

ORIGINAL ARTICLE

The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: Experience in 19 patients

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Background: There is a paucity of investigation on which to base the treatment of chronic urticaria after a patient fails maximum therapy with antihistamines. One prospective, open-label, uncontrolled study suggested that mycophenolate mofetil may be a successful second-line therapy.

Objective: We sought to evaluate the efficacy and safety of mycophenolate mofetil in 19 patients with autoimmune and chronic idiopathic urticaria.

Methods: In a retrospective chart review, records of patients with autoimmune and chronic idiopathic urticaria who were evaluated between 2001 and 2009 were analyzed.

Results: Improvement in urticaria was observed in 89% of patients, specifically 91% of patients with autoimmune urticaria and 88% with chronic idiopathic urticaria. Time to initial improvement ranged from 1 to 9 weeks. In 59% of these patients, complete control of urticaria was achieved, which included 70% of patients with autoimmune urticaria and 43% with chronic idiopathic urticaria. Mean time to complete control was 14 weeks, with a range of less than 1 to 31 weeks. The dose of mycophenolate mofetil at complete control ranged from 1000 to 6000 mg divided twice daily. Mycophenolate mofetil was tapered in 7 of these 10 patients after an average of 7 weeks. Six of the 7 patients tapered then discontinued mycophenolate mofetil with remissions lasting between 2 and 16 weeks up to when the chart review ended. Mycophenolate mofetil was well tolerated with no serious infections or laboratory abnormalities. Gastrointestinal symptoms were most common.

Limitations: This was a retrospective chart analysis. The number of patients was relatively small.

Conclusions: Mycophenolate mofetil is a useful and well-tolerated second-line therapy for patients with autoimmune and chronic idiopathic urticaria in whom antihistamines and other therapeutic agents have failed. (J Am Acad Dermatol 10.1016/j.jaad.2011.06.004.)

Key words: angioedema; autoimmune urticaria; chronic idiopathic urticaria; hives; immunomodulators; mycophenolate mofetil; treatment.

Episodes of chronic urticaria, which persist for greater than 6 weeks, may be divided into autoimmune urticaria and chronic idiopathic urticaria.¹ Autoimmune urticaria is characterized by the presence of histamine-releasing IgG autoantibodies directed against IgE or the alpha subunit of

the high-affinity IgE receptor in patients with or without concomitant autoimmune conditions.²

For patients with chronic urticaria who are resistant to conventional management with antihistamines, the immunomodulatory agent mycophenolate mofetil has shown promise as an effective therapy. One

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Funding sources: None.

Conflicts of interest: None declared.

Accepted for publication June 2, 2011.

Reprints not available from the authors.

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Published online July 22, 2011.

0190-9622/\$36.00

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doi:10.1016/j.jaad.2011.06.004

prospective, open-label, uncontrolled trial demonstrated a favorable therapeutic response to mycophenolate mofetil in 9 patients with autoimmune urticaria, who were not controlled with antihistamines and systemic glucocorticoids.³ We present a retrospective chart review that describes our experience in 19 patients with autoimmune or chronic idiopathic urticaria, who were treated with mycophenolate mofetil.

METHODS

After approval from the institutional review board at New York University Langone Medical Center, a retrospective chart review of 140 patients with a diagnosis of autoimmune or chronic idiopathic urticaria, who presented to our institution between 2001 and 2009, was performed. Nineteen patients treated with mycophenolate mofetil were identified (13 women, 6 men). Eleven had autoimmune urticaria and 8 had chronic idiopathic urticaria. In 14 patients, a chronic urticaria test was performed on blood as a surrogate test to detect autoantibodies against IgE or the alpha subunit of the high-affinity IgE receptor. The CU Index (IBT Reference Laboratory, Lenexa, KS) and the Histamine Release (Chronic Urticaria) Test (Quest Diagnostics, San Juan Capistrano, CA) measure basophil histamine release, and the CD203c Test (National Jewish Health, Denver CO) measures up-regulated CD203c expression on basophils using flow cytometry.⁴⁻⁶ Serologic evaluation was not performed in 5 patients, who were included in the chronic idiopathic urticaria group.

Mycophenolate mofetil was initiated at a dose of 500 mg twice daily (BID) and titrated to a maximal effective dose by increments of 500 mg BID at intervals of 2 to 4 weeks. Improvement in urticaria was based on interviews and physical examinations that were performed during office visits. Improvement was indicated by a decrease in pruritus; duration and number of wheals; number of episodes of urticaria and angioedema; and systemic symptoms. Complete control was defined by the absence of urticaria, angioedema, and systemic symptoms. After complete control of urticaria for approximately 2 months, the dose of mycophenolate mofetil was tapered by 500 mg BID at intervals of every 2 to 4 weeks and, if possible, discontinued.

Laboratory monitoring during treatment included a complete blood cell count and chemistry profile with liver function tests obtained with each increase in dose of mycophenolate mofetil and approximately every 3 months when a stable dose was achieved.

RESULTS

Patients with chronic urticaria presented to our center at an average age of 45 years (median 44 years, range 12-77 years). The average age at diagnosis of urticaria and angioedema was 40 years (median 40 years, range 1-77 years).

Before initiating mycophenolate mofetil, none of the patients was controlled with multiple H1-receptor antagonists and the addition of H2-receptor antagonists in 10 of 19 patients. The majority of patients had been treated with additional alternative agents, which included leukotriene inhibitors (zileuton

in 9 patients, zafirlukast in two patients, and montelukast in 7 patients), colchicine in 9 patients, dapsone in 9 patients, sulfasalazine in one patient, doxepin in 9 patients, and systemic glucocorticoids in 7 patients.

Seventeen of 19 (89%) patients experienced improvement in urticaria with the use of mycophenolate mofetil, including 10 of 11 (91%) patients with autoimmune urticaria and 7 of 8 (88%) patients with chronic idiopathic urticaria. Of the patients who experienced improvement, 10 of 17 (59%) experienced complete control of urticaria, including complete control in 7 of 10 (70%) patients with autoimmune urticaria and 3 of 7 (43%) patients with chronic idiopathic urticaria.

The average dose of mycophenolate mofetil at initial improvement was 2150 mg daily, divided BID (median 2000 mg, range 1000-4000 mg). Range of time to initial improvement was 1 to 9 weeks (median 4 weeks, average 4 weeks).

In the 10 patients who achieved complete control, the average dose at complete control was 3800 mg, divided BID (median 4000 mg, range 1000-6000 mg). Range of time to complete control was less than 1 week (in a patient on concomitant prednisone) to 31 weeks (median 12 weeks, average 14 weeks). Complete control was maintained an average of

CAPSULE SUMMARY

- Few data guide the treatment of chronic urticaria after a patient fails maximum therapy with antihistamines.
- Nineteen patients with chronic autoimmune or idiopathic urticaria were treated with mycophenolate mofetil. Seventeen patients improved of which 10 achieved complete control. Gastrointestinal distress was a common side effect. There were no serious infections or laboratory abnormalities.
- Mycophenolate mofetil is a useful and safe second-line therapy for treating autoimmune and chronic idiopathic urticaria.

7 weeks (median 8 weeks, range 4-12 weeks). After complete control, the dose of mycophenolate mofetil was tapered in 7 of 10 patients. Regarding the 3 patients in whom mycophenolate mofetil was not tapered, one patient discontinued the medication and experienced a flare of urticaria, and two patients experienced subsequent flares of urticaria that thus prevented tapering and required initiating different therapy.

Mycophenolate mofetil was successfully discontinued in 6 of the 7 patients in whom it was tapered. The one patient who did not discontinue medication was controlled on 500 mg by mouth BID and was then lost to follow-up. The 6 patients who discontinued mycophenolate mofetil experienced remissions of between 2 and 16 weeks up to the time the chart review ended.

There were no laboratory abnormalities observed in the complete blood cell count and chemistry profile. The most frequent side effect was gastrointestinal intolerance, which was observed in 10 of 19 (53%) patients. The only infection was one episode of viral gastroenteritis.

DISCUSSION

H1-antihistamines are the most frequently used agents that are used in the treatment of urticaria and angioedema and are often therapeutically successful with or without the use of additional agents, which include H2-antagonists, leukotriene inhibitors, doxepin, nifedipine, colchicine, dapsone, hydroxychloroquine, sulfasalazine, systemic glucocorticoids, methotrexate, cyclosporine, mycophenolate mofetil, omalizumab, plasmapheresis, autologous whole blood, and intravenous immunoglobulin.⁷⁻²⁸ Few reports or controlled studies exist on which to base treatment after a patient fails maximal therapy with antihistamines.

Mycophenolate mofetil is an immunomodulatory agent approved by the Food and Drug Administration for the management of solid-organ transplant rejection and is used off-label to treat a variety of dermatologic conditions.^{29,30} Although the exact immunomodulatory mechanism of mycophenolate mofetil in chronic autoimmune and idiopathic urticaria remains unknown, undoubtedly there are multiple mechanisms.

In our retrospective review, 91% of patients with autoimmune urticaria and 88% of patients with chronic idiopathic urticaria who were treated with mycophenolate mofetil experienced improvement in urticaria and angioedema. Of these patients, 70% with autoimmune urticaria and 43% with chronic idiopathic urticaria achieved complete control of symptoms. Thus, mycophenolate mofetil may be a

remittive agent for some patients with chronic urticaria.

Mycophenolate mofetil was well tolerated. The most common side effects were mild gastrointestinal symptoms, which are consistent with other studies with this agent.^{29,30} Gastrointestinal side effects usually improve over time on therapy.³¹ No serious infections were observed. This finding is in contrast to some prior studies in dermatologic patients, in which herpes zoster or herpes simplex virus infections, herpes retinitis, cutaneous or systemic *Staphylococcus aureus* infections, and fungal infections were observed during treatment with mycophenolate mofetil.^{29,30} Similarly, no serious laboratory abnormalities were observed. There was no erythropenia, leukopenia, or thrombocytopenia, in contrast to prior reports of red cell aplasia in patients with renal transplantation treated with mycophenolate mofetil in whom dose reduction or cessation of the agent resulted in prompt resolution of the condition.³²

There is one prospective study in the literature on the use of mycophenolate mofetil in autoimmune urticaria.³ It was an open-label, uncontrolled trial in 9 patients, who were previously treated with antihistamines, glucocorticoids, or both. Patients received mycophenolate mofetil (1000 mg) by mouth BID for 12 weeks after which all patients had decreased urticaria and were able to discontinue systemic glucocorticoids. At the 6-month follow-up period, there were no recurrences in urticaria. The agent was well tolerated. All patients received the same dose of mycophenolate mofetil, thus their investigation did not determine a minimal effective dose for each patient. Furthermore, the study did not include patients with chronic idiopathic urticaria.

CONCLUSION

In our experience, as outlined in this retrospective review, mycophenolate mofetil is a useful and well-tolerated second-line therapy for patients with autoimmune and chronic idiopathic urticaria who have failed therapy with antihistamines or other therapeutic agents. Of 19 patients treated with mycophenolate mofetil at our center, 17 patients experienced improvement and 10 patients experienced complete control of urticaria. Improvement occurred at an average of 4 weeks and at a range of dose of 1000 to 4000 mg. Complete control occurred at an average of 14 weeks and at a range of dose of 1000 to 6000 mg. Prospective studies are needed to further delineate the use of mycophenolate mofetil for the use of chronic autoimmune and chronic idiopathic urticaria.

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