Low Dose Methotrexate Therapy is Effective in Late-Onset Atopic Dermatitis and Idiopathic Eczema

Lilach Zoller MD, Michal Ramon MD and Reuven Bergman MD

Department of Dermatology, Rambam Health Care Campus, Haifa, Israel

Key words: atopic dermatitis, eczema, methotrexate

Abstract

Background: Atopic dermatitis or atopic eczema is an itchy inflammatory skin condition with a predilection of the skin flexures. Most cases start in children although some have been reported in adults. Patients with moderate to severe disease refractory to topical corticosteroid or calcineurin inhibitors may require second-line treatment such as phototherapy or systemic immunosuppressants. Methotrexate therapy has been suggested as a useful immunosuppressant in adult atopic dermatitis.

Objectives: To further determine the efficacy of low dose methotrexate therapy in adults with new-onset atopic dermatitis or with idiopathic eczema.

Methods: All adult patients with new-onset atopic dermatitis or idiopathic eczema treated by methotrexate in our clinics from 2004 to 2006 were included in the study. All had failed prolonged therapy with oral antihistamines and local corticosteroid creams. Methotrexate, 10–20 mg, was given orally once a week along with folic acid supplements 5 days a week. Additional therapies included predominantly emollients. During the entire treatment period the investigators made global assessments of the clinical response.

Results: Nine patients diagnosed with late-onset atopic dermatitis (n=6) or idiopathic eczema (n=3) were treated with methotrexate. All patients responded to the drug. The initial response was noted after 3–7 weeks. Six patients achieved complete remission after 3 months of methotrexate therapy and three patients had significant improvement. One patient's condition worsened after achieving a complete response while on methotrexate and the drug was withdrawn completely. No serious adverse events were noted during treatment.

Conclusions: Low dose methotrexate is an effective therapeutic alternative for late-onset atopic dermatitis or idiopathic eczema in patients unresponsive to local and other systemic therapies.

IMAJ 2008;10:413–414

Atopic dermatitis or atopic eczema is an itchy inflammatory skin condition with a predilection of the skin flexures [1]. It is characterized by poorly defined erythema with edema, vesicles, and weeping in the acute stage and skin thickening (lichenification) in the chronic stage [2]. Most cases start in children [3], although 10% of cases seen in a hospital setting were in adults [4]. Apart from the most typical flexural localization and eczematous pattern in adults, patients may also have a non-flexural distribution [5] and other morphological variants such as a nummular or prurigo-like pattern [6-8]. In addition, adult-onset atopic dermatitis has been reported to be better diagnosed using Hanifin and Rajka's criteria than using the UK Working Party's criteria [8]. Adult patients suffering from dermatitis not fully fulfilling the Hanifin and Rajka criteria and for which no cause is found are often diagnosed with idiopathic eczema. Patients with moderate to severe atopic dermatitis that is refractory to treatment with topical corticosteroid or calcineurin inhibitors may require second-line treatment such as phototherapy or systemic immunosuppressants [9]. In adult patients there are often limitations to systemic therapy due to concomitant diseases.

Methotrexate is a very effective treatment for chronic inflammatory conditions such as psoriasis and rheumatoid arthritis, and has been documented in anecdotal reports and small retrospective studies of patients to be effective in palmoplantar pompholyx [10], eczema in the elderly [11] and adult atopic dermatitis [8,12,13]. The present study was performed to further determine the efficacy of low dose methotrexate treatment in adults with new-onset atopic dermatitis and with idiopathic eczema.

Patients and Methods

The study group comprised all adult patients with new-onset atopic dermatitis or idiopathic eczema treated with methotrexate in our clinics from 2004 to 2006. The diagnosis of eczema was confirmed by skin biopsies in all patients. The criteria for the diagnosis of atopic dermatitis were those of Hanifin and Rajka [14]. The remaining patients who did not fully meet these criteria and in whom no other causes were found, including the ruling out of allergic contact dermatitis by using patch tests, were diagnosed as having idiopathic eczema. All patients failed prolonged therapy with oral antihistamines and local treatment with corticosteroid creams. Most patients also failed therapy with systemic oral corticosteroids and topical calcineurin inhibitors, some patients failed phototherapy, and a few did not benefit from oral cyclosporine.

Patients were given a test dose of 5 mg methotrexate in week 1, increasing by 5 mg each successive week to reach a maximum of 25 mg per week. If a patient was clearly responsive to a given dose then no further increases were made. Blood tests (complete blood count, urea, creatinine, liver function tests) were performed weekly for the first 4 weeks and every 4 weeks thereafter. Folic acid supplements were given 5 days a week, excluding the day of methotrexate administration and the following day. Local therapy consisted of emollients only. During the entire treatment period the investigators made global assessments of the clinical response with a score on a scale of 1 to 4, where 1 = no improvement, 2 = mild improvement, 3 = significant improvement, and 4 = complete remission.

Results

Between 2004 and 2006 nine patients diagnosed either with late-onset atopic dermatitis or idiopathic eczema were treated with methotrexate. Six patients (67%) were males and 3 (33%) were females, aged 52–85 years (mean 75 years). Six patients had late-onset atopic dermatitis and three had idiopathic eczema. The patients were treated with up to 20 mg methotrexate a week. The duration of therapy ranged from 14 to 114 weeks, with a cumulative dose of 200–647 mg.

All patients responded to the drug. The initial response was noted after 3–7 weeks. Six patients achieved complete remission after 3 months of treatment and the remaining three patients showed significant improvement. One patient's condition worsened after achieving a complete response on methotrexate and it was withdrawn completely.

No serious adverse events were noted during the treatment. One patient suffered transient numbness, which did not require cessation of therapy. None of the patients had abnormal routine laboratory tests.

Discussion

Adult-onset atopic dermatitis and idiopathic eczema of the elderly may be recalcitrant to classic treatment modalities, thus requiring adjuvant therapy. Throughout the years multiple adjuvant therapies have been suggested [15] but their use is limited especially in the elderly due to concomitant diseases. For example, adjuvant therapy with cyclosporine is time limited due to a cumulative risk of nephritis. Azathioprine commonly causes side effects such as myelosuppression and hepatotoxicity, and multiple drug interactions limit its use in the elderly. Even phototherapy, a safe second-line therapy, may be contraindicated in the elderly due to severe sun damage or medical history of skin cancer. In the quest for a safe adjuvant therapy for recalcitrant disease, methotrexate used successfully in T cell-mediated skin disease is a reasonable candidate.

In our study, initial response was evident after 3–7 weeks after the initiation of therapy. All patients responded to methotrexate, achieving significant improvement or complete remission (scored 3–4 of 4). Maximal response was observed after 3 months therapy. The clinical response was maintained throughout the entire period of treatment except in one patient whose condition worsened while on maximal methotrexate therapy. No serious adverse events were noted and the treatment was well tolerated by the patients.

Recently, Weatherhead et al. [13] conducted an open-label dose-ranging study of 12 patients with adult atopic eczema treated with methotrexate. The investigators found the drug to be both effective and well tolerated. The patients' responses were apparent after 12 weeks of treatment and appeared to compare favorably with other second-line treatment modalities such as phototherapy. None of their patients, however, achieved complete remission [13]. The results of our present study are comparable with these results with regard to the length of time needed to reach a significant improvement, but demonstrate higher rates of complete remission. These differences may be due to the relatively small numbers of patients in both series.

The onset of atopic dermatitis in adulthood is not common, and the clinical manifestations may diverge from the classic distribution. Our patients were patch tested to relevant series in order to exclude the possibility of allergic contact dermatitis.

Goujon and co-workers [12] conducted an open retrospective study of 20 patients with adult atopic dermatitis. In this large series methotrexate was beneficial in 75% of patients, most of whom achieved significant improvement (> 70% improvement). As in our study, the initial response was evident between the fourth and the eighth week after treatment was initiated. In their series, however, 25% suffered side effects, mostly nausea and elevated liver enzymes, and discontinuation was required in two patients (10%). Nausea may be ameliorated by dividing the dose into two half doses a day.

We conclude that low dose methotrexate may be an effective therapeutic alternative for late-onset atopic dermatitis or idiopathic eczema patients unresponsive to local and systemic treatments.

References

1. Aoki T, Fukuzumi T, Adachi J, Endo K, Kojima M. Re-evaluation of skin lesion distribution in atopic dermatitis: analysis of cases 0 to 9 years of age. *Acta Derm Venereol Suppl* (*Stockh*) 1992;176:19–23.
2. Williams HC. Clinical practice. Atopic dermatitis. N *Engl* J *Med* 2005;352:2314–24.
3. Williams HC, Wüthrich B. The natural history of atopic dermatitis. In: Williams HC, ed. Atopic Dermatitis: The Epidemiology, Causes, and Prevention of Atopic Eczema. Cambridge, UK: Cambridge University Press, 2000:41–59.
4. Bannister MJ, Freeman S. Adult onset atopic dermatitis. *Australas* J *Dermatol* 2000;41:225–8.
5. Ingordo V, D'Andria G, D'Andria C. Adult-onset atopic dermatitis in a patch test population. *Dermatology* 2003;206:197–203.
6. Herzberg J. Wenig bekannte Formen der Neurodermitis. *Hautarzt* 1973;24:47–51.
7. Wüthrich B. Die klinischen Manifestationsformen der Neurodermitis atopica im Kindesalter. *Hautarzt* 1983;34:395–6
8. Ozkaya E. Adult-onset atopic dermatitis. J *Am Acad Dermatol* 2005;52:579–82.
9. Brown S, Reynolds NJ. Atopic and non-atopic eczema. BMJ 2006;332:584–8,
10. Egan CA, Rallis TM, Meadows KP, Krueger GG. Low-dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. J *Am Acad Dermatol* 1999;40:612–14.
11. Shaffrali FC, Colver GB, Messenger AG, Gawkrodger DJ. Experience with low-dose methotrexate for the treatment of eczema in the elderly. J *Am Acad Dermatol* 2003;48:417–19.
12. Goujon C, Berard F, Dahel K, et al. Methotrexate for the treatment of adult atopic dermatitis. *Eur* J *Dermatol* 2006;16:155–8.
13. Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. Br J *Dermatol*. 2007;156:346–51.
14. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl* (*Stockh*) 1980;92:44–7.
15. Meagher LJ, Wines NY, Cooper AJ. Atopic dermatitis: review of immunopathogenesis and advances in immunosuppressive therapy. *Australas* J *Dermatol* 2002;43:247–54.

Correspondence: Dr. L. Zoller, Dept. of Dermatology, Rambam Medical Center, Haifa 31096, Israel.
Phone: (972-4) 854-2154; Fax: (972-4) 854-2951
email: l_zoller@rambam.health.gov.il