

## CLINICAL REPORT

# Evidence for Methotrexate as a Useful Treatment for Steroid-dependent Chronic Urticaria

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**Chronic urticaria is a relatively common disorder that can be severe and may impair quality of life. The management of recalcitrant chronic urticaria that is not responding to histamine antagonists includes short-term systemic corticosteroids, anti-inflammatory drugs (colchicine, dapsone and sulfasalazine) and immunomodulatory agents, such as cyclosporine, methotrexate, plasmapheresis and intravenous immunoglobulin. We report here our retrospective experience with the use of methotrexate in 8 patients (2 males and 6 females) with recalcitrant chronic urticaria who were not responding to high-dose first- and second-generation antihistamines. The mean duration of the disease prior to methotrexate treatment was  $12 \pm 8$  months. Patients were treated for a mean duration of 4.5 months with a mean dose of 15 mg methotrexate/week. A complete response was achieved in 7 out of 8 patients (87%). Five out of the 7 patients were disease-free during a period of 1–10 months follow-up after discontinuing methotrexate and prednisone therapy. No serious adverse effects were reported. Methotrexate is an effective and safe treatment for chronic urticaria in patients who are not responsive to conventional therapy. Key words: chronic urticaria; antihistamine; corticosteroids; methotrexate.**

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Chronic urticaria (CU) is a relatively common disorder with an estimated 0.5% lifetime prevalence in the general population (1). The condition can be severe and debilitating and may impair quality of life. The management of CU is based on H1-antihistamines as a first-line therapy, especially second-generation antihistamines, which lack sedating side-effects. For patients with recalcitrant disease, other therapeutic options are added, including short-term systemic corticosteroids for acute flares, high-dosage second-generation H1-antihistamines, first-generation H1-antihistamines, H2-antihistamines, tricyclic antidepressants, such as doxepin, or leukotriene modifiers. Anti-inflammatory drugs, such as colchicine, dapsone and sulfasalazine, may also be beneficial in

some cases. The use of immunomodulatory agents was encouraged by the demonstration that approximately 30% of patients with CU produce autoantibodies against IgE or the high-affinity IgE receptor (2–5). This led to the use of immunomodulatory agents such as cyclosporine, methotrexate (MTX), plasmapheresis and intravenous immunoglobulin in refractory cases of CU (6–12).

Among the immunomodulatory agents, the literature regarding the use of MTX in the treatment of CU is scarce (13–16). In this retrospective series, we report our experience with MTX in patients with recalcitrant CU.

## MATERIALS AND METHODS

### Patients

The medical records of all patients with CU treated in the dermatology department and outpatient clinic in a tertiary referral medical centre in the years 2005 to 2009 were reviewed. A retrospective medical chart review for patients diagnosed with chronic spontaneous CU (defined as at least two weekly attacks during a period of at least 6 weeks) and subsequently treated with MTX was performed. Inclusion criteria included the following:

- CU defined as urticarial eruption of more than 6 weeks duration characterized by hives or wheals.
- Skin biopsy demonstrated features of urticaria, i.e. sparse to moderate mixed perivascular inflammatory infiltrate composed of lymphocytes, neutrophils, eosinophils and mast cells (17, 18).
- Patients received MTX treatment for at least 6 weeks.

As this is the protocol in our institution, all patients underwent an extensive laboratory and imaging evaluation to exclude internal diseases and other causes for CU. This included physical factors, drug allergy, food allergy, bacterial and viral infections and internal diseases such as thyroid diseases, connective tissue disease and paraproteinaemia. Laboratory work-up included erythrocytes sedimentation rate, complete blood count, blood chemistry, serological tests for hepatitis B and C, complement level, rheumatoid factor, anti-nuclear factor, stool for occult blood and parasites, protein electrophoresis, IgE levels, iron, B12 and folic acid levels, TSH levels, anti-thyroid peroxidase and anti-thyroglobulin antibodies, HIV, *H. pylori* breath test, chest X-ray and abdominal ultrasonography.

### Treatment protocol

Patients were treated with MTX after ruling out contraindications, such as liver or lung disease and positive serological tests for hepatitis B and C. This protocol is similar to the guidelines established for MTX treatment in psoriasis and to the protocol we have previously used in patients with atopic dermatitis (19, 20). In

general, the initial dose of MTX was 15 mg/week. 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. Folic acid supplements were given in a weekly dose of 5 mg, one day after the last dose of MTX. When gastrointestinal side-effects were encountered, therapy was substituted to intramuscular route at the same dose. If the patient did not respond to the initial dose during a 4-week period, the dose was increased by 5 mg every 2 weeks to a maximum of 25 mg. If a patient was partially responding to a given dose, expressed by a decrease in severity and frequency of urticarial attacks, no further increases were made. Had no urticarial events occurred for at least 2 weeks, the weekly dose of MTX was decreased by 5 mg every 4 weeks. At each visit, patients underwent physical examination, including dermatological examination, and were interviewed for possible MTX-induced side-effects. Complete blood count and liver function tests 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, MTX was either discontinued or the dosage was reduced, depending on the extent of abnormality and the presence of other side-effects.

Patients continued with their previous antihistamine treatment throughout the study, as needed. With regard to steroid therapy, it is our general practice, when partial response was noticed, to taper down the prednisone dose by 10 mg every 4 days.

#### Assessment of response and follow-up measurements

Patients were evaluated every 2 weeks for the first month of treatment, then every month at the outpatient clinic. Patients were categorized into three groups according to their subjective report of symptoms severity (number of wheals and pruritus) and frequency compared with that in the previous visit:

- Complete response (no symptoms, either no treatment except for MTX with or without antihistamines therapy but off steroids).
- Partial response (decrease in urticarial severity and/or frequency, reduction in steroid dose).
- No response.

Table I. Patients, treatment protocol, efficacy and follow-up

Patient	Age at diagnosis (years)/ gender/duration of disease prior to MTX treatment (months)	MTX protocol			Efficacy			Follow-up period (months)	Side-effects
		Route	Dose (mg/week)	Duration (months)	Remission onset (week)	Duration of remission (months)	Remission type		
1	74/M/9	PO	15	1	4	8	CR <sup>a</sup>	11	None
		PO	10	1					
		PO	5	1					
2	65/M/12	PO	15	3	4	4	CR	5	Elevated LFT
		PO	10	2					
		PO	25	3					
3	41/F/6	PO	15	2	4	15	NR	13	None
		PO	25	3					
		PO	25–2.5	7 <sup>b</sup>					
4	69/F/3	PO	15	3	4	4	CR <sup>a</sup>	5	None
5	39/F/30	PO	15	2	3	9	CR <sup>a</sup>	10	None
6	18/F/9	PO	15	1	4	14	CR <sup>a</sup>	15	GI
		IM	15	2					
		IM	10–5	2 <sup>b</sup>					
7	60/F/12	PO	7.5	2	–	–	NR	2	Weakness
8	65/F/12	PO	15	1	5	4	CR	5	GI
		IM	15	4					

<sup>a</sup>Complete remission off MTX therapy.

<sup>b</sup>Gradual taper of MTX dose.

MTX: methotrexate; CR: complete response; PR: partial response; NR: no response; GI: gastrointestinal; LFT: liver function tests; PO: per os; by mouth; F: female; M: male.

## RESULTS

### Patients

Among 88 patients with CU in the years 2005 to 2009, 8 patients (2 males and 6 females) were treated with MTX and fulfilled the inclusion criteria. The mean age at diagnosis was  $54 \pm 19$  years (age range 18–74 years) and the mean duration of the disease prior to MTX treatment was  $12 \pm 8$  months (range 3–30 months) (Table I). Seven patients had angioedema associated with the urticarial lesions. In all patients the laboratory and imaging evaluations were normal.

All patients were treated with high-dose sedative and non-sedative antihistamines prior to MTX treatment. In addition, patients required intermittent or long-term daily treatment with 3–10 repeated course of steroids to control their urticaria. The initial dose was 30–40 mg/day which was tapered down during a 2–4-week period. One patient was on oral prednisone continuously for a 6-month period. Four patients were given a single continuous intravenous hydrocortisone treatment during hospitalization due to unresponsiveness to oral corticosteroids. Other therapies included doxepin, colchicine and dapsone.

Seven patients received an initial dose of 15 mg MTX/week and one started on 7.5 mg/week due to a misunderstanding (number 7). Patients were treated for a mean duration of  $4.5 \pm 3$  months (range 2–12 months).

### Efficacy

Seven patients (87%) achieved complete remission of their urticaria during MTX treatment (Table I). The period elapsed until response to MTX was observed varied

from 3 to 8 weeks (mean  $4.6 \pm 1.6$  weeks). In the one patient (no. 7) who did not respond, we were not able to increase the MTX dose beyond 7.5 mg/week due to poor compliance (patient's refusal of dose increment). One patient (no. 3) had no response on a dose of 15 mg MTX/week. When the dose was increased gradually to 25 mg/week, a partial response for 3 months followed by a complete response was observed in this patient. The response persisted during MTX tapering as well as one month after discontinuation of the drug. Patients were followed up during and after the termination of MTX treatment for a total period of  $8.25 \pm 4.6$  months (range 2–15).

Five out of the 7 patients who entered complete clinical remission were able to discontinue MTX and prednisone therapy and were disease-free during a range of 1–10 months follow-up. At the time of analysing the data, two patients are still under MTX treatment: patient no. 2 is tapering down MTX dose without recurrence of urticaria. Patient no. 8 had a relapse of urticaria on tapering MTX dose and required a constant dose of 15 mg/week. Yet, both these 2 patients do not require steroids to control their symptoms.

### Safety

No serious adverse effects were reported during the treatment and follow-up period. A mild increase in liver enzymes (up to twice the normal values) was observed in one patient (number 2) and resolved after reducing MTX dosage. Gastrointestinal discomfort was reported in two patients and resolved after changing to an intramuscular injection route. The one patient who did not respond complained of subjective fatigue (Table I).

### DISCUSSION

MTX is an anti-metabolite used in the treatment of many chronic inflammatory diseases (20–22). Several pharmacological mechanisms for MTX action have been proposed, both in respect to its immunomodulatory and anti-inflammatory effects (23–26).

We report our experience with the use of MTX in eight patients with recalcitrant, steroid-dependent CU. The literature regarding the treatment of refractory CU with MTX is scarce. In 1989, Weiner (16) reported successful treatment of one patient with corticosteroid-resistant urticaria with MTX. Gach et al. (13) described two patients treated with MTX for steroid-dependent CU. Perez et al. (15) retrospectively assessed MTX effect in 16 steroid-dependent CU patients, who were treated with 10–15 mg MTX/week. They demonstrated complete response in two patients, considerable benefit in seven patients and some benefit in three patients. Four of their patients and three of the responders had urticarial vasculitis. Furthermore, those with consider-

able response and some benefit still needed steroids to control their disease.

In accordance with these previous reports, our study demonstrates a beneficial role of MTX in treating recalcitrant CU. During the treatment we observed a complete response rate of 87% (7/8 patients). This response lasted for weeks after the cessation of MTX treatment in most of the patients. Furthermore, all our patients who were steroid-dependent were able to discontinue systemic corticosteroid treatment. In contrast to the rapid response to MTX treatment of 2 weeks mentioned in previous reports (13, 16), MTX clinical response in our study was noticeable only after a mean of 4 weeks following MTX initiation. Yet, this period is shorter than that required for clinical effect in other inflammatory skin disease, and may be related to the sparse inflammatory infiltrate seen in classic urticaria. It is noteworthy that in the one non-responder, MTX has not exhausted itself. We therefore believe that doses lower than 15 mg/week are not sufficient to cause a prompt clinical response, as demonstrated in other inflammatory diseases (19).

We did not encounter any serious adverse effects during MTX treatment. In addition, the intra-muscular route proved to be beneficial in eliminating minor gastrointestinal side-effects. Since we believe that MTX is a relatively safe drug (20), it became our immunomodulating drug of choice when treating patients with recalcitrant, steroid-dependent CU. Furthermore, the vast experience that dermatologists have with this drug and its low economic impact advocate its usage. In cases where longer treatment with MTX is needed, dermatologists can apply the well-established guidelines for its usage (19).

One cannot ignore the limitations of this study: a retrospective assessment, a small number of patients included, lack of quantization of health-related quality of life and a relatively short follow-up period. However, the impressive effect of MTX treatment in recalcitrant CU, as demonstrated herein and in previous reports, point to its role in the therapeutic armoire in CU.

In conclusion, MTX is a safe and useful treatment for patients with recalcitrant CU, regardless of its mechanism. As there is currently a low level of evidence for its use in CU (12), further placebo-controlled prospective clinical trials are needed in order to define the exact role of MTX in refractory CU. Differentiating patients into idiopathic, autoimmune and other types of urticaria can further determine whether MTX is more effective in a particular subset of patients, and define guidelines on the treatment of the various forms of CU.

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