

Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids

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Abstract

Background Urticarial patients are usually treated with oral antihistamines and 50% respond well to this treatment; however, the other 50% do not respond to antihistamines and need a more aggressive approach, such as short or prolonged courses of oral corticosteroids or cyclosporine. Potential adverse effects, however, limit this regimen.

Objective To determine the efficacy of mycophenolate mofetil, an immunomodulatory drug, in the treatment of patients with severe chronic urticaria.

Methods In an open-label, uncontrolled trial, nine patients with documented chronic urticaria who had been treated previously with antihistamines and/or corticosteroids with poor response were enrolled in the trial. After 2 weeks of baseline assessment, patients received 1000 mg twice daily of mycophenolate mofetil for 12 weeks. Improvement was monitored using the urticarial activity score, which is the sum of the wheal number score and itch severity score. Patients also recorded their daily need for other medications to control allergic symptoms.

Results There was a significant decrease in the urticarial activity score relative to the baseline assessment at the end of the study period ($P < 0.001$). All patients were able to stop prednisone on completion of the study. There was also a decrease in antihistamine dose, but this did not reach statistical significance. Treatment with mycophenolate mofetil was not associated with significant adverse effects.

Conclusions Mycophenolate mofetil may be a valuable and safe treatment for patients with chronic urticaria who do not respond to antihistamines and/or corticosteroids, and who require aggressive treatment to control their disease symptoms. Further controlled clinical studies are needed to determine its value.

Introduction

Chronic idiopathic urticaria (CIU) is one of the most common and frustrating diseases for both patients and physicians. Most patients have self-limited disease with a duration of less than 6 weeks; however, 50% of patients continue to suffer from urticaria beyond 6 months, and 20% continue with the disease for more than 10 years.¹ In most cases, no etiologic agent can be identified.² In recent years, an autoimmune process has been described in 30–50% of patients with treatment-resistant CIU, and autoantibodies against the high-affinity immunoglobulin E (IgE) receptor or IgE have been detected in the serum of most of these patients.³

Urticarial patients are treated with oral antihistamines and 50% respond well to this treatment;⁴ however, 50% do not respond to antihistamines and require a more aggressive approach, such as short or prolonged courses of oral

corticosteroids⁵ or cyclosporine.⁶ In addition, other immunomodulating drugs have been tested in CIU patients, including hydroxychloroquine, dapsone, sulfasalazine, intravenous immunoglobulins, and methotrexate.⁷ Other modalities of treatment, such as combinations of H₁ and H₂ antihistamines,⁸ antidepressants, and hormonal drugs,⁹ have been used with very poor clinical response. In recent years, several studies have demonstrated the efficacy of antileukotriene drugs in CIU patients.¹⁰

Despite the large number of different agents used to control the symptoms of CIU, they are often insufficient, and there is a need for the addition of high doses of corticosteroids alone or combined with other agents. Potential adverse effects limit these regimens. More effective drugs are needed to treat these patients.

Mycophenolate mofetil (MM) is an immunosuppressive agent that has been used for several years in the prophylactic

treatment of transplant recipients and in a few autoimmune conditions.¹¹ A few reports have shown the efficacy of oral MM in the treatment of atopic dermatitis,^{12,13} psoriasis,¹⁴ urticarial vasculitis,¹⁵ and other skin disorders,¹⁶ but not in CIU. Considering the effectiveness of MM in the above-mentioned conditions, and the lack of significant adverse effects, we decided to conduct an open-label study to evaluate the efficacy of oral MM in the treatment of patients with severe CIU unresponsive to conventional therapy.

Methods

Patients were recruited from the Allergy and Dermatology Clinics at Rambam Medical Center, Haifa, Israel. All patients had suffered from severe CIU for over six consecutive weeks not responding adequately to antihistamines and/or more than two short cycles of oral prednisolone given for at least 1 week during the last 2 months prior to the initiation of the study. Patients with physical urticaria, urticarial vasculitis, C1 esterase inhibitor deficiency, pharmacologic urticaria, or urticaria induced by any other known cause, and patients with a history of atopic diseases, were excluded from the study. Pregnant women without medically approved contraception, lactating women, and patients with any chronic infection, known malignancy, hepatic, psychiatric, endocrine, or other systemic disease were also excluded.

All patients signed an informed consent. They completed a 2-week baseline assessment (week -2, week -1), which included a skin test to common environmental aeroallergens, food allergens, and autologous serum, as described previously,¹⁷ and began to take MM, 1000 mg twice daily (week 0), for 12 weeks. They visited the clinic every 2 weeks (weeks 2, 4, 6, 8, 10, and 12) and recorded daily the urticarial activity score, which is the sum of the wheal number score and itch severity score, as described previously.¹⁷ Patients also recorded the number of antihistamines and oral prednisone tablets they took per week during both the 2-week baseline assessment and study period.

Baseline investigations in all patients included complete blood count, erythrocyte sedimentation rate, biochemical profile, antinuclear antibody, and C4 component of complement (as a screen for C1 esterase inhibitor deficiency). Laboratory tests to evaluate for potential adverse effects were performed monthly, and included complete blood counts, renal and hepatic function tests, serum lipase, serum amylase, blood glucose, serum electrolytes, and routine urinalysis.

Physical examination was performed at each visit, with special consideration and awareness of fever or other signs of infection and signs/symptoms of persistent gastrointestinal intolerance (unrelenting diarrhea, nausea, or vomiting), to monitor for any possible adverse effects of MM.

The patients were instructed to take oral antihistamines as needed to control symptoms and to include details in their daily record.

The study was approved by the ethics committee of Rambam Medical Center, Haifa, Israel.

Table 1 Baseline patient characteristics

Number	9
Female/male	5/4
Mean age (years)	42.8 (median, 42; range, 32–52)
Duration (months)	43.6 (median, 42; range, 18–72)
ASST positivity	9 (100%)
Previous treatment	
H1 blocker only	9
H1 and H2 blocker	9
H1 and H2 blocker, prednisone	9

ASST, autologous serum skin test.

Changes in the urticarial activity score and antihistamine and oral corticosteroid doses between the baseline assessment period and treatment period were compared by the Wilcoxon signed-rank test for paired data and paired *t*-test. All statistical tests were two-tailed, and a *P* value of less than 0.05 was considered to be statistically significant.

Results

The study population consisted of nine adult patients (five women and four men), aged 32–52 years (mean $\pm$ SD, 42.8 $\pm$ 7 years), with a mean urticaria duration of 43.6 $\pm$ 19.1 months. All patients had been treated previously with different regimens, including antihistamine alone or in combination with repeated courses of oral corticosteroids (see Table 1). Baseline laboratory investigations were within normal limits. The autologous serum skin test was positive in all patients and the skin test to environmental aeroallergens and food allergens was negative.

Patient compliance was excellent and all patients completed the study according to the protocol. No adverse side-effects and no laboratory test abnormalities were found during the study period.

There was a significant improvement in the individual urticarial activity score at the end of the treatment period (week 12) ($P < 0.001$) relative to the baseline assessment (week -2, week -1) (Fig. 1). After 6 weeks of MM treatment, the wheal and itching scores were reduced significantly ($P < 0.004$ and $P < 0.002$, respectively) (Fig. 2).

There was also a statistically significant decrease in the mean weekly oral prednisone dose after 4 weeks of treatment relative to the baseline assessment period ($P < 0.028$). All patients stopped taking oral prednisone at the end of the study (Fig. 3). With regard to the weekly intake of antihistamine tablets, there was a non-statistically significant decrease at the end of the study period relative to the baseline assessment ($P < 0.066$) (Fig. 4).

Six months after concluding the study, there was no rebound in the urticaria and patients continued to be asymptomatic.

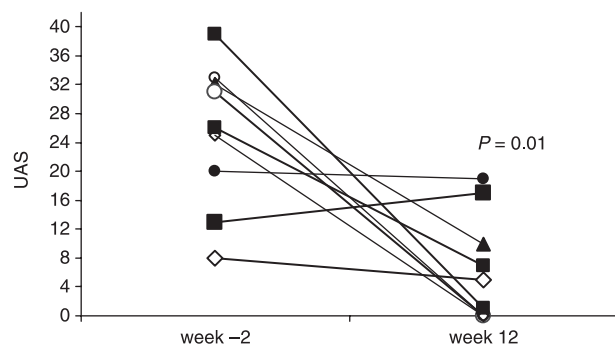


Figure 1 Total individual urticarial activity score (UAS) during baseline assessment and the treatment period

Discussion

In this study, we have shown that treatment with MM significantly reduced active urticarial symptoms in a small population of patients with severe chronic autoimmune urticaria. In addition, MM was demonstrated to be a steroid-sparing medication. Patients in this study had been treated previously with repeated courses of oral corticosteroids, and all were able to stop taking oral corticosteroids after treatment with MM. We also demonstrated a decrease in the number of antihistamine tablets taken by patients to control urticarial symptoms, although the results were not statistically significant. This non-significant reduction may be explained in part by the reluctance of patients to stop taking antihistamines. No adverse effects or laboratory abnormalities were observed in patients treated with MM during the study period.

MM acts as a reversible inhibitor of inosine monophosphate dehydrogenase, which is unique to lymphocytes and is involved in the synthesis of purines. Lymphocytes require purine synthesis for proliferation, and MM reversibly blocks the *de novo* synthesis of guanine nucleotides for DNA and RNA synthesis.¹¹ Therefore, it acts as a selective antimetabolite for

lymphocytes and affects *in vitro* T- and B-cell proliferation. MM also reduces the expression of adhesion molecules on endothelial cells and inhibits the invasion of leukocytes into the skin.¹¹

We suppose that MM may be effective in urticaria by inhibiting the production of autoantibodies to the high-affinity IgE receptor and/or IgE,¹¹⁻¹⁸ and also by reducing the expression of adhesion molecules on endothelial cells, and thereby inhibiting the invasion of leukocytes into the skin.

One-half of patients with CIU respond well to antihistamines. In unresponsive patients, different treatment modalities are available, but their efficacy is limited by adverse effects. Long-term therapy with oral corticosteroids is associated with many known adverse effects, such as diabetes mellitus, hypertension, osteoporosis, and gastrointestinal bleeding. Thus, the corticosteroid dose must be kept as low as possible.⁵ Low doses of cyclosporine have been shown to be effective, but potentially serious adverse effects limit its administration to patients with severe unremitting urticaria.⁶

MM is safe compared with other immunosuppressive agents. The principal adverse effects reported in transplanted patients were infections (especially cytomegalovirus), gastrointestinal tract symptoms (e.g. nausea, dyspepsia, vomiting, and diarrhea), and hematologic side-effects (e.g. anemia and thrombocytopenia). These side-effects were seen in transplanted patients treated with high doses (more than 2 g daily), and receiving MM as part of a combination immunosuppressive regimen. An increased rate of malignancy has not been observed in patients treated with MM.¹¹

When MM was used in different clinical entities as a single immunosuppressive agent (not as in transplant patients), at doses of 2 g daily or less, only mild gastrointestinal symptoms were observed.¹¹

In conclusion, to the best of our knowledge, our study is the first to use MM to treat patients with CIU. Our data demonstrate a dramatic improvement in the urticarial activity score, a decrease in the number of antihistamine tablets taken to

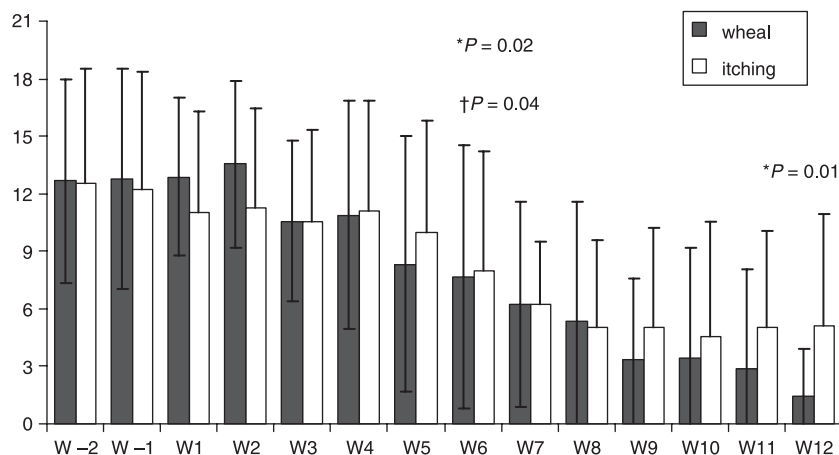


Figure 2 Mean baseline wheal score (week 6: * $P = 0.02$; week 12: * $P = 0.01$). Mean baseline itching score (week 6: † $P = 0.04$)

Figure 3 Mean prednisone (mg per week) per patient during baseline assessment and the treatment period (week 6: $P = 0.028$)

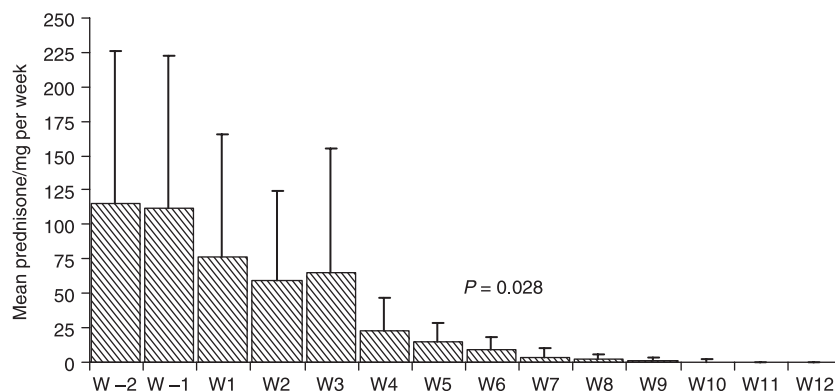
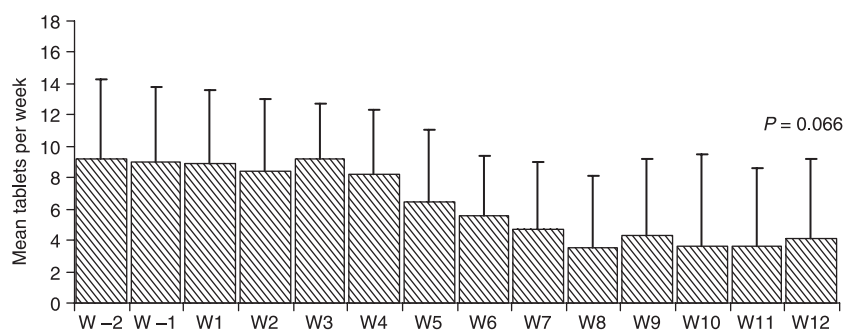


Figure 4 Mean weekly antihistamine tablets (number per patient) during baseline assessment and the treatment period (week 12: $P = 0.066$)



control symptoms, corticosteroid sparing, and an absence of adverse effects. Nevertheless, as this is a small, open-label, uncontrolled trial, it should be confirmed by larger controlled trials.

References

- O'Donnell BF, Lawlor F, Simpson J, *et al.* The impact of chronic urticaria on quality of life. *Br J Dermatol* 1997; **136**: 553–556.
- Middleton's Allergy: Principle and Practice, 6th edn. Mosby: Elsevier, 2003; 1551–1559.
- Greaves MW. Pathophysiology of chronic urticaria. *Int Arch Allergy Appl Immunol* 2002; **127**: 3–9.
- Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. *Br J Dermatol* 1998; **138**: 635–638.
- Kaplan AP. Chronic urticaria and angioedema. *N Engl J Med* 2002; **946**: 175–179.
- Grattan CEH, O'Donnell BF, Francis DM, *et al.* Randomized double-blind study of cyclosporine in chronic idiopathic urticaria. *Br J Dermatol* 2000; **143**: 365–372.
- Tedeschi A, Airaghi L, Lorini M, *et al.* Chronic urticaria: a role for newer immunomodulatory drugs? *Am J Clin Dermatol* 2003; **4**: 297–305.
- Simons FE, Sussman GL, Simons KJ. Effect of the H₂-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H₁-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. *Allergy Clin Immunol* 1995; **95**: 685–693.
- Cusack C, Gorman DJ. Role of thyroxine in chronic urticaria and angio-oedema. *J R Soc Med* 2003; **96**: 571.
- Saini SS. Addition of zafirlukast to cetirizine in the treatment of chronic urticaria. *Curr Allergy Asthma Rep* 2004; **4**: 262.
- Moder KG. Mycophenolate mofetil: new applications for this immunosuppressant. *Ann Allergy, Asthma, Immunol* 2003; **90**: 15–19.
- Hansen ER, Buus S, Deleuran M, *et al.* Treatment of atopic dermatitis with mycophenolate mofetil. *Br J Dermatol* 2000; **143**: 1324–1326.
- Neuber K, Schwartz I, Itschert G, *et al.* Treatment of atopic eczema with oral mycophenolate mofetil. *Br J Dermatol* 2000; **143**: 385–391.
- Geilen CC, Tebbe B, García-Bartels C, *et al.* Successful treatment of erythrodermic psoriasis with mycophenolate mofetil. *Br J Dermatol* 1998; **138**: 1101–1102.
- Worm M, Sterry W, Kolde G. Mycophenolate mofetil is effective for maintenance therapy of hypocomplementaemic urticarial vasculitis. *Br J Dermatol* 2000; **143**: 1324.
- Nousari HC, Sragovich AS, Kimyai-Asadi A, *et al.* Mycophenolate mofetil in autoimmune and inflammatory skin disorders. *J Am Acad Dermatol* 1999; **40**: 265–268.
- O'Donnell BF, Barr RM, Black AK, *et al.* Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **138**: 101–106.
- Sabroe RA, Grattan CE, Francis DM, *et al.* The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**: 446–452.