

## CASE SERIES

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# Safety of Methotrexate in Chronic Urticaria Unresponsive to Omalizumab

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## ABSTRACT

Omalizumab (humanized anti-immunoglobulin IgE) is currently the first choice of treatment for chronic urticaria refractory to high-dose second-generation antihistamines (sgAH). Despite its high safety profile, response to omalizumab is insufficient in one-third of patients. Some studies have suggested that methotrexate is effective in antihistamine-refractory chronic urticaria, but there are no studies on its efficacy and safety in patients unresponsive to omalizumab. This retrospective study aimed to investigate the clinical effectiveness and adverse effects of methotrexate in patients with chronic urticaria unresponsive to omalizumab+high-dose sgAH.

The patients were evaluated in terms of age at disease onset, duration of the urticaria episode before methotrexate therapy, treatment before methotrexate therapy, final treatment, treatment responses, 7-day urticaria activity score (UAS7) before and after treatment, and total IgE levels. Methotrexate was administered subcutaneously at a dose of 15 mg once weekly as monotherapy or in combination with other drugs to 10 chronic urticaria patients with a history of nonresponse to omalizumab+high-dose sgAH.

The mean age of the patients was  $44.6 \pm 11.5$  (31-65) years, and 9 (90%) of the patients were female. The mean duration of methotrexate therapy was  $5.1 \pm 2.4$  months (1.5-9 months). Complete response or well-controlled response was observed in 70% of the patients and partial response was observed in 1 patient (10%).

Methotrexate was well tolerated by 80% of the patients. Methotrexate seems to be a useful treatment option both as monotherapy or combined therapy in patients resistant to omalizumab+sgAH.

**Keywords:** Chronic urticaria; Methotrexate; Omalizumab; Safety; Therapeutics

## INTRODUCTION

Chronic urticaria is characterized by episodes of skin redness, swelling, and itching lasting longer than 6 weeks. It affects 0.5% to 1% of the population and the

mean disease duration is between 1 and 5 years.<sup>1</sup> Second-generation antihistamine (sgAH) and omalizumab (humanized anti-immunoglobulin IgE) are commonly used in the treatment of chronic urticaria. Antihistamines are the first choice of treatment due to their efficacy and low cost, and can be used up to 4 times a day. In patients who are unresponsive to high doses of antihistamine, omalizumab (300 mg/4 weeks, subcutaneous) is added to treatment. Although

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omalizumab has a high safety profile, it is reported to be ineffective in a third of patients.<sup>2</sup> The EAACI/GA<sup>2</sup>LEN/EDF/WAO international chronic urticaria guideline recommends cyclosporine as the first choice for patients unresponsive to omalizumab + high-dose sgAH.<sup>3</sup> However, the use of cyclosporine in this area is limited considerably by its severe adverse effects,<sup>4,5</sup> the risk of lymphoproliferative disease with long-term use,<sup>6</sup> and the fact that chronic urticaria can persist for years. Thus, the search continues for a safer drug for chronic urticaria patients nonresponsive to omalizumab + high-dose sgAH. While there have been a few promising No studies with small patient series suggesting that methotrexate is useful and safe in antihistamine-refractory or steroid-dependent chronic urticaria,<sup>7,8</sup> no studies are investigating the efficacy and safety of methotrexate in patients who are unresponsive to omalizumab + high-dose sgAH.

This retrospective study aimed to investigate the clinical effectiveness and adverse effects of methotrexate in patients with chronic urticaria unresponsive to omalizumab + high-dose sgAH.

### MATERIALS AND METHODS

#### Patients

Patients with chronic urticaria who were treated with methotrexate due to partial response or nonresponse to high-dose (4 doses/day) sgAH+omalizumab therapy between 2019 and 2020 were included in the study. Urticaria type based on chronic urticaria classification, age at disease onset, duration of urticaria episodes before methotrexate therapy (months), treatment before methotrexate therapy, 7-day urticaria activity score (UAS7) before and after treatment, and total IgE were recorded. Clinical data of all patients included in the study were collected in face-to-face interviews with the same allergist. The study was approved by the ethics committee of the Near East University Faculty of Medicine (Ethics committee no: YDU/2020/80-1126).

#### Treatment Protocol

Patients with partial response or no response despite omalizumab (3 times, 300 mg/monthly) +high dose antihistamine for at least 3 months were considered as refractory.

For patients who showed a partial response to regular high-dose sgAH+ omalizumab therapy,

methotrexate (15 mg, once a week, subcutaneous) was added to their existing treatment. If patients showed no response to at least 3 months of high-dose sgAH+omalizumab therapy, methotrexate was initially administered together with sgAH. SgAH was discontinued in patients with a complete response and was reinitiated if there was urticaria recurrence after cessation.

Throughout treatment, all patients received 5 mg/day of folic acid orally.

#### Treatment Response

Treatment response was determined according to UAS7 and clinical findings. UAS7=0 was accepted as a complete response; UAS7=1-6 as a well-controlled response; UAS7=7-27 and/or less severe but persistent urticaria as a partial response; and UAS7=28-42 and/or no reduction in urticaria severity or continuing need for systemic glucocorticoids to suppress urticaria as nonresponsive.

#### Adverse Effects

At follow-up visits, all patients receiving methotrexate were asked if they had any problems related to the drug. Before initiating treatment, hepatitis markers (anti-HCV, HBsAg, anti-HBS), chest x-ray, and routine blood samples including complete blood count, liver and kidney function tests including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, urea, creatinine, and blood glucose were analyzed. All blood tests except hepatitis serology were repeated 2 weeks after starting methotrexate therapy. Patients were reevaluated every month and blood tests were repeated monthly.

#### Statistics

Continuous variables are reported as mean±standard deviation (SD). Categorical data are reported as numbers and percentages. C-reactive protein (CRP) concentrations were dichotomized as >5.0 and ≤5.0 mg/L and IgE concentrations as >100 mg/dl and ≤100 mg/L for comparisons. The skin prick test was considered positive if there was aeroallergen sensitivity. Statistical significance was set at  $p<0.05$ . Data were analyzed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY).

## RESULTS

A total of 10 patients with partial or nonresponse to omalizumab (300 mg monthly) + high-dose sgAH therapy were included in the study. The mean age was  $44.6 \pm 11.5$  (31–65) years, and 9 (90%) of the patients were female. All patients had chronic spontaneous urticaria. Age at disease onset, duration of disease before treatment, previous treatment, UAS7 before and after treatment, and total IgE levels of the patients are shown in detail in Table 1.

Four of the patients were previously treated with cyclosporine. Methotrexate was administered as monotherapy to 4 patients (40%) and given as part of combination therapy in the other 6 patients (60%). Of the 6 patients that received combination therapy, 3 received sgAH + methotrexate, 2 received omalizumab + methotrexate, and 1 received sgAH + omalizumab +

methotrexate. Details regarding the patients' previous treatment, final treatment, and treatment response are presented in Table 1.

All patients received subcutaneous methotrexate at a dose of 15 mg once a week; in 1 patient, the dose was temporarily increased to 20 mg and returned to 15 mg. The mean duration of methotrexate therapy was  $5.1 \pm 2.4$  months (1.5–9 months). Of the 10 patients, response to methotrexate monotherapy or combined therapy was complete response in 6 (60%) (Cases 2–7), a well-controlled response in 1 (10%) (Case 8), partial response in 1 (10%) (Case 1), and nonresponse in 2 (20%) (Cases 9 and 10). Methotrexate dose and treatment duration for each patient are given in detail in Table 1.

There was a slight elevation in liver function tests in 1 patient (10%) (Case 10), who was also unresponsive to methotrexate therapy.

**Table 1. Demographic, laboratory, and clinical characteristics of the 10 chronic spontaneous urticaria patients included in the study**

Case	Sex/Age at CSU onset, years	Pre-MTX urticaria duration, months	Initial UAS7	IgE, IU/ml	Previous treatment	OMA treatment duration before MTX, months	Previous treatment response	Final treatment	MTX treatment duration, months / dose, mg	Final treatment response	Final UAS7
1	M/65	12	42	869	OMA + C(250) + sgAH(4)	13	PR	OMA+MTX +sgAH(4)	6.5/15	PR	10
2	F/41	24	42	-	OMA + C(200) + sgAH(4)	11	PR	OMA+MTX	2/15	CR	0
3	F/36	1	42	155	OMA+C(200) +sgAH(4)	6	PR	OMA + MTX	8.5/15	CR	0
4	F/59	8	42	4	OMA + C(200)	8	NR	MTX	5.5/15	CR	0
5	F/31	2	28	6	OMA + sgAH(4)	3	NR	MTX	3/15	CR	0
6	F/54	12	-	-	OMA + sgAH(4)	6	NR	MTX	6/15	CR	0
7	F/34	3	42	-	OMA + sgAH(4)	3	NR	MTX	7/15	CR	0
8	F/25	6	42	1283	OMA + sgAH(4)	5	NR	MTX+sgAH (2)	9/15	WCR	5
9	F/45	20	42	377	OMA + sgAH(4)	21	NR	MTX+sgAH(4)	1.5/15	NR	42
10	F/46	120	42	8	OMA + sgAH(4)	6	NR	MTX+sgAH (4)	1/15	NR	42

CSU: Chronic spontaneous urticaria, MTX: Methotrexate, OMA: Omalizumab, M: Male, F: Female, UAS7: 7-day urticaria activity score, NR: Nonresponse, PR: Partial response, WCR: Well-controlled response, CR: Complete response, sgAH: Second-generation antihistamine (dose, number/day), C: Cyclosporine (dose, mg).

Liver function tests were found elevated in case 10 in the blood analysis of the 4<sup>th</sup> week.

Another patient (case 5) showed a favorable clinical

response to the first injection but had urticaria recurrence before the next weekly injection. Therefore, the methotrexate dose was increased to 20 mg/week. In

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the first 2 days after injection at the higher dose, the patient experienced a burning sensation in the stomach, exacerbation of preexisting gastroesophageal reflux, vomiting, and diarrhea. Despite reducing the methotrexate dose back to 15 mg, there was no improvement in the gastrointestinal adverse effects, and treatment was discontinued. The other 8 patients (80%) exhibited no adverse effects.

### DISCUSSION

The EAACI/GA<sup>2</sup>LEN/EDF/WAO international chronic urticaria guideline states that there is low-quality evidence for methotrexate as a treatment for chronic urticaria. Although there have been very few studies on the efficacy and safety of methotrexate in antihistamine-refractory chronic urticaria, the results of these studies support the use of methotrexate in this patient group.<sup>7,8</sup> As omalizumab is not adequately effective in a third of patients with chronic urticaria and cyclosporine has a high adverse effect rate, methotrexate may be a good alternative to cyclosporine for the treatment of chronic urticaria unresponsive to omalizumab. The present study is the first evaluation of the efficacy and safety of methotrexate in chronic urticaria nonresponsive to omalizumab + sgAH therapy.

Our results indicate that methotrexate was helpful for 70% of patients with chronic urticaria who are unresponsive to omalizumab + sgAH or omalizumab + sgAH + cyclosporine combination therapies. Complete response or well-controlled response was observed in 70% of the patients and partial response was observed in 10%. These are promising results for these difficult-to-treat patients. In this study, methotrexate was used either as a monotherapy or in combination with sgAH and/or omalizumab. Monotherapy was effective in 4 patients (cases 4-7). One patient (case 5) had no complaints about the first 5 days after methotrexate administration but experienced an urticaria exacerbation 2 days before the next injection. Complete response was observed within 2 weeks of increasing the methotrexate dose to 20 mg, but the dose was reduced back to 15 mg due to gastrointestinal adverse effects. Although there was no urticaria recurrence after dosage reduction, treatment was discontinued because the patient could not tolerate the gastrointestinal adverse effects. The other 7 patients who responded to treatment tolerated methotrexate very well. Four (40%)

(Cases 1-4) of the 10 patients included in the study had been treated previously with cyclosporine. Of these 4 patients who were unresponsive to cyclosporine, 3 (Cases 2-4) showed complete response to methotrexate monotherapy or combination therapy. The effect of methotrexate therapy was observed within the first 4 weeks in all patients.

In a retrospective study by Sagi et al, 15 mg methotrexate was administered orally or intramuscularly once a week to 8 chronic urticaria patients unresponsive to high-dose antihistamine therapy. While 7 of these 8 patients showed a complete response to methotrexate, 1 was unresponsive. One of these 7 patients who responded completely to methotrexate did so after the dose was increased to 25 mg. One patient showed a slight elevation in liver function test results during treatment which normalized when the methotrexate dosage was decreased. Methotrexate was effective within the first 4 weeks.<sup>7</sup> The results of that study are similar to ours in terms of efficacy and adverse effects. In our study, methotrexate was slightly less effective, which may be attributed to the difference in patient populations. Urticaria was more severe in our patient group. The patients included in our study were not only unresponsive to sgAH, but also to combination therapies including drugs that are very effective in chronic urticaria (omalizumab + sgAH or omalizumab + sgAH + cyclosporine). Perez et al. retrospectively evaluated the efficacy of methotrexate in 10 chronic urticaria and 2 isolated angioedema patients. All patients included in that study were unresponsive to at least 2 of the following: antihistamine, azathioprine, colchicine, montelukast, sulfasalazine, doxepin, dapsone, intravenous immunoglobulin, and cyclosporine. Of the 10 patients with chronic urticaria, 9 were unresponsive to cyclosporine treatment. The patients were given 5–25 mg methotrexate once a week. Under methotrexate therapy, urticaria symptoms regressed with no change in steroid dose in 3 patients, urticaria symptoms regressed with reduced steroid dose in 4 patients, urticaria resolved with steroid cessation in 1 patient, and no response was observed in 2 patients. While 1 of the 2 patients with angioedema was unresponsive to methotrexate, both angioedema severity and steroid dose decreased in the other patient. Methotrexate was well-tolerated by all patients. Hair thinning and fatigue were observed as adverse effects.<sup>8</sup> The patient population of this study comprised patients with severe

urticaria, similar to our study. Although the effectiveness of methotrexate was lower than our results, of these 12 patients, disease activity decreased in 8 patients (66.6%), complete response was achieved in 1 patient (8.3%), need for steroids was reduced in 5 patients (41.6%), and steroid therapy was discontinued in 1 patient (8.3%). Methotrexate was safely tolerated by all patients.

The EAACI/GA<sup>2</sup>LEN/EDF/WAO international chronic urticaria guideline recommends cyclosporine as the first choice in patients unresponsive to omalizumab + high-dose sgAH therapy.<sup>3</sup> Although there are studies in the literature demonstrating the efficacy of cyclosporine in chronic urticaria refractory to high-dose antihistamines, the incidence of adverse effects is high.<sup>4,5</sup> In a study investigating the efficacy of cyclosporine in chronic urticaria, treatment was discontinued due to adverse effects in 20 (16.5%) of 120 patients. A review on the same topic showed that adverse effects were reported in 57% of patients who received a moderate dose of cyclosporine.<sup>5</sup>

In conclusion, methotrexate, either as monotherapy or in combination with sgAH and/or omalizumab, seems to be a beneficial treatment option for patients with chronic urticaria refractory to omalizumab + sgAH treatment. In patients who partially respond to omalizumab + sgAH treatment, methotrexate can be added to the existing treatment regimen. In patients unresponsive to omalizumab, methotrexate can be administered either in combination with sgAH or as monotherapy, depending on treatment response. Our results indicate that methotrexate can be effective as monotherapy or combination therapy even in patients who are unresponsive to omalizumab and cyclosporine. Moreover, since methotrexate has a much better safety profile than cyclosporine, methotrexate offers an alternative to cyclosporine for patients unresponsive to omalizumab + sgAH therapy. Further studies with larger patient series and more real-life data are necessary to corroborate these findings.

#### CONFLICT OF INTEREST

The author has no conflict of interest.

#### ACKNOWLEDGEMENTS

None

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