

Therapeutic Challenges in Chronic Spontaneous Urticaria

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Abstract

Chronic spontaneous urticaria (CSU) involves cutaneous symptoms of swelling, redness, and itching that persist for longer than 6 weeks. These episodes can continue for months or years, with a disease duration of 1 to 5 years on average. The prevalence of CSU is estimated to be 0.5% to 1%. Frequent recurring episodes of generalized urticaria and angioedema reduce the quality of life for those patients with CSU. Treatment with second-generation antihistamines is insufficient in 36.8% of patients, even at high doses. Although omalizumab (humanized anti-immunoglobulin IgE) is also indicated for the treatment of this condition and has been used to treat patients who are unresponsive to high-dose second-generation antihistamines, omalizumab therapy is ineffective in one-third of those cases. Therefore, the current conventional treatments, including omalizumab, still do not provide adequate relief for some patients with CSU. This review discusses the therapeutic challenges, off-label drug use, and combined drug therapies in CSU patients who do not respond to the current conventional drug therapy.

Cyclosporine and methotrexate may be beneficial in the management of CSU which is unresponsive to conventional treatments. The combined use of these drugs with conventional therapies may increase the effectiveness of the treatment in difficult-to-manage cases. Methotrexate may be an effective alternative to cyclosporine for those CSU patients who cannot tolerate cyclosporine due to its high incidence of adverse effects.

Keywords: Chronic urticaria, omalizumab, cyclosporine, methotrexate, treatment

INTRODUCTION

Chronic spontaneous urticaria (CSU) involves cutaneous symptoms of swelling, redness, and itching that persist for longer than 6 weeks. These episodes can continue for months or years, with a disease duration of 1 to 5 years on average. The prevalence of CSU in the population is estimated to be 0.5% to 1%, and it is more common in women. Although onset can occur at any age, it is more common between 20 and 40 years of age.¹ Therefore, it is generally a serious health problem for adults. In a substantial proportion of patients (33%–67%), urticaria is accompanied by angioedema. Frequently recurring episodes of generalized urticaria and angioedema impair the quality of life in patients with CSU.¹

Treatment of Chronic Urticaria

The recommended first-line treatment for CSU is second-generation antihistamines. Antihistamines are effective, inexpensive, and can be taken up to 4 times a day. However, a proportion of CSU patients do not respond to standard or high-dose antihistamines. A meta-analysis

of responses to antihistamine therapy in CSU showed that 38.6% of patients responded at standard doses and 63.2% of those who were unresponsive to the standard dose responded after up-dosing.²

For those patients who do not respond to antihistamine up-dosing, omalizumab (humanized anti-immunoglobulin IgE) is added to the treatment at a standard dose of 300 mg subcutaneously every 4 weeks.³ Despite the favorable safety profile of omalizumab, at the standard dose, it is also ineffective in approximately one-third of patients.⁴ For this reason, the search continues for new monoclonal anti-IgE antibodies which may be more effective in those CSU patients who do not respond to the available treatments.

Ligelizumab is another humanized recombinant monoclonal anti-IgE antibody, like omalizumab. However, as it has a 50-fold higher IgE binding capacity than omalizumab, ligelizumab more potently suppresses IgE-mediated mast cell degranulation.⁵ In a phase 2b trial of ligelizumab by Maurer et al.,⁶ patients received 3 different doses of ligelizumab (24 mg, 72 mg, and 240 mg) and omalizumab 300 mg at 4-week intervals.

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At the end of 12 weeks, a complete response was observed in 30%, 44%, and 40% (respectively) of those patients treated with ligelizumab and 26% of the patients treated with omalizumab. Although the frequency of adverse events was similar to that with a placebo and omalizumab, injection site reactions and injection site erythema were more common in those patients who received 72 mg and 240 mg ligelizumab. The efficacy of omalizumab was lower in that study than in many previous studies. In placebo-controlled phase III trials, 43%–48% of CSU patients who received omalizumab 300 mg every 4 weeks showed a complete response.⁷⁻⁹ The results of the phase III studies were later supported by real-life studies of omalizumab at standard doses (300 mg every 4 weeks). Complete response rates of 47.2% and 55.6% were reported in two different real-life studies of omalizumab.^{10,11} According to the results of the real-life studies^{10,11} and phase III trials,⁷⁻⁹ ligelizumab seems to have similar effectiveness to omalizumab in CSU. Head-to-head studies with large patient samples are needed to clarify whether ligelizumab will be more effective than omalizumab.

Off-Label Treatments for Chronic Urticaria

Other than second-generation antihistamines and omalizumab, no new drugs have been indicated for the treatment of chronic urticaria. Phase trials of ligelizumab are ongoing. There is a lack of consensus on how to treat those patients who do not respond to current conventional treatments due to the lower effectiveness and less favorable safety profiles of other drugs. However, there are a few articles about off-label drug use for CSU in the literature.¹¹⁻¹⁵ As described above, the four-tier treatment algorithm proposed in the EAACI/GA²LEN/EDF/WAO International Guideline on CSU recommends second-generation antihistamine (a single daily dose as a first-line therapy and up to 4 doses/day as a second-line therapy), followed by a combination of second-generation antihistamine and omalizumab as a third-line therapy. If these approaches fail, a combination of second-generation antihistamine and cyclosporine is recommended as a fourth-line therapy. Cyclosporine is the only drug recommended in the guideline for off-label use due to low-quality evidence supporting the efficacy of sulfasalazine, methotrexate, interferon, plasmapheresis, phototherapy, intravenous immunoglobulins, and other treatment options.³ There are literature data indicating that cyclosporine (3 mg/kg/day and 1–5 mg/kg/day) is effective in patients with antihistamine-refractory CSU,^{12,13} but there has been little research into the effectiveness and safety of cyclosporine in those patients who are unresponsive to omalizumab and high-dose second-generation antihistamine.¹¹ Cyclosporine is believed to act by directly suppressing mast cell mediator release.^{16,17} In a study by Kessel and Toubi¹², 120 patients who did not respond to second-generation antihistamines were started on 3 mg/kg/day cyclosporine and 20 (16.6%) of these patients discontinued treatment because of severe adverse effects (severe headache, peripheral neuropathy, abdominal pain and/or diarrhea). Of the 100 patients who received 3 months of cyclosporine treatment, complete response was observed in 30 patients (30%) and moderate response in 32 patients (32%). A review investigating the effectiveness of cyclosporine in a similar patient group showed that cyclosporine at low (2 to <4 mg/kg/day) and moderate (4–5 mg/kg/day) doses was effective for chronic urticaria unresponsive to antihistamine. One or more adverse events (headache, gastrointestinal symptoms, infection, hypertension, paresthesia, abnormal serum creatinine, and/or hirsutism) were observed in 23% of those taking low-dose cyclosporine and 57% of those taking moderate-dose cyclosporine.¹³ In a retrospective study, 12 patients who did not respond to omalizumab and high-dose second-generation antihistamine were

treated off-label with 2.5 mg/kg/day cyclosporine.¹¹ Six of these patients responded to cyclosporine; one of those patients used cyclosporine and omalizumab, one used cyclosporine and twice daily antihistamine, and four patients used cyclosporine alone. The other six patients terminated treatment due to nonresponse and/or severe adverse effects. Three of the patients (25%) did not respond to cyclosporine and five patients (41.6%) discontinued treatment because of severe adverse effects despite receiving low-dose (2.5 mg/kg/day) therapy. The high rate of cyclosporine-related adverse effects (hypertension, hyperlipidemia, hirsutism, gingival hypertrophy) was consistent with previous clinical studies.^{12,13} In summary, cyclosporine may be effective in some CSU patients who do not respond to the current conventional drug treatments, including omalizumab, and can be used off-label for the treatment of CSU with careful patient selection and close monitoring for adverse effects.

As with other drugs, cyclosporine is not sufficient to treat all CSU patients because of its serious adverse effects and/or lack of effectiveness. In the literature, there have been a few promising studies with small patient series suggesting that methotrexate is useful and safe in antihistamine-refractory or steroid-dependent chronic urticaria^{14,15} but again, there are few studies on the effectiveness and safety of methotrexate in those patients who are unresponsive to omalizumab and high-dose second-generation antihistamine.¹⁸ In a retrospective study by Sagi et al.¹⁴, 15 mg methotrexate was administered orally or intramuscularly once a week to eight chronic urticaria patients unresponsive to high-dose antihistamine therapy. Seven of these eight patients showed a complete response with methotrexate, while the other was unresponsive. One of the seven patients who responded completely with 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. Perez et al.¹⁵ retrospectively evaluated the efficacy of methotrexate in 10 chronic urticaria and two isolated angioedema patients. All patients included in that study were unresponsive to at least two of the following: antihistamine, azathioprine, colchicine, montelukast, sulfasalazine, doxepin, dapson, intravenous immunoglobulin, and cyclosporine. Of the 10 patients with chronic urticaria, nine 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 three patients, urticaria symptoms regressed with reduced steroid dose in four patients, urticaria resolved with steroid cessation in one patient, and nonresponse was observed in two patients. While one of the two 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, with mild adverse effects such as hair thinning and fatigue reported. In another retrospective study, subcutaneous methotrexate 15 mg/week was administered to 10 patients who did not respond to high-dose second-generation antihistamine and omalizumab and/or cyclosporine.¹⁸ Four of the patients had been previously treated with cyclosporine. The mean duration of methotrexate therapy was 5.1 months (1.5–9 months). Of these 10 patients, methotrexate monotherapy or combined therapy resulted in complete response in six (60%), a well-controlled response in one (10%), partial response in one (10%), and nonresponse in two patients (20%). Methotrexate was administered as monotherapy to four patients (40%) and given as part of combination therapy in the other six

patients (60%). Of the six patients who received combination therapy, three received second-generation antihistamine and methotrexate, two received omalizumab and methotrexate, and one received second-generation antihistamine, omalizumab, and methotrexate. There was a slight elevation in liver function tests in one patient (10%) who was also unresponsive to methotrexate therapy. Another patient discontinued treatment because she experienced a burning sensation in the stomach, exacerbation of preexisting gastroesophageal reflux, vomiting, and diarrhea. Despite encouraging results from small studies suggesting methotrexate may be safe and effective in CSU,^{14,15,18} methotrexate was found to have no benefit over the placebo according to a meta-analysis that included 104 patients in two placebo-controlled studies investigating the effectiveness of combined antihistamine and methotrexate in antihistamine-resistant CSU.¹⁹

Despite methotrexate having adverse effects and contradictory results, cyclosporine or methotrexate may be off-label treatment options for those CSU patients who do not respond to monoclonal antibody therapy and high-dose second-generation antihistamines.

The literature contains mostly monotherapy drug studies in CSU. Few studies have examined responses to combined therapy.^{11,20} However, in real life, these drugs are used in combination to treat chronic urticaria. Cyclosporine or methotrexate can be used as monotherapies or in combination with omalizumab and second-generation antihistamines. In a clinical trial including 21 CSU patients who were nonresponsive to omalizumab (300 mg every 4 weeks) and cyclosporine (3 mg/kg/day), after 4 months of receiving the drugs in combination the response rate increased to 76.1% with no increase in adverse effects.²⁰ In another retrospective study, 126 patients in a chronic urticaria drug trial were treated with omalizumab (300 mg every 4 weeks), second-generation antihistamine (1–4 doses/day), cyclosporine (2.5 mg/kg/day), and methotrexate (15 mg/week) alone or in combination on a case-by-case basis (omalizumab monotherapy in 70.6%, combined therapy in 25.4%, and cyclosporine or methotrexate monotherapy in 4% of patients), and complete response was reported in 77.8% of these patients, well-controlled response in 18.3%, partial response in 3.2%, and nonresponse in 0.8% of the patients.¹¹ This study provided evidence that combined drug use may be much more effective than monotherapy in CSU.

CONCLUSION

Methotrexate, either as monotherapy or in combination with second-generation antihistamine and/or omalizumab, seems to be a beneficial treatment option for patients with chronic urticaria refractory to omalizumab with second-generation antihistamine treatment. In those patients who partially respond to omalizumab and second-generation antihistamine treatment, methotrexate can be added to the existing treatment regimen. In those patients unresponsive to omalizumab, methotrexate can be administered either in combination with second-generation antihistamine or as monotherapy, depending on treatment response. 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 those patients unresponsive to omalizumab and second-generation antihistamine. Further studies with larger patient series and more real-life data are necessary to corroborate these findings.

MAIN POINTS

- CSU is characterized by episodes of skin redness, swelling, and itching which last for more than 6 weeks. CSU can last for many years, with its average duration being 1–5 years, and it affects between 0.5% and 1% of the population.
- At present, second-generation antihistamines and omalizumab (humanized anti-immunoglobulin IgE) are widely used in the treatment of CSU.
- For those patients who do not respond to antihistamine up-dosing, omalizumab (300 mg every 4 weeks, subcutaneous) is added to the treatment.
- Omalizumab is ineffective in one-third of patients treated at the standard dosage.
- Cyclosporine or methotrexate can be used in combination with omalizumab and second-generation antihistamines or as a monotherapy.

ETHICS

Peer-review: Externally peer-reviewed.

DISCLOSURES

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