marked improvement in 3 and excellent response in 7 patients (Fig. 3b).

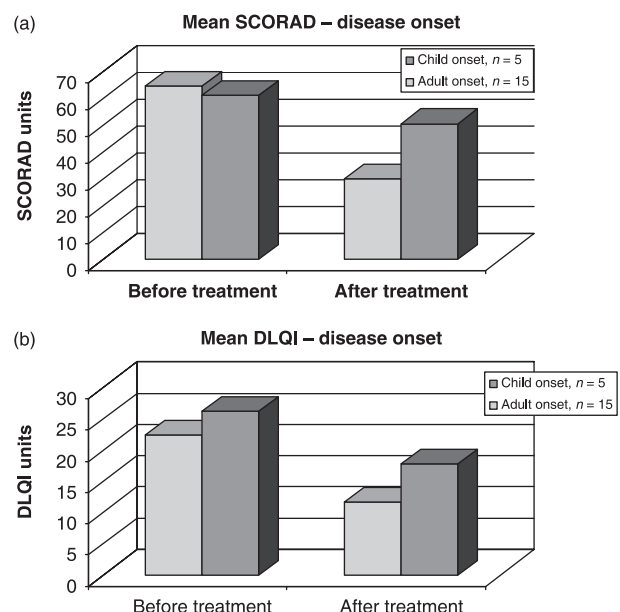


Figure 2 Differences in disease activity between adult onset and childhood onset AD: (a) mean SCORAD before/after the MTX treatment. (b) mean DLQI before/after the MTX treatment.

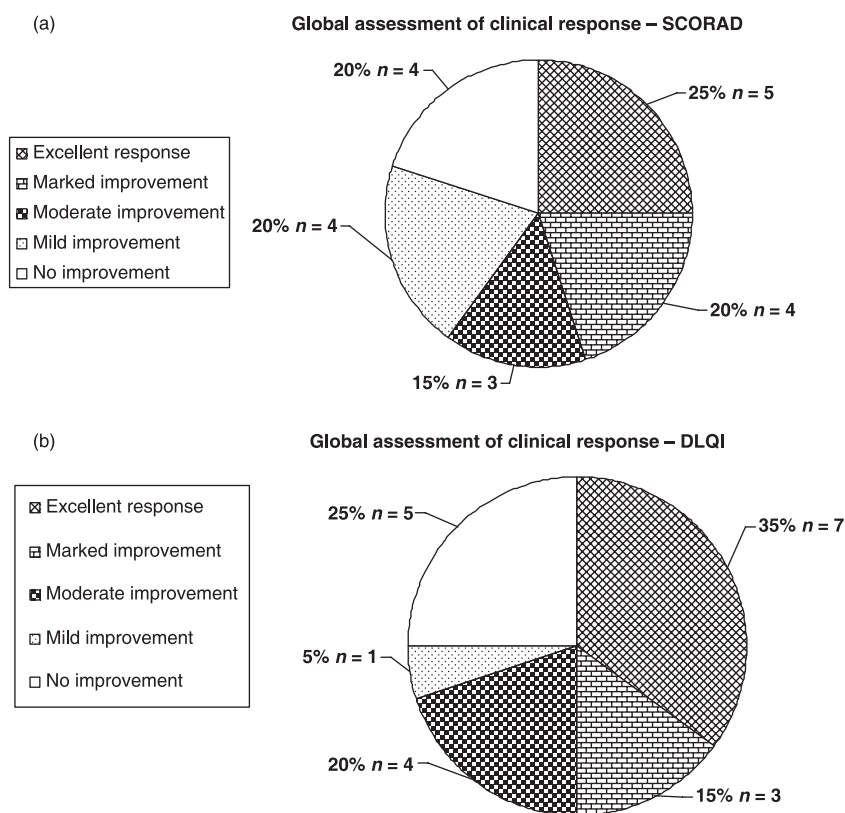


Figure 3 Global assessment of the clinical response. (a) SCORAD. (b) DLQI.

Safety

No serious adverse effects occurred in this study. Nausea and mild increase of liver enzymes (SGOT and SGPT up to twice of normal values) were observed in 5 patients and required a transient lowering of the dosage of MTX in 3 patients. One patient developed mild peripheral neuropathy which also resolved several weeks after the discontinuation of MTX.

Follow-up

Follow-up of patients continued between 2 months and 2 years. Of 20 participants, 7 patients are still continuing the MTX treatment, while 13 patients stopped the treatment, 9 because of significant improvement and are treated only with first-line medications for AD, and 4 because of no response. From the 7 patients who continue the treatment, 6 patients are in clinical remission, but need the MTX maintenance – 3 patients are in remission under the MTX weekly dose of 15 mg, 2–12.5 mg, and 2–7.5 mg. One patient who continues the MTX is in partial remission under the MTX weekly dose of 12.5 mg.

Discussion

AD is a chronic disease with variable severity. Although most of the patients need only topical agents and sedating antihistamines, about 10% are refractory to these conventional modalities. In

such cases, a range of options could be considered. These include phototherapy and systemic immunosuppressive agents.¹⁴ Phototherapy can be a useful option in the treatment of AD. High-dose UVA-1 phototherapy can give better results than UVA-UVB, but it is only available in a few centres.¹⁵ Phototherapy requires frequent trips to the medical centre, which may cause logistical problems. It may also carry the risk of future skin cancer and/or photoaging.

Cyclosporin A is an effective treatment of AD. It has long-term efficacy, but the response is rarely sustained after the drug discontinuation. In addition, cyclosporine can cause side-effects, which may include cumulative renal toxicity, hypertension, increased risk of infections and lymphoma. These together with the drug's high cost preclude its use in all but the most severe AD patients.¹⁶

Antimetabolites, including azathioprine (AZT) and mycophenolate mofetil, have also been used with reported success. These agents also have the potential for systemic toxicities. The main drawbacks of using AZT are the slow onset of action and the need to perform the test for the serum thiopurine methyltransferase level, which is not available in most treatment centres.^{17,18}

Several studies, most of them retrospective, regarding the use of MTX in AD have been published.^{5–8} Methotrexate (MTX) is a very effective treatment for chronic inflammatory diseases such as psoriasis, rheumatoid arthritis, ulcerative colitis and asthma.^{19–21}

Its mode of action in these conditions has not been fully elucidated, although several mechanisms have been postulated. MTX is a potent inhibitor of the enzyme dihydrofolate reductase leading to the inhibition of purine and pyrimidine synthesis and the reduction in T-cell proliferation. In addition, it is believed that the anti-inflammatory action of MTX is also mediated by the accumulation of extracellular adenosine which acts as an endogenous anti-inflammatory agent. Adenosine can occupy specific adenosine receptors and inhibit lymphocyte proliferation as well as production of the pro-inflammatory cytokines TNF- α , IL-6, and IL-8, while stimulating transcription of the IL-1 receptor antagonist and the production of IL-10.^{22,23} It was shown that successful treatment of AD with MTX is accompanied by a selective loss of activated allergen-specific T cells.²⁴ The advantage of MTX besides its efficacy is that side-effects are relatively easily prevented by a monthly follow-up.

Ergan *et al.*,⁹ reported successful treatment with MTX of 5 patients with severe pompholyx. Two additional retrospective studies included that of Shaffrali *et al.*,¹⁰ who described 5 elderly patients with eczema treated with MTX, and that of Goujon *et al.* who showed a beneficial effect of MTX in 20 patients with adult-onset AD.⁵ There is only one recent open-prospective study, that of Weatherhead *et al.*,⁶ who evaluated 12 patients with AD treated with MTX. In this study the assessment of efficacy of MTX was based on SASSAD (Six Area Six Sign Atopic Dermatitis)²⁵ score and DLQI.¹³

In accordance with the previous reports, our study supports the efficacy of MTX in AD. Following the treatment, we observed the decrease of more than 50% in the disease severity in 9 or 45% of the 20 participants. There was also significant improvement in quality of life with higher than a 50% decrease of DLQI for 10 (50%) of the patients. Furthermore, from our follow-up, it should be noted, that MTX can be used as either chronic treatment or for short periods for flares of the disease. In addition, we observed that the treatment is more effective in adult onset AD than in childhood onset, although our findings were not statistically significant. We also found that intramuscular injections cause more prompt responses and a more prominent decrease in SCORAD and DLQI, than oral treatment. No serious side-effects occurred in this study. This was probably due to the low dose of MTX, dose dividing and the folic acid supplementation given. We conclude that low weekly doses of MTX are safe enough for routine use. Furthermore, based on this study, we also believe that, like in psoriasis, the lesser doses are not sufficient to cause a prompt clinical response.

Although our study is retrospective in methodology, it has much in common with the only prospective study mentioned.⁶ This is due to our strict treatment protocol used for patients with AD treated with MTX. The specificity of our study is the way in which MTX was administrated and the method in evaluating the clinical response. Most previous reports describe a protocol of one weekly dose, except one study in which MTX was given on 4 days out of

7, in a dose of 2.5–5 mg per day.²⁶ Similar to psoriasis treatment, we started the treatment from a dose of 10–25 mg per week. The weekly dose was divided into three sub-doses with 12-h intervals. Folic acid supplementation was given in a weekly dose of 5 mg starting on the next day following the last sub-dose of MTX.

In the absence of a gold standard measure of AD severity, the most widely validating indices are essential. It was recently reported that SCORAD and EASI scores allow the best interpretation of AD severity.²⁷ In this study, we determined the efficacy of MTX in AD by using the SCORAD index to evaluate the severity of AD, and DLQI for the assessment of the impact of the treatment on the quality of life.

One cannot ignore that our study has several potential limitations including a relatively small number of patients and the relatively short period of a follow-up after cessation of the treatment in some patients, and, most importantly, the lack of a placebo control group. Unmanageably large numbers of these scarce patients would have been needed for a placebo-controlled study. Although a statistically significant improvement has been noted in all clinical parameters, this positive effect of MTX treatment should be addressed by larger studies in the future with a control group and a follow-up period to assess the clinical effect after stopping administration of the drug. In this context, it should be emphasized that AD is a chronic disease with a relapsing and remitting course, influenced by many factors, making it difficult to assess the efficacy of various treatments and their long-term effect.

Our results confirm and extend the results obtained in previous reports that clearly show that MTX is beneficial in patients with AD. We suggest that the treatment with MTX, prescribed during exacerbation, would be either tapered off, when the disease subsided, or maintained at the lowest efficient dose. If the patient requires long-term treatment and relapses when the drug administration is stopped, consideration may be given to either a continuous treatment with MTX or a rotational approach which diminishes the risk of cumulative toxicity from every treatment modality. In that respect, AD should be regarded as psoriasis.

In this study, we showed that MTX treatment is more effective in adult onset AD than in childhood onset, and that intramuscular injections cause more prompt responses than oral treatment. Although our findings were not statistically significant, these may be useful as a parameter for a clinician to decide which treatment to use and how.

In conclusion, the results of our study together with previous reports demonstrate that MTX have proven to be a safe and useful treatment for the patients with moderate-to-severe AD. The findings invite more prolonged, placebo-controlled prospective clinical trials in order to define the MTX as a second-line therapy in moderate-to-severe AD.

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