

Methotrexate use in allergic contact dermatitis: a retrospective study

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Summary

Background. Methotrexate, a folate antimetabolite, is used to treat atopic dermatitis and psoriasis. Although methotrexate's therapeutic efficacy has been noted in the literature, there are few data on the efficacy of methotrexate treatment for allergic contact dermatitis.

Objective. To evaluate the efficacy and tolerability of methotrexate in treating allergic contact dermatitis at a single institution, and also to assess methotrexate efficacy in patients with chronic, unavoidable allergen exposure.

Methods. We performed a retrospective chart review of 32 patients diagnosed with allergic contact dermatitis by positive patch test reactions, and who received treatment with methotrexate from November 2010 to November 2014. Demographic and treatment-associated data were collected from electronic medical records. Ten patients were identified as allergen non-avoiders secondary to their occupation, and were subgrouped as such.

Results. Seventy-eight per cent (25/32) of patients showed either a partial or a complete response. Methotrexate had a comparable efficacy rate in the allergen non-avoiders subset, at 10 of 10. Of the 32 patients, 23% (5/22) had complete clearance of their dermatitis, and 1/10 of allergen non-avoiders had complete clearance of their dermatitis.

Conclusion. Methotrexate is a well-tolerated and effective treatment for allergic contact dermatitis, and shows comparable efficacy to immunomodulatory agents such as cyclosporine and azathioprine, with robust efficacy despite persistent allergen exposure in patients with allergic contact dermatitis.

Key words: allergic contact dermatitis; contact dermatitis; drugs; methotrexate; occupational.

Allergic contact dermatitis has many clinical presentations. Often, it will present as pruritic, erythematous, oedematous papules, vesicles and/or plaques at the site of allergen contact. At other times, it can present as

chronic dermatitis or delayed wound healing. Although allergic contact dermatitis is initially limited to the principal site of exposure, it can spread to distant cutaneous sites (auto-eczematization) and can result in a more serious clinical presentation (1). Overall, allergic contact dermatitis is a common, potentially chronic, disease with a significant impact on quality of life. For some patients, the culprit allergen(s) can be quickly identified by patch testing, and removed from the patient's environment. However, often, the allergenic sources are either unidentifiable or unavoidable – two situations that require symptomatic and potentially immunosuppressive therapy to reduce the effects of the disease.

A variety of medications for use in the treatment of allergic contact dermatitis have been reported in

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controlled trials, case series, and reviews (2–8). These medications fall under the categories of corticosteroids, non-steroidal drugs, immunomodulators, barrier creams, and emollients. In the category of immunomodulators, azathioprine and cyclosporine are described in the literature as treatment options for allergic contact dermatitis (9–13). However, there are very few reports on the use of methotrexate in allergic contact dermatitis, and there have been no controlled clinical trials on its use in this setting. Handa et al. showed that methotrexate is as efficacious as azathioprine in the treatment of *Parthenium hysterophorus* allergic contact dermatitis, but with a shorter treatment time (6). Additionally, methotrexate may be useful in treating severe *P. hysterophorus* dermatitis that is unresponsive to conventional treatment (7, 8).

Methotrexate is a folate analogue antimetabolite that is used in the treatment of a broad range of inflammatory diseases. In dermatology, methotrexate has been proven to be effective in the treatment of psoriasis, atopic dermatitis, and other T cell-mediated skin diseases (14–16). Methotrexate is known to have several mechanisms of action. In psoriasis specifically, it targets proliferating lymphoid cells and inhibits the migration of activated T cells into certain tissue sites (17). Methotrexate also has immunosuppressive effects by inhibiting DNA synthesis in immunologically active cells, and suppressing primary and secondary antibody responses. Additionally, methotrexate increases adenosine production and thus has anti-inflammatory effects (18).

The objective of this study was to evaluate the use of methotrexate in the treatment of allergic contact dermatitis at a single institution. The aim was to better understand the efficacy and tolerability of methotrexate in patients with allergic contact dermatitis, and to determine the patient characteristics and disease-specific scenarios in which methotrexate may be most effective. It is of note that methotrexate is not currently Food and Drug Administration-approved for use in allergic contact dermatitis.

Methods

Data for the study were obtained from a retrospective chart review of patients diagnosed with allergic contact dermatitis between November 2010 and November 2014 in the Dermatology Department at Saint Louis University. Inclusion criteria included a diagnosis of allergic contact dermatitis via positive patch test reactions, and treatment with methotrexate for > 3 months. A total of 770 patient charts were extracted, of which 37 matched the inclusion criteria. Of the 37 charts, 5 were excluded because of insufficient data.

The patients in this study were patch tested with the North American Contact Dermatitis Group (NACDG) baseline series, which contained up to 65 allergens. Many patients were tested with additional allergen series, depending on clinical suspicion. Testing was performed with the Finn Chamber® system (Epitest, Tuusula, Finland) on Scanpor® tape (Norgesplaster Alfarma, Vennesla, Norway). Allergens were supplied by Chemotechnique Diagnostics (Vellinge, Sweden). Patches were applied to the patient's back for 48 h before removal. Readings were completed on day (D) 3 and D5 for all patients. The reactions were graded as doubtful, +, ++, or +++, on the basis of the NACDG grading protocol (19).

Data extracted included: sex, age, ethnicity, occupation, rash distribution, previous treatment(s), disease severity, concomitant diseases, rash initiation, methotrexate start/stop dates, response to methotrexate, that is, efficacy, maximum dose of methotrexate achieved (g/week), tolerability of methotrexate taper, reason for discontinuation, name/number of allergens, methotrexate side-effects, and any concurrent treatments.

Results

The study included 32 patients at Saint Louis University who were diagnosed with allergic contact dermatitis via positive patch test reactions between November 2010 and November 2014, and were subsequently treated for allergic contact dermatitis with a once-weekly oral dose of methotrexate for > 3 months. These patients' charts were reviewed. Among the 32 patients, a subset of 10 patients were identified as being exposed to 'occupational hazards/unavoidable allergens'. Patients in this subset included those whose professions or hobbies introduced constant unavoidable exposure to at least one relevant allergen. Some examples from the subset include hairdressers, welders, nurses, and photographers. Within this category, 9 of 10 patients showed at least a partial response to treatment with methotrexate; 1 of 10 tapered off because of clearance of allergic contact dermatitis, and 8 of 10 patients remained on methotrexate. All 10 patients in this subset showed methotrexate efficacy, defined as either partial or complete efficacy.

Among all other patients, 5 of 22 (23%) showed complete clearance and 10 of 22 (45%) showed a partial response. The overall efficacy in this group was 15 of 22 (68%). Table 1 shows the total number of positive allergens tested in each patient, along with important methotrexate treatment parameters in both subsets of patients.

Overall, of the 32 patients treated with methotrexate, only 2 discontinued methotrexate use completely, owing

Table 1. Allergen and methotrexate treatment data by patient subset

Number	No. of positive allergens/total allergens	Maximum dose of methotrexate achieved (g/week)	Methotrexate duration (days)	Methotrexate response
Occupational hazards/allergen non-avoiders ^[1]				
1	20/100	20	1017	Yes, clear
2	5/107	22.5	706	Yes, partial
3	5/106	22.5	330	Yes, partial
4	18/118	25	395	Yes, partial
5	16/107	15	790	Yes, partial
6	29/799	25	500	Yes, partial
7	39/107	20	224	Yes, partial
8	6/118	15	282	Yes, partial
9	23/802	22.5	Unknown	Yes, partial
10	22/88	25	528	Yes, partial
All other patients ^[2]				
1	24/047	20	141	Yes, clear
2	24/746	15	731	Yes, clear
3	23/863	20	363	Yes, clear
4	32/143	25	311	Yes, clear
5	6/114	15	Unknown	Yes, clear
6	9/114	25	895	Yes, partial
7	6/122	20	462	Yes, partial
8	21/133	20	Unknown	Yes, partial
9	23/67	15	517	Yes, partial
10	32/264	20	224	Yes, partial
11	3/106	15	136	Yes, partial
12	8/107	15	107	Yes, partial
13	9/107	15	96	Yes, partial
14	35/490	30	1214	Yes, partial
15	2/65 + 5/114*	25	529	Yes, partial
16	8/114	25	350	No
17	15/106	25	602	No
18	10/121	25	113	No
19	14/65	25	348	No
20	15/108	30	165	No
21	3/107	25	1620	No
22	5/100	22.5	Unknown	No

*Patient was patch tested twice on two different dates.

^[1]Patients with professions/hobbies forcing constant, unavoidable exposure to at least one relevant allergen.

^[2]Patients who didn't have an occupational exposure and had the ability to avoid their allergen.

to fatigue and pulmonary infection. The remaining 30 of 32 patients (94%) found it tolerable and continued treatment. Altogether, 78% of patients (25/32) showed methotrexate efficacy, and 22% (7/32) showed failure, including the 2 patients who discontinued use because of intolerable side-effects (Fig. 1).

The most common side-effects noted among all of the 32 patients were gastrointestinal discomfort (21%) and fatigue (16%). Laboratory abnormalities included ALT over 56 U/L and/or AST over 40 U/L (31%), anaemia (15%), elevated creatinine (8%), leukopenia (6%), and thrombocytopenia (3%). It is of note that all documented laboratory abnormalities were mild, were transient, and resolved without dose adjustments.

Discussion

This retrospective analysis of patients at a single institution shows the potential of methotrexate for the treatment of recalcitrant allergic contact dermatitis. Of the 32 patients treated with methotrexate, 78% (25/32) showed clinical improvement and 22% (7/32) failed to respond. Of the 25 responders, 6 of 25 (24%) were noted to have complete clearance of allergic contact dermatitis, and 19 of 25 (76%) were reported to have partial clearance. The 22% of non-responders included those patients who stopped using methotrexate because the medication simply showed no benefit, or caused an intolerable side-effect.

Azathioprine and cyclosporine have long been used as pharmacotherapies in the treatment of allergic contact

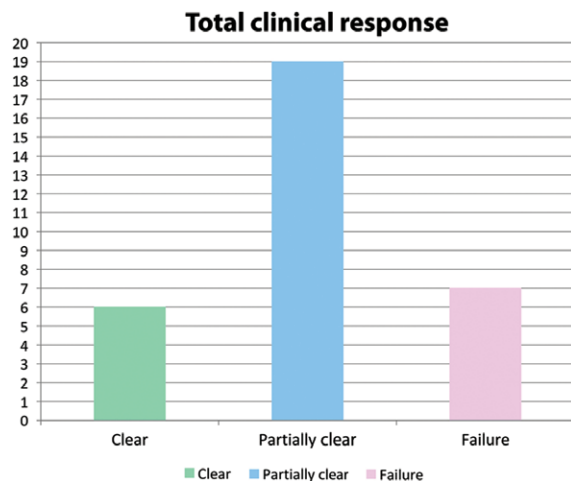


Fig. 1. Of the 32 patients treated with methotrexate for allergic contact dermatitis, 78% (25/32) showed a clinical response, with 59% (19/32) showing partial clearance and 19% (6/32) showing full clearance of their allergic contact dermatitis. Twenty-two per cent (7/32) had treatment failure or were not able to tolerate methotrexate treatment.

dermatitis (9). Some studies have established the efficacy of azathioprine for the treatment of allergic contact dermatitis caused by *P. hysterothorus* (10–13). However, a systematic review of azathioprine use in dermatology showed that there is a strong clinical recommendation for the use of azathioprine in atopic dermatitis, whereas only moderate-quality data exist for its use in off-label settings such as allergic contact dermatitis (20). Moreover, a randomized trial conducted on patients suffering from allergic contact dermatitis caused by *P. hysterothorus* weed comparing azathioprine with methotrexate showed that methotrexate had similar efficacy as azathioprine, with a shorter treatment time being needed to achieve clearance. In the group treated with azathioprine, the clinical severity score (CSS) was reduced by > 75% in 9.5 weeks, whereas the group treated with methotrexate achieved a > 75% reduction in CSS in 5.6 weeks. Fifty per cent of the improvement in the methotrexate group was seen in the first month, and there was a sustained decrease in the dermatitis score with continuation for 6 months (6). Another study showed that methotrexate, both alone and in combination with a topical corticosteroid, is a useful option in severe *P. hysterothorus* dermatitis that is unresponsive to conventional treatment (7, 8). Methotrexate has also shown better efficacy than azathioprine in the treatment of atopic dermatitis in multiple studies (21, 22). Schram et al. showed similar reductions in the Severity Scoring of Atopic Dermatitis Score (SCORAD) (23) (42% with methotrexate and 39% with azathioprine) at week

12 of treatment in 42 adults with severe atopic dermatitis; however, patients on azathioprine experienced more adverse events, including gastrointestinal events, abnormalities in blood counts, and increased liver enzymes (15). Similarly, Garritsen et al. showed that azathioprine was more likely than methotrexate to cause influenza-like symptoms, pancytopenia, and liver dysfunction (24). Cyclosporine has shown efficacy in chronic hand eczema, but has also led to exacerbations of allergic contact dermatitis (25–27). Another study examining drug survival, that is, the length of time that a patient is on a particular medication, which is a well-recognized measure of drug effectiveness, in patients treated with cyclosporine for atopic dermatitis showed a drug survival rate of only 18% after 2 years, and cited side-effects and ineffectiveness as the two main reasons for decreased drug survival (28). The predominant side-effects leading to discontinuation of cyclosporine treatment were hypertension, gastrointestinal symptoms, headache, and an increase in serum creatinine (28). Our study shows that methotrexate has similar efficacy to both azathioprine and cyclosporine in the treatment of allergic contact dermatitis, but with less potential for significant side-effects or adverse events.

Additionally, this study has shown the potential use of methotrexate as a treatment method for allergic contact dermatitis in a special subset of patients, that is, 'occupational allergen/unavoidable allergen', which accounted for 31% of all patients reviewed. Within this subset alone, 9 of 10 patients showed at least partial effectiveness of methotrexate; 1 of these patients had complete clearance of the dermatitis, and 2 stopped treatment because of significant improvement. The remaining 7 remain on methotrexate treatment and continue to show improvement. All patients in this subset had a longer duration of treatment than the average among the 32 patients (530 days versus 470 days). This may suggest that long-term consistent treatment with methotrexate may be needed to control disease, rather than that methotrexate induces long-lasting remission.

The conclusions that can be drawn from this study are limited in the following ways. First, the number of cases reviewed is small, and specific to a demographic area. Therefore, these data cannot be easily generalized. The retrospective nature of this study means that it cannot fully evaluate the full potential of methotrexate as a treatment method in various subsets of allergic contact dermatitis. Moreover, owing to the retrospective nature of this study, there was no standardized definition of partial or complete response, and usual methodological requirements, such as the collection of body surface area and quality of life index, could not be met. Suggestions

for further studies include prospectively evaluating the efficacy of methotrexate in a larger group of patients with chronic allergen exposure.

In conclusion, allergic contact dermatitis is a common disease that affects a wide range of patient subsets.

Although various medications have been used thus far, methotrexate shows robust efficacy in the treatment of patients with persistent allergen exposure, as shown in a group of patients treated for allergic contact dermatitis at a single institution.

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