

Methotrexate in the Treatment of Moderate to Severe Atopic Dermatitis: A Retrospective Study

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Abstract

Background: Atopic dermatitis is a common inflammatory condition of the skin. Moderate to severe cases not responding to topical treatments and lifestyle changes may need second-line therapy. Methotrexate has been suggested as an effective treatment in such cases.

Objective: This study was done to determine the efficacy, adverse effects, and safety profile of methotrexate therapy in patients with atopic dermatitis.

Materials/Methods: All adult patients with moderate to severe atopic dermatitis seen in the dermatology clinic at this tertiary hospital from January 2015 to December 2015 who were treated with methotrexate were reviewed in a retrospective chart review.

Results: Forty-one patients (19 female, 22 male, mean age 45 years, range 19-90 years) were enrolled. Of these, 29% were naive to any systemic treatments in the past, including systemic corticosteroids. Methotrexate treatment resulted in excellent improvement (>75%) in 93% of patients, good (50%-75% improvement) in 5%, and partial (25%-50% improvement) in 2%. Median duration of therapy was 26 months, and 80% of patients were still on treatment at last review. Transient nonsignificant elevation of transaminases was the most common adverse effect noted in 20%, followed by nausea in 12% and fatigue in 7%. A fibroscan was done in 10 patients at cumulative doses ranging from 2 to 11 g methotrexate. No liver fibrosis was seen in these patients.

Conclusion: Methotrexate is an effective treatment for moderate to severe atopic dermatitis with an acceptable safety profile. A low dose can be used to control the disease for prolonged periods without significant risk.

Keywords

methotrexate, atopic dermatitis, therapy

Atopic dermatitis is a common inflammatory skin disease with a significant impact on psychosocial well-being and reduced quality of life in affected individuals. The reported prevalence of the condition ranges from 10% to 30% in children and 2% to 10% in adults.^{1,2}

Atopic dermatitis is managed with topical or systemic therapies, depending on the severity. Topical corticosteroids are widely used in atopic dermatitis in addition to topical calcineurin inhibitors.³ Severe cases often warrant systemic therapies, which include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil.⁴

In this study, we reviewed the charts of patients treated with methotrexate for this condition and assessed the efficacy, adverse effects, and complication profile of these patients.

Material and Methods

The clinical records of adult patients with moderate to severe atopic dermatitis seen in the dermatology clinic at Sunnybrook

hospital from January 2015 to December 2015 who were treated with methotrexate were reviewed in this retrospective study. The study was approved by the institutional review board and ethics committee. The demographic details, as well as clinical details along with previous treatments and response to methotrexate, were analyzed. The clinical response to methotrexate was assessed in terms of patients' assessment of response, improvement in skin lesions, decrease in itching, decreased use of topical corticosteroids, and a global

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Table 1. Past Treatments.

Past Treatments	No.	%
Phototherapy	11	27
Oral corticosteroids	17	41
IM triamcinolone acetonide	12	29
Azathioprine	7	17
Cyclosporine	5	12
Methotrexate	3	7
Antibiotics	3	7
Mycophenolate mofetil	1	2
Others	1	2

Abbreviation: IM, intramuscular.

physician assessment by the examining dermatologist. Treatment response was categorized as clear, excellent (>75% improvement), good (50%-75% improvement), partial (25%-50% improvement), no response (<25% improvement), and worsening.

The diagnosis of atopic dermatitis was made clinically in these patients. These patients were poorly controlled with topical treatments or with repeated courses of prednisone. Several patients had also received phototherapy or other systemic treatments. Methotrexate in weekly doses of 10 to 25 mg was used orally or subcutaneously with folic acid supplementation 5 mg/d, 6 days a week. A workup was done before starting the treatment, which included a complete blood count, liver function, renal function, hepatitis serology, and a chest X-ray. A tuberculosis skin test was done only in select patients. After starting treatment, a complete blood count, liver function, and renal function were done every 4 weeks for 3 months and thereafter every 3 months if the parameters were stable.

Results

Forty-one patients (19 female, 22 male) with atopic dermatitis were seen during the review period who were on methotrexate. Mean age of these patients was 45 years (range, 19 to 90 years).

All patients had moderate to severe eczema. Twenty-seven (66%) had childhood onset of eczema, of which 8 (20%) had worsened in adulthood. Fourteen patients (34%) had adult onset of eczema.

All patients had been treated with topical steroids previously, and several of them had been treated with phototherapy, systemic corticosteroids, antibiotics, or other systemic immunosuppressive agents (Table 1).

Three patients (7%) who had been treated with methotrexate in the past stopped due to getting better or due to concerns with the medication.

Mean starting dose of methotrexate was 13.7 mg (range, 7.5-20 mg). Median starting dose was 15 mg. Mean maximum or maintenance dose was 17.9 mg (range, 10-25 mg), with the median at 20 mg. After a variable period of time, the

Table 2. Response to Treatment.

Response	No.	%
Clear or almost clear	29/41	71
Excellent (>75% improvement)	9/41	22
Good (50%-75% improvement)	2/41	5
Partial (25%-50% improvement)	1/41	2
Treatment continued	33/41	80
Treatment stopped	8/41	20

dose of methotrexate was tapered when disease control was achieved.

Improvement was first noted at 4 to 6 weeks with further improvement up to 24 weeks.

Response was recorded as clear or almost clear in 29 patients (71%), excellent (>75% improvement) in 9 patients (22%), good (50%-75%) in 2 patients (5%), and partial (25%-50%) in 1 patient (2%). Hence, a total of 93% patients had >75% improvement (Table 2).

Mean duration of methotrexate therapy was 36.8 months (range, 1 month to 11 years). Median duration of treatment was 26 months.

The doses were titrated in accordance with disease flares. Patients were educated to increase the weekly dose by 2.5 to 5 mg if there was a flare. If the disease was controlled and stable, an attempt to taper the weekly dose was made and the dose that maintained clearance was continued. Disease was controlled on as low a dose as 5 mg of methotrexate weekly.

Antibiotics (often cephalexin) were given in 14 patients (34%) and were often prescribed when a patient developed a flare despite being on treatment in order to reduce secondary colonization with *Staphylococcus aureus*. Some of these patients were given prescription for antibiotics, which they took on their own when they had a flare, and this helped them achieve better control of the disease. Seventeen patients (41%) received intramuscular triamcinolone acetonide injection on at least 1 occasion. Twelve (29%) received 1 to 2 injections at the beginning, whereas 5 (12%) had injections on an as-needed basis ranging from an interval of 4 weeks to 12 months.

Two patients (7%) were on tapering doses of prednisone while methotrexate therapy was initiated.

One patient (2%) was on cyclosporine 150 mg, which was tapered from a dose of 150 mg to 100 mg after 4 weeks of starting methotrexate and stopped subsequently after 2 more weeks.

One patient (2%) was on suppressive doses of valacyclovir to prevent recurrent Kaposi varicelliform eruption.

Methotrexate treatment was stopped in 8 patients (20%) due to good control, 5 continued to be clear, and 3 restarted treatment due to flare of disease, which occurred within 4 to 8 months. Five patients who remained clear had been clear for a period of 4 months to 3 years at the time of review. The duration for which they had received methotrexate ranged from 1

Table 3. Patients Who Remained Clear at the Time of Review After Discontinuation of Methotrexate.

Patient No.	Duration Remaining Clear	Duration of Methotrexate
1	3 years	6 years
2	15 months	12 months
3	9 months	14 months
4	8 months	14 months
5	4 months	18 months

year to 6 years (Table 3). Three other patients (7%) discontinued for other reasons. One had good control for 1 year but flared after that and did not respond for 3 months; hence, methotrexate was discontinued and mycophenolate mofetil started. In the second patient, methotrexate was discontinued because of low immunoglobulin levels. The third patient discontinued for future conception. Thirty-three patients (80%) were still on medication at the time of data collection.

Eight (20%) patients had transient increases in transaminases, which were less than double the normal values. Nausea occurred in 5 (12%) patients and fatigue in 3 (7%) patients (Table 4). Three patients with nausea were started on subcutaneous dosing, 1 patient was prescribed ondansetron, and another was given methotrexate in 2 divided doses, which mitigated the symptoms. Decreased hemoglobin and transient decrease in platelets were noted in 1 (2%) patient. Hemoglobin was maintained at 107 to 120 g/L in this patient, and platelet level was normal on subsequent investigations. Another patient had decreased platelets, but the levels were maintained at 128 to 140 million/mL.

Mean cumulative dose was 2.6 g, and median cumulative dose was 2 g. Fibroscan evaluation was done in 10 patients, at cumulative doses ranging from 2 to 11 g methotrexate (mean, 4.9 g; median, 4.5 g). No fibrosis was reported.

Discussion

Methotrexate inhibits dihydrofolate reductase and thymidylate synthetase enzymes, thereby inhibiting DNA synthesis. This inhibits proliferation of lymphocytes and induces apoptosis of the mitogen-activated T cells. Methotrexate also causes accumulation of extracellular adenosine, which has immunomodulatory effects.^{5,6}

Our findings confirm that methotrexate is a relatively safe drug for atopic dermatitis and can result in significant improvement in the signs and symptoms and quality of life. Thirty-eight (93%) patients on therapy with methotrexate had >75% improvement in dermatitis. The drug was stopped in 8 patients due to good control, of whom 5 were still off the drug at the time of review. Our experience suggests that low doses ranging from 10 to 25 mg can suffice. The dose can be increased initially until control is achieved and thereafter decreased again and maintained at the lowest dose that prevents a relapse. There were a few patients whose disease was

Table 4. Adverse Effects.

Adverse Effect	No.	%
Nausea	5/41	12
Fatigue	3/41	7
Elevated transaminases	8/41	20

controlled on as low a dose as 2.5 mg/wk. Patients sometimes titrated the dose themselves depending on flares. Initial improvement was noted at 4 to 6 weeks, and further improvement occurred up to 24 weeks. Adverse effects were minimal and not severe enough to warrant cessation of therapy. Liver fibrosis was not observed in patients who were tested with fibroscan who had reached higher cumulative doses or who had risk factors.

There have been prior studies on methotrexate in atopic dermatitis as a second-line treatment.⁷⁻¹² Weatherhead et al⁷ reported the safety and efficacy of oral methotrexate in 12 adults with moderate to severe atopic eczema in an open-label, dose-ranging, prospective trial. Seven of the 12 patients had >50% improvement. They increased the dose of methotrexate by 2.5 mg every 4 weeks (up to a maximum of 22.5 mg) until a response was achieved, after which dose stabilization was maintained. They reported 47% improvement in Six Area, Six Sign Atopic Dermatitis (SASSAD) scores in the first 12 weeks of therapy, with a further improvement of only 5% in the subsequent 12 weeks.⁷

Lyakhovitsky et al⁸ reported the results of a retrospective study of 20 adults with moderate to severe atopic dermatitis treated with methotrexate in doses ranging from 10 to 15 mg/wk. Sixteen patients achieved clinical improvement between 2 and 12 weeks. They suggest that methotrexate may be prescribed during exacerbations and tapered off after disease control or maintained at the lowest effective dose. Zoller et al⁹ reported 9 patients treated with methotrexate at a dose ranging from 10 to 20 mg every week. The earliest response was noted at 3 to 7 weeks, and all the patients responded to the treatment.

Deo et al¹⁰ reported results in 31 patients (children and adolescents) treated with methotrexate. They found it to be effective or very effective in 75% and ineffective in 25%.

El-Khalawany et al,¹¹ in a prospective randomized study, compared the efficacy of methotrexate and cyclosporine A. They reported a mean absolute reduction in the severity scoring for atopic dermatitis (SCORAD) score of 26.25 ± 7.03 in patients treated with methotrexate and a mean absolute reduction of 25.02 ± 8.21 in patients treated with cyclosporine A at 12 weeks. They reported no statistically significant difference in the reduction of SCORAD score between both groups ($P = .93$).

Schram et al,¹² in a randomized single blinded trial, compared the efficacy of methotrexate with azathioprine. At 12 weeks, there was relative reduction of 42% with methotrexate and 39% with azathioprine. There was no statistically significant difference in the 2 groups ($P = .89$).

The findings of these studies are consistent with our study in that methotrexate was safe and effective as a second-line treatment for atopic eczema. Adverse effects were usually mild and did not result in cessation of therapy. Improvement usually appeared at around 4 to 12 weeks in most studies and appeared to plateau, suggesting that 12 weeks is a reasonable time frame trial period.

We suggest that methotrexate is a useful second-line drug for atopic eczema, and therapy may be started with 10 to 15 mg/wk. In the beginning, intramuscular triamcinolone acetonide or a short course of oral corticosteroids may be required to bridge the patient until methotrexate reaches full efficacy. Additional treatments may be required intermittently, including intramuscular corticosteroids and antibiotic treatments, along with supplemental topical therapies. Methotrexate can, however, minimize the number of treatments with these agents; in turn, these short-term treatments minimize the risks and side effects that would occur with higher doses of methotrexate and also delay the increase in cumulative dose. If the disease has been controlled for a long time, a trial of cessation of therapy may be tried. If there is a recurrence, it may be possible to go back to methotrexate or an alternative agent as well. Prospective studies with a more controlled study setting may provide further insight regarding the best dosing regimen, tapering, and duration of remissions that may be expected. Longer experience with less invasive methods of assessing liver fibrosis like fibroscan may allow the physicians to continue methotrexate for longer periods and higher cumulative doses.

This study is retrospective in nature, and objective methods for assessing improvement were not employed. Prospective comparative studies with other modalities of treatment for atopic dermatitis with intention-to-treat analysis will likely yield more realistic results.

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