

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



Sharon Seth, MD, and David A. Khan, MD *Dallas, Texas*

**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. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:165-70)

**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).<sup>1</sup> 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.<sup>1</sup> 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.<sup>1</sup> 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

Division of Allergy and Immunology, University of Texas Southwestern Dallas, Dallas, Texas

The Vanberg Family Foundation supported this study.

Conflicts of interest: S. Deol's institution has received money from the Vanberg Family Foundation. S. Deol has received compensation from the Texas Regional Asthma and Allergy Center as employee after completing her fellowship. D. A. Khan has received a grant from the Vanberg Family Foundation, speaker's honoraria from Genentech, and compensation from Aimmune as a Data Safety Monitoring Board member.

Received for publication February 29, 2016; revised July 22, 2016; accepted for publication August 23, 2016.

Available online October 13, 2016.

Corresponding author: Sharon Seth, MD, Texas Regional Asthma and Allergy Center, 900 E Southlake Blvd, Suite 300, Southlake, TX 76092. E-mail: [sharonjd111@gmail.com](mailto:sharonjd111@gmail.com).

2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2016.08.010>

**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.<sup>2,3</sup>

**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](http://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](http://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](http://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](http://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](http://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](http://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](http://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

**TABLE II.** The average highest dose of each alternative agent as well as the total duration of treatment with the alternative agent at any dose

| Medication         | Average highest dose | Average duration (mo) | Patients | AEs            | Discontinuation due to AE | Serious AE   |
|--------------------|----------------------|-----------------------|----------|----------------|---------------------------|--------------|
| Dapsone            | 102.7 mg             | 7.6 (0.25-72)         | 73       | 53.4% (n = 39) | 5.5% (n = 4)              | 2.7% (n = 2) |
| Sulfasalazine      | 2.3 g                | 4.8 (0.25-53)         | 47       | 40% (n = 19)   | 17% (n = 8)               | NA           |
| Hydroxychloroquine | 402.0 mg             | 9.3 (0.25-96)         | 45       | 16% (n = 7)    | 6.7% (n = 3)              | NA           |
| Tacrolimus         | 4.1 mg               | 7.6 (0.25-52)         | 36       | 42% (n = 15)   | 1.7% (n = 5)              | 1% (n = 6)   |
| Mycophenolate      | 2.5 g                | 9.8 (0.25-62)         | 27       | 31% (n = 9)    | 7.4% (n = 2)              | 3.7% (n = 1) |
| Omalizumab         | 300 mg every 4 wk*   | 15 (2-70)             | 24       | 13% (n = 3)    | NA                        | NA           |
| Cyclosporine       | 272.7 mg†            | 13 (2-53)             | 8        | 75% (n = 6)    | NA                        | NA           |

NA, Not applicable/available.

\*Omalizumab regimens varied. Most patients received 300 mg every 4 wk. Other regimens included 150 mg every 4 wk and 375 mg every 2 wk.

†Starting dose usually ~3 mg/kg/d.

**TABLE III.** The most common AEs and reasons for discontinuation of the most commonly used agents

| Medication (no. of patients treated) | Most common AEs                       | Reason for discontinuation (no. of patients)                                                     |
|--------------------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------|
| Dapsone (73)                         | Asymptomatic drop in hemoglobin level | Symptomatic methemoglobinemia (2)<br>Racing heart (1)<br>Paresthesias (1)                        |
| Sulfasalazine (47)                   | GI symptoms and headaches             | GI symptoms (6)<br>Flu-like symptoms (1)<br>Drop in WBC count (1)                                |
| Hydroxychloroquine (45)              | GI symptoms                           | GI symptoms (1)<br>Pruritus and rash (1)<br>Headaches (1)                                        |
| Tacrolimus (36)                      | GI symptoms and headaches             | GI symptoms (1)<br>Headaches (2)<br>Rise in creatinine level (1)<br>Increased blood pressure (1) |
| Mycophenolate (27)                   | GI symptoms and headaches             | Leukopenia (1)<br>Irritability (1)                                                               |
| Omalizumab (24)                      | Mild flushing (rare)                  | *                                                                                                |
| Cyclosporine (8)                     | GI symptoms                           | *                                                                                                |

\*Medication not discontinued.

**TABLE IV.** AEs experienced on other alternative agents as well as discontinuation rates

| Medication                 | Patients | AEs                              | Discontinued |
|----------------------------|----------|----------------------------------|--------------|
| Colchicine                 | 4        | Diarrhea (n = 1)                 | 0            |
| Sirolimus                  | 3        | Lower extremity swelling (n = 1) | 0            |
| Intravenous immunoglobulin | 3        | None                             | 0            |
| Methotrexate               | 2        | GI upset (n = 1)                 | 1            |
| Etanercept                 | 1        | Injection site reaction (n = 1)  | 0            |
| Stanozolol                 | 1        | None                             | 0            |
| Heparin                    | 1        | None                             | 0            |

pain 40 minutes after omalizumab dose, which resolved with observation alone. No serious AEs were reported.

## Other alternative agents

Other alternative agents were used, though to a lesser extent than the aforementioned agents. AEs are outlined in Table IV.

**Efficacy.** The efficacy of the major alternative agents is reported in Table V. It is possible that some of the “Complete control” patients also achieved remission. Many of the patients were given a plan for discontinuation of the alternative agent upon their last visit and instructed to return if symptoms recurred.

## DISCUSSION

After reviewing the charts of 126 patients who have failed traditional treatment of chronic idiopathic urticaria (CIU), the comparative safety of multiple alternative agents has been reviewed (Figure 1). A single provider was selected for review because he used alternative agents more than 95% of the time and was the primary referral for patients with refractory CU. Specialists such as dermatologists and other allergists referred many of these patients. Often, these patients had been to more than 1 specialist and had tried an alternative agent in the past. This conglomerate of refractory patients accounts for the multiple trials of alternative agents used in this clinical practice. Although other authors have examined the use of many alternative agents in the treatment of patients with CU,<sup>4</sup> this is the

**TABLE V.** Efficacy of alternative agents

| Alternative agent  | Insufficient duration | Failed | Partial | Partial control | Complete control | Remission |
|--------------------|-----------------------|--------|---------|-----------------|------------------|-----------|
| Dapsone            | 2                     | 11     | 7       | 3               | 13               | 8         |
| Sulfasalazine      | 10                    | 19     | 14      | 2               | 3                | 2         |
| Hydroxychloroquine | 7                     | 21     | 9       | 2               | 6                | 6         |
| Tacrolimus         | 2                     | 11     | 7       | 3               | 13               | 8         |
| Mycophenolate      | 4                     | 9      | 5       | 1               | 6                | 4         |
| Omalizumab         | 0                     | 6      | 5       | 2               | 13               | 0         |
| Cyclosporine       | 0                     | 1      | 3       | 1               | 1                | 5         |

"Insufficient duration" indicates that the patient or the provider discontinued the medication before an effective length of treatment. "Failed" indicates that the patient was on the medication for an effective length of time, but did not have any clinical benefit. "Partial" indicates that the patient had some relief from symptoms, but the alternative agent was changed because of lack of enough clinical benefit. "Partial control" indicates that the patient was not 100% symptom free, but was having adequate benefit and continued on the alternative agent with decrease or discontinuation in other medications or steroids. "Complete control" indicates that the patient was 100% symptom free and continued on the alternative agent with discontinuation of other medications or steroids. "Remission" indicates that the patient was 100% symptom free for at least 3 mo after discontinuation of the alternative agent and all other medications.

largest series focusing on the comparative safety of alternative agents reported to our knowledge.

### Dapsone

As has been previously reported with dapsone therapy, the most common AE experienced by patients was a predictable drop in hemoglobin level.<sup>1,5</sup> In most patients, this drop was asymptomatic and did not result in a discontinuation or a decreased dose of dapsone therapy. Five patients' doses were decreased for asymptomatic anemia. Two patients' doses were decreased for exertional dyspnea during intense physical activity with improvement of symptoms after dose decrease. Two patients experienced symptoms such as nausea, dyspnea, and palpitations concerning for methemoglobinemia. Although methemoglobin levels were less than 20%, symptoms were concerning enough to continue dapsone avoidance. Both patients' symptoms resolved after stopping therapy. The patient with a "racing heart" did not have a drop in hemoglobin level or any other symptoms consistent with methemoglobinemia. On further review of the medical records, we found that this patient continued to experience a racing heart months after the discontinuation of dapsone, leading us to believe that this was unrelated. The 2 patients who developed thrombocytopenia on dapsone therapy were taking 200 mg dapsone daily at the time of presentation to our clinic. The thrombocytopenia resolved with decreased doses of dapsone. This side effect was not seen in any patient on 100 mg or less of dapsone daily. No patients had hemolysis while on dapsone, another known hematologic side effect of dapsone therapy. The hematologic AEs of dapsone therapy are more pronounced in patients with glucose-6-phosphate dehydrogenase deficiency, and thus all patients were screened for this genetic deficiency before initiation with dapsone therapy.<sup>5</sup> No patients with glucose-6-phosphate dehydrogenase deficiency were treated with dapsone therapy. The patient who experienced paresthesias on dapsone also experienced paresthesias with cyclosporine therapy, as well as other nonspecific symptoms with other alternative agents. Monitoring for hepatotoxicity is also recommended in patients on chronic dapsone therapy.<sup>6,7</sup> Four patients experienced transient and mild increases in transaminases, but did not require dose adjustments before resolution. Two patients were concomitantly taking acetaminophen above the recommended dose at the time of transaminase elevation, and this was thought to be the primary etiology of the elevated transaminase. A previous double-blind placebo-controlled study of 22

patients with refractory CIU on dapsone therapy did not find any serious AE.<sup>8</sup>

### Sulfasalazine

GI symptoms and headaches were the most commonly reported AEs of patients taking sulfasalazine. This is concurrent with other non-CIU studies reporting on the safety of sulfasalazine.<sup>9</sup> A 2006 sulfasalazine CIU study reported a similar AE profile in 37% of patients and no patient discontinued because of AE.<sup>10</sup> In our study, 6 patients discontinued sulfasalazine secondary to GI adverse effects. Aminosalicylates such as sulfasalazine are also known to cause bone marrow toxicity.<sup>6</sup> In a study with similar patient characteristics, 19.4% of patients required modification of their dosages secondary to hematologic AEs and 1 patient required discontinuation due to leukopenia.<sup>11</sup> In our study, 2 patients experienced drops in total white blood cell (WBC) counts. One patient had a mild leukopenia (WBC count of 3500/ $\mu$ L while on sulfasalazine 3 g daily). This was monitored and remained stable while the patient continued therapy. The other patient had leukopenia (WBC count of 2900/ $\mu$ L from a baseline of 6500/ $\mu$ L while on 2 g sulfasalazine daily). Sulfasalazine was discontinued in this patient by the provider with return of her WBC count to normal levels. One patient self-discontinued sulfasalazine for flu-like symptoms while taking 1 g twice a day. He had initially tolerated 500 mg twice for 1 week before increasing his dose. Symptoms resolved over the few days following discontinuation of the medication, and sulfasalazine was not tried again because of patient preference. Flu-like symptoms are not a commonly reported side effect from this medication and further details of patient's symptoms are not known. The aforementioned study with similar patient characteristics required discontinuation of a second patient due to rhabdomyolysis.<sup>11</sup> The patient in our study did not specifically describe symptoms consistent with rhabdomyolysis.

### Hydroxychloroquine

Two patients reported ocular side effects while on hydroxychloroquine. One patient reporting "blurry vision" was evaluated by ophthalmology and found to have a refractive error and was provided new eyeglasses. This was not thought to be attributable to the hydroxychloroquine. The other patient described "floaters," which were occurring along with daily headaches. The headaches and ocular symptoms resolved after discontinuation of therapy. No patients were thought to have retinal toxicity from

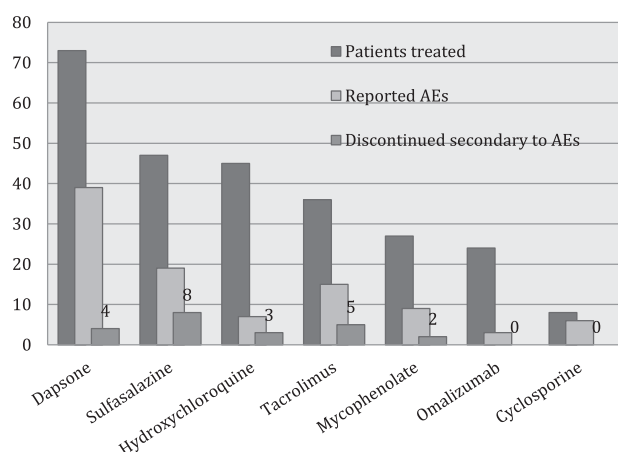


**FIGURE 1.** Frequency of adverse effects and need for discontinuation of alternative agents for CU.

hydroxychloroquine, a known and serious side effect of hydroxychloroquine.<sup>12</sup> Baseline ophthalmologic examinations were recommended within the first year of use in those who remained on hydroxychloroquine in accordance with the most recently revised recommendations by the American Academy of Ophthalmology.<sup>13</sup> Patients thought to be high risk for retinopathy were generally not started on this therapy. GI symptoms were infrequent in patients, though they are the most commonly reported side effects of hydroxychloroquine.<sup>7,14</sup> Only 1 patient discontinued because of nausea and diarrhea. One patient self-discontinued after noting pruritus, the most common cutaneous adverse effect of hydroxychloroquine,<sup>14</sup> on day 1 of the medication and small itchy bumps on day 4. She again attempted to take the medication, but noted pruritus again and the medication was discontinued. The rash resolved before evaluation by the treating physician.

### Tacrolimus

GI symptoms, increased creatinine level, increased blood pressure, and neurologic symptoms are some of the most common symptoms experienced by patients on oral tacrolimus.<sup>15,16</sup> One patient discontinued secondary to GI side effects. Four patients had mild increases in creatinine level while on tacrolimus. All patients were observed, and 3 patients returned to their baseline creatinine level after completion of tacrolimus therapy. One patient went from a baseline creatinine level of 1.06 mg/dL to a creatinine level of 1.30 mg/dL while on a total of 6 mg daily. The tacrolimus level was 8.8 ng/mL, and the provider discontinued tacrolimus. The creatinine level remained elevated to a maximum value of 1.39 mg/dL despite discontinuation of tacrolimus. This patient was referred to nephrology, and upon further review of past medical records, this patient's initial baseline creatinine level obtained in clinic was found to be lower than it had been in previous years. It was unlikely that tacrolimus caused any long-term increase in creatinine level and the patient had no further renal complications. Headache, another commonly reported side effect of tacrolimus, was reported in 5 patients and required discontinuation in 2 patients.<sup>16</sup> One patient required discontinuation of tacrolimus because of difficult to control blood pressure. This was thought to be more likely secondary to the underlying uncontrolled hypertension rather

than the tacrolimus because it continued to fluctuate during subsequent visits. Nonetheless, tacrolimus was discontinued in this patient, and in general was not started in patients with known uncontrolled hypertension. Although paresthesias is generally considered a common side effect of tacrolimus, only 2 patients experienced this, and in 1 it was thought to be more likely secondary to comorbidities of diabetes because it seemed to be present both before and after tacrolimus use. The other patient had resolution of paresthesias after discontinuation of tacrolimus.

### Mycophenolate mofetil

More common AEs of mycophenolate include GI, genitourinary, neurologic, and hematologic symptoms.<sup>17</sup> In the reviewed patients, the most commonly reported symptoms were GI symptoms, which is in line with previous reports in patients with CU.<sup>18</sup> One patient discontinued the medication after 1 week after stating that he had increased irritability at home. The medication was discontinued for a second patient by the emergency room for WBC count of 3800/ $\mu$ L and absolute lymphocyte count of 800/mL in the setting of abdominal pain. The workup was negative in the emergency room and the patient was subsequently sent home. Given no perceived benefit from the medication, it was not restarted.

### Omalizumab

Three of 24 patients reported AEs on omalizumab; however, no patient discontinued secondary to AEs. One patient reported hair loss, which was not appreciated by the provider. One patient experienced mild flushing after the first injection only, and not on subsequent injections. The third patient experienced right upper chest pain and mild facial flushing 40 minutes after one of his injections. This was observed and resolved without treatment.

### Cyclosporine

Six of 8 patients (75%) on cyclosporine reported AEs, the highest percentage of any alternative agent. Three patients required a decrease in their dose secondary to AEs; however, no patient discontinued secondary to AEs. One patient necessitated a decrease in dose due to a rise in creatinine level after starting pravastatin, which led to increased cyclosporine levels. The creatinine level normalized with a decreased dose. One patient decreased the dose secondary to paresthesias, and 1 patient secondary to abdominal discomfort as well as paresthesias. The safety of cyclosporine has been variable in previous studies from as low as 0% reported AE in a mostly pediatric population to as high as a 16.5% discontinuation rate due to unacceptable AEs in a more comparable population to this study.<sup>19,20</sup> The later study reported GI AEs, peripheral neuropathy, and headaches as the most common AEs.<sup>20</sup>

### Other alternative agents and combination therapy

AEs were experienced by 33% of patients on sirolimus ( $n = 3$ ), 50% on methotrexate ( $n = 2$ ), and by a single patient on etanercept ( $n = 1$ ). No AEs were reported by patients on intravenous immunoglobulin, stanozolol, or heparin. Combination therapy did not result in an increased incidence of AEs as compared with monotherapy.

**Efficacy.** Sixty-one percent (78 patients) of the 126 patients were steroid dependent before starting an alternative agent. Seventy-four percent (58 patients) were able to either decrease or stop systemic steroids while being treated with an alternative agent. Limited efficacy data were collected during the chart review and are

reported in Table V. Patients with “Partial control,” “Complete control,” and “Remission” were able to decrease or discontinue systemic steroids if they were steroid dependent. It is possible that some of the “Complete control” patients also achieved remission. Many of the patients were given a plan for discontinuation of the alternative agent on their last visit and instructed to return if symptoms recurred.

## CONCLUSIONS

After the completion of this retrospective chart review of patients with refractory CU treated with alternative agents, it is the authors' opinion that treatment with these agents is generally safe. Although relatively low risk, the use of alternative agents must always be weighed against their benefit. Although the body of literature on the efficacy of these agents is less than robust, there will be times in clinical practice that alternative agents are the next best step for the patient. It is again noted that all patients included in this review were refractory to standard treatment, many were steroid dependent, and many had failed other alternative agents under other providers. It is the authors' opinion that these are the patients who should be considered for alternative agents after a thorough discussion of the risks and benefits. Proper laboratory as well as clinical monitoring is required with the use of these alternative agents, even at the doses used in CU. The limitations of this study include its retrospective design. A unique strength of this study is the ability to review AEs in a “real-life” clinical setting. Patients were sometimes inconsistent with laboratory and clinical monitoring, and limited quantities of refills were provided pending laboratory results and proper follow-up. Many patients communicated via electronic medical records messaging and reported AEs in this manner. Often, these patients could not be evaluated in a timely manner because of their distance from the academic center. Despite these “real-life” issues, serious AEs were rare and no patient experienced permanent complications when treated with an alternative agent at the doses recommended in CU.

## REFERENCES

- Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014;133:1270-7.
- Morgan M, Khan DA. Therapeutic alternatives for chronic urticaria: an evidence-based review, part 1. *Ann Allergy Asthma Immunol* 2008;100:403-11. quiz 12-4, 68.
- Morgan M, Khan DA. Therapeutic alternatives for chronic urticaria: an evidence-based review, part 2. *Ann Allergy Asthma Immunol* 2008;100:517-26. quiz 26-8, 44.
- Amin P, Levin L, Holmes SJ, Picard J, Bernstein JA. Investigation of patient-specific characteristics associated with treatment outcomes for chronic urticaria. *J Allergy Clin Immunol Pract* 2015;3:400-7.
- Orion E, Matz H, Wolf R. The life-threatening complications of dermatologic therapies. *Clin Dermatol* 2005;23:182-92.
- Wolverton SE, Remlinger K. Suggested guidelines for patient monitoring: hepatic and hematologic toxicity attributable to systemic dermatologic drugs. *Dermatol Clin* 2007;25:195-205. vi-ii.
- Khan DA. Alternative agents in refractory chronic urticaria: evidence and considerations on their selection and use. *J Allergy Clin Immunol Pract* 2013;1:433-440.e1.
- Morgan M, Cooke A, Rogers L, Adams-Huet B, Khan DA. Double-blind placebo-controlled trial of dapsone in antihistamine refractory chronic idiopathic urticaria. *J Allergy Clin Immunol Pract* 2014;2:601-6.
- Braun J, van der Horst-Bruinsma IE, Huang F, Burgos-Vargas R, Vlahos B, Koenig AS, et al. Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. *Arthritis Rheum* 2011;63:1543-51.
- McGirt LY, Vasagar K, Gober LM, Saini SS, Beck LA. Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine. *Arch Dermatol* 2006;142:1337-42.
- Orden RA, Timble H, Saini SS. Efficacy and safety of sulfasalazine in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2014;112:64-70.
- Marmor MF. Comparison of screening procedures in hydroxychloroquine toxicity. *Arch Ophthalmol* 2012;130:461-9.
- Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF. American Academy of Ophthalmology. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 2011;118:415-22.
- Al-Bari MA. Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. *J Antimicrobial Chemother* 2015;70:1608-21.
- Garritsen FM, Roekevisch E, van der Schaft J, Deinum J, Spuls PI, de Bruin-Weller MS. Ten years experience with oral immunosuppressive treatment in adult patients with atopic dermatitis in two academic centres. *J Eur Acad Dermatol Venereol* 2015;29:1905-12.
- Varghese J, Reddy MS, Venugopal K, Perumalla R, Narasimhan G, Arikichenin O, et al. Tacrolimus-related adverse effects in liver transplant recipients: its association with trough concentrations. *Ind J Gastroenter* 2014;33:219-25.
- Buell C, Koo J. Long-term safety of mycophenolate mofetil and cyclosporine: a review. *J Drugs Dermatol* 2008;7:741-8.
- Zimmerman AB, Berger EM, Elmariah SB, Soter NA. The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: experience in 19 patients. *J Am Acad Dermatol* 2012;66:767-70.
- Neverman L, Weinberger M. Treatment of chronic urticaria in children with antihistamines and cyclosporine. *J Allergy Clin Immunol Pract* 2014;2:434-8.
- Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy* 2010;65:1478-82.

**TABLE E1.** Combinations of alternative agents used in patients

| Alternative agents |                                                                                                                                                                                                                                                       |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                  | sulfasalazine + tacrolimus                                                                                                                                                                                                                            |
| 2                  | dapsone + hydroxychloroquine; dapsone + sulfasalazine                                                                                                                                                                                                 |
| 3                  | dapsone + hydroxychloroquine                                                                                                                                                                                                                          |
| 4                  | hydroxychloroquine + mycophenolate                                                                                                                                                                                                                    |
| 5                  | dapsone + sulfasalazine                                                                                                                                                                                                                               |
| 6                  | tacrolimus + hydroxychloroquine                                                                                                                                                                                                                       |
| 7                  | hydroxychloroquine + cyclosporine; hydroxychloroquine + sulfasalazine; hydroxychloroquine + tacrolimus; hydroxychloroquine + mycophenolate; tacrolimus + sulfasalazine; cyclosporine + mycophenolate; hydroxychloroquine + etanercept + mycophenolate |
| 8                  | tacrolimus + omalizumab, tacrolimus + hydroxychloroquine, tacrolimus + sulfasalazine                                                                                                                                                                  |
| 9                  | dapsone + sulfasalazine; sulfasalazine + tacrolimus                                                                                                                                                                                                   |
| 10                 | omalizumab + cyclosporine                                                                                                                                                                                                                             |
| 11                 | omalizumab + hydroxychloroquine                                                                                                                                                                                                                       |
| 12                 | dapsone + hydroxychloroquine                                                                                                                                                                                                                          |
| 13                 | IVIG + hydroxychloroquine                                                                                                                                                                                                                             |
| 14                 | dapsone + hydroxychloroquine; dapsone + sulfasalazine; dapsone + sulfasalazine + heparin; heparin + stanazolol                                                                                                                                        |
| 15                 | omalizumab + mycophenolate                                                                                                                                                                                                                            |
| 16                 | tacrolimus + hydroxychloroquine                                                                                                                                                                                                                       |
| 17                 | dapsone + hydroxychloroquine                                                                                                                                                                                                                          |
| 18                 | dapsone + sulfasalazine                                                                                                                                                                                                                               |
| 19                 | omalizumab + sulfasalazine; omalizumab + cyclosporine                                                                                                                                                                                                 |
| 20                 | tacrolimus + dapsone; hydroxychloroquine + dapsone; hydroxychloroquine + mycophenolate; hydroxychloroquine + sulfasalazine                                                                                                                            |
| 21                 | dapsone + hydroxychloroquine; omalizumab + mycophenolate                                                                                                                                                                                              |
| 22                 | dapsone + hydroxychloroquine                                                                                                                                                                                                                          |
| 23                 | dapsone + hydroxychloroquine                                                                                                                                                                                                                          |
| 24                 | mycophenolate + hydroxychloroquine                                                                                                                                                                                                                    |
| 25                 | dapsone + hydroxychloroquine                                                                                                                                                                                                                          |

**TABLE E2.** AEs experienced by patients treated with dapsone

| AEs reported with dapsone             |                 |
|---------------------------------------|-----------------|
| Reported AE                           | No. of patients |
| Asymptomatic drop in hemoglobin level | 21              |
| Elevated transaminase level           | 4               |
| Headache                              | 3               |
| Symptomatic drop in hemoglobin level  | 2               |
| Thrombocytopenia                      | 2               |
| Nausea                                | 2               |
| Methemoglobinemia                     | 2               |
| Palpitations                          | 2               |
| Restless legs                         | 1               |
| Fatigue                               | 1               |
| Hypoproteinemia                       | 1               |
| Paresthesias                          | 1               |
| Strange dreams                        | 1               |

If a patient reported more than 1 AE, the patient is accounted for more than once. If a patient reported the same AE with multiple trials of dapsone, the patient is accounted for only once.

**TABLE E3.** AEs experienced by patients treated with sulfasalazine

| AEs reported with sulfasalazine |                 |
|---------------------------------|-----------------|
| Reported AE                     | No. of patients |
| Diarrhea                        | 5               |
| Nausea                          | 5               |
| Headache                        | 4               |
| GI upset                        | 4               |
| Abdominal pain                  | 4               |
| Leukopenia                      | 2               |
| Constipation                    | 1               |
| Flu-like symptoms               | 1               |
| Myalgia                         | 1               |
| Dyspepsia                       | 1               |
| Anorexia                        | 1               |

**TABLE E4.** AEs experienced by patients treated with hydroxychloroquine

| AEs reported with hydroxychloroquine       |                 |
|--------------------------------------------|-----------------|
| Reported AE                                | No. of patients |
| Diarrhea                                   | 2               |
| Upper respiratory tract infection symptoms | 1               |
| Blurry vision                              | 1               |
| Headaches                                  | 1               |
| Eye floaters                               | 1               |
| Abdominal cramps                           | 1               |
| Nausea                                     | 1               |
| Rash                                       | 1               |

**TABLE E5.** AEs experienced by patients treated with tacrolimus

| AEs reported with tacrolimus |                 |
|------------------------------|-----------------|
| Reported AE                  | No. of patients |
| Headache                     | 5               |
| Nausea                       | 4               |
| Increased creatinine level   | 4               |
| Dyspepsia                    | 4               |
| Increase in blood pressure   | 2               |
| Abdominal pain               | 2               |
| Ankle swelling               | 2               |
| Tremor                       | 2               |
| Diarrhea                     | 2               |
| Paresthesias                 | 2               |
| Insomnia                     | 1               |
| Memory and speech problem    | 1               |
| Hair loss                    | 1               |
| Myalgia                      | 1               |
| Arthralgia                   | 1               |
| Irritability                 | 1               |
| GI upset                     | 1               |
| Dysphagia                    | 1               |

**TABLE E6.** AEs experienced by patients treated with mycophenolate

| AEs reported with mycophenolate |                 |
|---------------------------------|-----------------|
| Reported AE                     | No. of patients |
| Headaches                       | 3               |
| Fatigue                         | 2               |
| Drop in WBC count               | 2               |
| Dyspepsia                       | 1               |
| Diarrhea                        | 1               |
| GI upset                        | 1               |
| Back pain                       | 1               |
| Abdominal pain                  | 1               |
| Blurry vision                   | 1               |
| Nausea                          | 1               |
| Irritability                    | 1               |
| Difficulty concentrating        | 1               |

**TABLE E7.** AEs experienced by patients treated with cyclosporine

| AEs reported with cyclosporine |                 |
|--------------------------------|-----------------|
| Reported AE                    | No. of patients |
| Paresthesias                   | 2               |
| Abdominal discomfort           | 2               |
| Headache                       | 2               |
| Increased creatinine           | 2               |
| Dyspepsia                      | 1               |
| Nausea                         | 1               |
| Hypertrichosis                 | 1               |
| Tremor                         | 1               |

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.