Original Article

The Comparative Safety of Multiple Alternative Agents in Refractory Chronic Urticaria Patients

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What is already known about this topic? Certain alternative agents such as omalizumab and cyclosporine have been studied with reported safety profiles at doses used in chronic urticaria. Safety of other agents has been reported, but to a lesser degree.

What does this article add to our knowledge? The use of alternative agents in chronic urticaria is generally safe with proper laboratory and clinical monitoring.

How does this study impact current management guidelines? This study further adds to the body of literature supporting the relatively low risk of alternative agents used for chronic urticaria in patients who have failed treatment with steps 1 through 3 as recommended by the current Urticaria Practice Parameters.

BACKGROUND: Patients who have failed traditional treatment of chronic urticaria may require trials of alternative medications. Safety profiles, continuous laboratory monitoring, and physician comfort are often barriers to treatment.

OBJECTIVES: To evaluate the safety of alternative agents used in chronic urticaria.

METHODS: A retrospective chart review of electronic medical records from a single-center allergy and immunology clinic in a major academic hospital was conducted. One hundred twenty-six charts of patients with chronic urticaria treated with alternative agents were reviewed.

RESULTS: Adverse effects were reported in 39 of 73 (53%) patients on dapsone, 19 of 47 (40%) patients on sulfasalazine, 15 of 36 (42%) patients on tacrolimus, 7 of 45 (16%) patients on hydroxychloroquine, 9 of 27 (33%) patients on mycophenolate, 6 of 8 (75%) patients on cyclosporine, and 3 of 24 (4%) patients on omalizumab. Most of these adverse effects were mild, did not require discontinuation of the medication, and resolved after stopping the medication or decreasing the dose.

CONCLUSIONS: The use of alternative agents for the treatment of chronic urticaria angioedema is generally safe when proper laboratory and clinical monitoring is observed. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

Key words: *Chronic urticaria; Angioedema; Alternative agents; Dapsone; Sulfasalazine; Hydroxychloroquine; Tacrolimus; Mycophenolate*

Continuous or intermittent urticaria for a period of at least 6 weeks is termed *chronic urticaria* (CU).[1] Patients with CU incompletely managed on high-dose antihistamines who have failed step 3 therapy as defined by the 2014 Urticaria Practice Parameters are often referred to as suffering from refractory urticaria.[1] Although these patients may benefit symptomatically from systemic steroid use, their long-term use is not recommended because of the adverse effects (AEs) of long-term use.[1] There are multiple alternative agents for patients with refractory urticaria with varying degrees of evidence. Practitioners tend to shy away from these lesser-used medications for numerous reasons such as physician knowledge, prescribing comfort, patient comorbidities, frequent laboratory monitoring, and concern for safety. Although many studies have focused on the effectiveness of specific alternative agents, there is little information on the comparative safety of multiple alternative agents with refractory CU. Therefore, we sought to review our experience with alternative agents in a population of patients with refractory CU focusing on both subjective and objective AEs.

METHODS

With institutional review board approval, electronic medical records from a single provider practicing allergy and immunology at the University of Texas Medical Center were queried for all patients treated with dapsone, sulfasalazine, methotrexate, colchicine, cyclosporine, tacrolimus, mycophenolate, omalizumab, and intravenous immunoglobulin from January 1, 2001, to April 22, 2014. Two hundred seventeen charts were retrospectively reviewed. One hundred twenty-six patients were found to meet inclusion criteria, which included physician-diagnosed CU, treatment with an alternative

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Abbreviations used
AE- Adverse effect
CIU- Chronic idiopathic urticaria
CU- Chronic urticaria
GI- Gastrointestinal
WBC- White blood cell

agent for CU, and 18 years or older at the time of treatment with an alternative agent. Exclusion criteria included charts lacking sufficient documentation of follow-up and treatment with an alternative agent for indications other than CU.

Charts were reviewed for demographic information, maximally achieved dose of alternative agent, duration of medication at any dose, response to therapy, steroid dependency and ability to discontinue or decrease steroid dose, patient-reported AEs, physician-noted AEs, dose adjustments, and laboratory abnormalities. *Steroid dependency* was defined as daily oral steroids, or frequent recurrent oral steroid courses for at least 3 months. For patients initiated on alternative agents, blood pressure, dosing, baseline laboratories such as complete blood cell counts, basic metabolic panels, urinalysis, glucose-6-phosphate dehydrogenase, and monitoring laboratories as appropriate were obtained as in accordance with the Practice Parameters and additional literature.[2,3]

RESULTS

A review of 217 patient charts revealed 126 patients who met inclusion criteria. Demographics data are reported in Table I for the 126 patients. Twenty-five patients were treated with more than 1 alternative agent at a time. Different combinations used are listed in Table E1 in this article's Online Repository at www.jaci-inpractice.org. Patients with concurrent urticarial vasculitis and physical urticarias were included. Average dose, duration and AEs for the most common alternative agents are shown in Table II.

Dapsone

Seventy-three patients were treated with dapsone a total of 84 times. A total of 39 patients reported AEs. The most common AE was a predictable asymptomatic drop in hemoglobin level, defined by a drop of at least 5% from baseline. The average decrease in hemoglobin level was 19.2% (range, 9.61%-31.0%). Two patients experienced dyspnea on exertion from drops in hemoglobin level. Other AEs are reported in Table E2 in this article's Online Repository at www.jaci-inpractice.org. Six patients required dose adjustments with resolution of AEs. Dapsone was discontinued secondary to AEs in 4 patients, either by the patient or by the clinician. The most common AEs and reasons for discontinuation of dapsone and each proceeding medication are listed in Table III. Two patients had presumed methemoglobinemia based on dyspnea, palpitations, and nausea despite methemoglobin levels of less than 20%; this was considered a serious AE.

Sulfasalazine

Forty-seven patients were treated with a total of 51 courses of sulfasalazine. Nineteen patients reported AEs as described in Table E3 in this article's Online Repository at www.jaci-inpractice.org. Two patients required dose adjustments with resolution of their AE. Eight patients (17%) discontinued secondary to AEs of sulfasalazine, most commonly gastrointestinal (GI) disturbances. No serious AEs were reported.

TABLE I. Demographic characteristics of 126 patients with CU treated with alternative agents

Characteristic	Value
Mean age (y) (n = 126)	44 (18-69)
Sex (n = 126)	77% females, 23% males
Mean duration (range) of urticaria (mo)	44 (2-444)
Steroid dependent	78 patients (61%)
Able to stop or decrease oral steroids while treated with an alternative agent	58 patients (74%)
Chronic urticaria	102 patients
Urticarial vasculitis	6 patients
Physical urticarias*	28 patients
Other urticarias†	1 patient

*Delayed pressure urticaria (16 patients), symptomatic dermatographism (9 patients), cholinergic urticaria (1 patient), cold urticaria (1 patient), solar urticaria (1 patient).
†Autoimmune progesterone urticaria (1 patient).

Hydroxychloroquine

Hydroxychloroquine was used 51 times in 45 patients. Seven reported AEs are reported in Table E4 in this article's Online Repository at www.jaci-inpractice.org. Three patients (6.7%) discontinued hydroxychloroquine secondary to AEs. There was no clear predominant AE with hydroxychloroquine and no serious AEs were reported.

Tacrolimus

Forty-four trials of tacrolimus were used in 36 patients. Twenty-one patients experienced AEs as reported in Table E5 in this article's Online Repository at www.jaci-inpractice.org. Six patients (17%) discontinued the dose secondary to AEs. Two patients required dose adjustments with resolution of their AE. Four patients had elevation in their creatinine level by less than 0.5 mg/dL; all were reversible after discontinuation of tacrolimus. Tacrolimus was discontinued in 1 patient with elevated blood pressure. Elevated creatinine and elevated blood pressure were both considered serious AEs.

Mycophenolate

Twenty-seven patients were treated with mycophenolate 29 times. Nine patients reported AEs as listed in Table E6 in this article's Online Repository at www.jaci-inpractice.org, and 2 (7%) patients discontinued secondary to AEs. There was no clear predominant AE with mycophenolate. Leukopenia was considered a serious AE.

Cyclosporine

Eight patients were treated with 11 courses of cyclosporine. Six of 8 (75%) patients experienced AEs as outlined in Table E7 in this article's Online Repository at www.jaci-inpractice.org. Three patients required dose adjustments; however, no patient discontinued the therapy secondary to AEs, and no serious AEs were reported.

Omalizumab

Twenty-four patients were treated with 26 courses of omalizumab. No one discontinued therapy secondary to AEs. One patient reported mild flushing on the first dose only; 1 reported hair loss. One patient reported flushing and right upper chest