



Contents lists available at ScienceDirect



Efficacy and safety of sulfasalazine in patients with chronic idiopathic urticaria

Roy Anthony Orden, MD^{*}; Hersha Timble[†]; and Sarbjit S. Saini, MD[†]

^{*} Johns Hopkins Bayview Medical Center, Baltimore, Maryland

[†] Division of Allergy and Clinical Immunology, Johns Hopkins School of Medicine, Baltimore, Maryland

ARTICLE INFO

Article history:

Received for publication June 25, 2013.

Received in revised form September 24, 2013.

Accepted for publication September 27, 2013.

ABSTRACT

Background: There are limited data regarding alternative treatments for antihistamine refractory chronic idiopathic urticaria (CIU). Patients with recalcitrant skin disease often cannot gain satisfactory symptom control with standard therapies and may require prolonged courses of oral corticosteroids. There is a lack of information describing the degree and duration of sulfasalazine's efficacy, the frequency and nature of adverse reactions, and the appropriate safety monitoring parameters.

Objective: To present a case series detailing the efficacy and safety of sulfasalazine therapy in patients with CIU.

Methods: A retrospective chart review was conducted of 39 patients with sulfasalazine-treated CIU evaluated at Johns Hopkins Asthma and Allergy Center from October 2007 to March 2012. Eight patients were excluded from the final analysis.

Results: Twenty-six patients (83.9%) showed an improvement in symptoms within the first 3 months, with 51.6% of patients (n = 16) becoming asymptomatic within the first 6 months of starting sulfasalazine. Eleven patients (35.4%) achieved complete relief of symptoms after tapering off sulfasalazine therapy. Five of the 31 patients (16.1%) failed treatment, defined as worsening symptoms and pursuit of an alternative therapy. Six of 31 patients (19.4%) had a modified course of sulfasalazine therapy owing to abnormal hematologic parameters. Serious adverse events leading to drug discontinuation occurred in 6.5% of patients (n = 2) and included a patient with drug-induced leukopenia and one with rhabdomyolysis.

Conclusion: Sulfasalazine is a highly effective treatment for patients with antihistamine resistant CIU. The frequency of adverse events leading to an alteration of sulfasalazine treatment supports the need for close monitoring of these patients.

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

There is limited information regarding the use of alternative agents in chronic idiopathic urticaria (CIU), also recently termed *chronic spontaneous urticaria*, that is refractory to traditional, widely accepted therapies such as antihistamines, leukotriene modifiers, and corticosteroids.¹ This paucity of research regarding treatment can be linked to the continually evolving understanding of the pathogenesis of CIU, the lack of disease-specific histologic markers, and the clinical heterogeneity of urticaria.² With an estimated prevalence of 0.5% to 1.0% across patient populations in different countries, a duration commonly longer than 1 year with observations longer than 15 years, and a course that can be complicated by angioedema and other types of urticaria (eg, physical, inducible), effective and safe CIU treatments have been sought by affected patients who have failed to gain symptom control with high-dose antihistamines and leukotriene antagonists.³

Although a recent review of the efficacy and overall safety of other therapies, including dapson, sulfasalazine, hydroxychloroquine, colchicine, calcineurin inhibitors, mycophenolate, and intravenous immunoglobulin, described several promising outcomes, it also highlighted the rather weak evidence on which these regimens are based.^{4,5} Sulfasalazine, in particular, is approved for use in rheumatoid arthritis and inflammatory bowel disease. However, the evidence base for these indications is robust,^{6–8} as is the information regarding common adverse reactions, including headache, rash, gastrointestinal distress (anorexia, dyspepsia, nausea, vomiting), and reversible oligospermia. A prior report of sulfasalazine use in oral steroid-dependent CIU cases described symptom improvement in approximately three fourths of treated patients and complete cessation or a decrease in steroids in most cases.⁹ In the present case series, the authors aimed to identify the timing of clinical response, duration of therapy, safety, and long-term outcome of sulfasalazine treatment in patients with CIU.

Methods

A retrospective chart review was conducted of patients with CIU initially evaluated from October 2007 through March 2012 at the

Reprints: Sarbjit S Saini, MD, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Room 2B. 71B, Baltimore, MD 21224; E-mail: ssaini@jhmi.edu.

Disclosures: Dr Saini has consulted for and received grant support from Novartis/Genentech.

Johns Hopkins Asthma and Allergy Center, a specialty care clinic at a large tertiary care center. The study was approved by the Johns Hopkins institutional review board. In this study, all patients were given a diagnosis of CIU based on clinical history, physical examination, and laboratory evaluation. Thirty-nine patients with a suboptimal response to antihistamine therapy or the need for systemic corticosteroid therapy were identified. Eight patients were excluded from the analysis because of: (1) insufficient data regarding laboratory results on sulfasalazine therapy and/or an incomplete record of symptom reports ($n = 4$); (2) loss to follow-up ($n = 3$); or (3) a shorter than 6-week trial of sulfasalazine therapy without evidence of toxicity ($n = 1$). Thus, a total of 31 patients diagnosed with CIU and treated with sulfasalazine were included and found to have sufficient data to evaluate overall therapeutic response and measurements of safety on sulfasalazine therapy.

The following information was obtained from chart review: demographic characteristics, baseline laboratory values before initiation of sulfasalazine therapy (complete blood count [CBC], aspartate aminotransferase [AST], alanine aminotransferase [ALT]), subjective clinical response to sulfasalazine therapy, surveillance laboratory values during the course of treatment, changes in sulfasalazine dosage during the course of treatment, duration of therapy, skin biopsy findings, CIU therapies before and after sulfasalazine therapy, prior use of leukotriene receptor antagonists, prior use of immunomodulators, and current use of levothyroxine.

Sulfasalazine Therapy

In general, patients were treated with sulfasalazine according to a protocol for monitoring and titration based on established regimens for conditions more commonly treated with the drug (ie, rheumatoid arthritis).^{10,11} Patients had laboratory studies (CBC, AST/ALT) completed before the initiation of sulfasalazine therapy and then were treated with an escalating dose of sulfasalazine. For most patients (27 of 31, 87%), sulfasalazine was initiated at a dosage of 500 mg/d and increased by 500 mg each week based on clinical tolerance and assessment of the safety laboratory values. Sulfasalazine dosages were titrated up weekly after review of safety laboratory studies (see below) until a dose of 2,000 mg/d was achieved. In all cases, a target dose of 2,000 mg/d was the therapeutic goal unless altered owing to abnormal laboratory values. For 15 patients, sulfasalazine doses were further escalated to a dose higher than 2,000 mg to assess therapeutic response. Four patients were started on sulfasalazine by a referring provider shortly before their first evaluation at Johns Hopkins and were initially titrated according to an unknown schedule. In general, patients were continued on a clinically effective maintenance dose of sulfasalazine for at least 3 months before initiating a slow taper of sulfasalazine.

Assessments of Sulfasalazine Safety

Serial safety monitoring laboratory values obtained over the course of treatment were coded as no laboratory abnormality; abnormal CBC, AST, or ALT (defined as a value outside the laboratory reference range) leading to no change in sulfasalazine therapeutic course; or abnormal CBC, AST, or ALT leading to a change in therapeutic course (Fig 1). The frequency of laboratory studies was weekly while increasing the dose to 2 g/d, monthly for the next 3 months, and quarterly thereafter.

Assessment of Sulfasalazine Efficacy

The effectiveness of sulfasalazine over the course of treatment was assessed by patient reports at clinic visits and during telephone updates. Patient responses were coded according to the evolution of symptoms and the modifications made to their medication regimens (Fig 2). Remission was defined as the absence of

- 1A: Abnormal CBC leading to dose change
- 1B: Abnormal LFT leading to dose change
- 2: Abnormal CBC & LFT no dose change
- 3A: Abnormal CBC no dose change
- 3B: Abnormal LFT no dose change
- 4: No CBC or LFT abnormality

Figure 1. Characterization of sulfasalazine clinical laboratory monitoring. (1A) Abnormal complete blood count (CBC) leading to dose change. (1B) Abnormal liver function test (LFT) leading to dose change. (2) Abnormal CBC count and LFT result without dose change. (3A) Abnormal CBC count without dose change. (3B) Abnormal LFT result without dose change. (4) No CBC count or LFT abnormality.

symptoms and the complete cessation of sulfasalazine after a gradual taper. All patients who achieved remission were continued on some form of antihistamine therapy after cessation of sulfasalazine. Failure was defined as worsening symptoms and pursuit of an alternative immunomodulator therapy. The assessment of efficacy between the extremes of remission and failure was based on a combination of symptom description (worsening, unchanged, improved, or absent) and CIU medication adjustments (increased, unchanged, or decreased).

Results

Patient Characteristics

Within this series of patients, the median age at the time of sulfasalazine initiation was 45 years (Table 1). Nineteen patients (61%) were women. Although all patients were on an antihistamine regimen at the time of sulfasalazine therapy, 65% were on at least 3 medications for CIU. Before the initiation of sulfasalazine, 24 of 31 patients (77.4%) obtained an urticarial lesion skin biopsy to exclude alternative diagnoses, such as vasculitis, and to characterize the urticarial leukocyte infiltrate. In this study, the most common finding was a leukocyte infiltrate composed of lymphocytes and eosinophils. Ten patients (32%) were on steroids for longer than 1 month before starting sulfasalazine therapy and 3 patients (10%) had previously tried an immunomodulator therapy, including

- 1: Failure = worsening skin symptoms, alternate therapy
- 2: Worsening skin symptoms, more medications
- 3: Worsening skin symptoms, no change in medications
- 4: No change in skin symptoms, no change in medications
- 5: No change in skin symptoms, less medications
- 6: Improvement in skin symptoms, no change in medications
- 7: Improvement in skin symptoms, less medications
- 8: No skin symptoms, no change in medications
- 9: No skin symptoms, less medications
- 10: Remission = no skin symptoms, no sulfasalazine

Figure 2. Characterization of sulfasalazine clinical efficacy. (1) Failure, defined as worsening skin symptoms and pursuit of alternative therapy. (2) Worsening skin symptoms, more medications. (3) Worsening skin symptoms, no change in medications. (4) No change in skin symptoms, no change in medications. (5) No change in skin symptoms, fewer medications. (6) Improvement in skin symptoms, no change in medications. (7) Improvement in skin symptoms, fewer medications. (8) No skin symptoms, no change in medications. (9) No skin symptoms, fewer medications. (10) Remission, defined as no skin symptoms and no sulfasalazine.

Table 1
Individual patient demographics and characteristics

Age	Sex	Steroids >30 d before sulfa	Reported duration of CIU at presentation	With angioedema	Medical regimen before sulfa therapy	Medical regimen at end of sulfa therapy/observation period	Prior use of immunomodulator	Prior/current use of LTA	Taking levothyroxine	Skin biopsy findings
38	F	no	22 mo	yes	fexofenadine 180 mg/d; hydroxyzine 25 mg nightly; cetirizine 10 mg/d; ranitidine 150 mg/d	failed; started omalizumab	no	no	no	lymphocytic/eosinophilic infiltrate
26	F	no	19 mo	yes	doxepin 50 mg nightly; cyproheptadine 4 mg TID; prednisone taper	failed; started dapsone	no	no	no	lymphocytic/eosinophilic infiltrate
45	F	no	8 mo	no	montelukast 10 mg/d; fexofenadine 180 mg/d	failed; rhabdomyolysis	no	yes	no	lymphocytic infiltrate
66	M	no	31 mo	yes	cetirizine 10 mg/d	failed; no significant improvement	no	yes	no	lymphocytic/eosinophilic infiltrate
37	F	no	16 y	no	cetirizine 10 mg/d; diphenhydramine 50 mg PRN	failed; started omalizumab	no	yes	no	eosinophilic infiltrate
52	F	no	20 y	yes	cetirizine 10 mg/d	cetirizine 10 mg/d	no	yes	yes	lymphocytic/eosinophilic infiltrate
46	M	no	5 y	yes	levocetirizine 5 mg/d	levocetirizine 5 mg/d	yes; dapsone	no	no	lymphocytic/eosinophilic infiltrate
35	F	no	1.5 mo	yes	levocetirizine; ranitidine; hydroxyzine	loratadine 10 mg/d	no	no	no	NA
55	F	no	5 y	yes	fexofenadine 180 mg/d; hydroxyzine 150 mg nightly; levocetirizine 5 mg/d; doxepin 50 mg nightly	fexofenadine 180 mg/d; hydroxyzine 50 mg AM, 100 mg PM	no	yes	yes	NA
30	F	no	7 y	yes	cetirizine 10 mg/d; montelukast 10 mg nightly	cetirizine 10 mg/d	no	yes	no	lymphocytic/eosinophilic infiltrate
43	F	yes	16 mo	yes	prednisone 2.5 mg/d; levocetirizine 10 mg/d; cyproheptadine 1 tablet daily; montelukast 10 mg/d; doxepin 40 mg nightly; ranitidine 300 mg/d	montelukast 10 mg/d; doxepin 40 mg/d; ranitidine 300 mg/d	no	yes	no	neutrophilic/eosinophilic infiltrate
51	M	yes	4 y	yes	prednisone 5 mg BID; fexofenadine	cetirizine 10 mg BID; prednisone	no	yes	no	lymphocytic/eosinophilic infiltrate
24	F	no	3 mo	yes	cetirizine 10 mg BID; fexofenadine 180 mg/d	fexofenadine 180 mg/d	no	yes	no	NA
46	M	no	7 mo	yes	cetirizine 10 mg BID; montelukast 10 mg/d; doxepin 20 mg/d; diphenhydramine PRN; hydroxyzine PRN	cetirizine 10 mg/d	no	yes	no	lymphocytic infiltrate
44	M	yes	13 mo	yes	prednisone 15 mg/d; diphenhydramine 50 mg BID; ranitidine 150 mg BID	cetirizine 10 mg BID	no	no	no	"hypersensitivity reaction, consistent with urticaria"
60	M	no	8 mo	yes	loratadine; diphenhydramine; doxepin 10 mg nightly	cetirizine 10 mg/d; doxepin 20 mg nightly	no	no	no	NA
47	M	no	5 y	no	cetirizine 10 mg/d; fexofenadine 180 mg/d; doxepin 20 mg/d	doxepin 30 mg/d; fexofenadine 180 mg/d	no	yes	no	lymphocytic/eosinophilic infiltrate
37	F	no	14 y	no	loratadine 5 mg/d; doxepin 10 mg/d	cetirizine 10 mg/d	no	no	no	lymphocytic/eosinophilic infiltrate
46	F	no	29 mo	yes	doxepin 30 mg nightly; montelukast 10 mg/d	cetirizine 10 mg/d	no	yes	yes	lymphocytic/eosinophilic infiltrate
25	M	no	9 mo	no	doxepin 30 mg/d	doxepin 25 mg/d	no	yes	no	NA
45	F	yes	6 mo	no	levocetirizine 5 mg/d; prednisone 17.5 mg/d; hydroxychloroquine	remitted; levocetirizine 5 mg/d	yes; cyclosporine, mycophenolate, tacrolimus	yes	yes	NA
38	F	yes	10 mo	no	doxepin 75 mg/d; fexofenadine 180 mg/d; ranitidine 150 mg/d; montelukast 10 mg/d; prednisone 10 mg/d	remitted; cetirizine 10 mg/d; ranitidine 150 mg/d	no	yes	no	lymphocytic/eosinophilic infiltrate
61	M	no	4 mo	yes	montelukast 10 mg/d; fexofenadine 180 mg/d; cetirizine 10 mg nightly; doxepin 40 mg/d	remitted; fexofenadine	yes; cyclosporine	yes	no	lymphocytic/eosinophilic infiltrate
36	F	yes	12 y	no	prednisone 5 mg/d; levocetirizine 5 mg/d; diphenhydramine PRN; hydroxyzine PRN	remitted; cetirizine 10 mg/d; prednisone PRN; diphenhydramine PRN	no	yes	yes	lymphocytic/eosinophilic infiltrate
43	F	yes	3 mo	yes	prednisone 10 mg/d; hydroxyzine 75 mg nightly; levocetirizine 5 mg nightly; cetirizine 20 mg BID; desloratadine 5 mg/d; montelukast 10 mg nightly	remitted; montelukast 10 mg/d; cetirizine 10 mg/d	no	yes	no	NA

(continued on next page)

Table 1 (continued)

Age	Sex	Steroids before sulfa	Reported duration of CIU at presentation	With angioedema	Medical regimen before sulfa therapy	Medical regimen at end of sulfa therapy/observation period	Prior use of immunomodulator	Prior/current use of LTA	Taking levothyroxine	Skin biopsy findings
47	M	yes	6 mo	yes	doxepin 20 mg nightly; hydroxyzine 100 mg BID; montelukast 10 mg/d	remitted; fexofenadine 180 mg/d; montelukast 10 mg/d	no	yes	yes	lymphocytic/eosinophilic infiltrate
52	M	no	14 y	no	fexofenadine 180 mg/d; ranitidine 150 mg BID; cetirizine 10 mg/d; doxepin 50 mg nightly; montelukast 10 mg/d	remitted; fexofenadine 180 mg/d; ranitidine 150 mg BID	no	yes	no	lymphocytic/eosinophilic infiltrate
30	F	no	12 mo	yes	montelukast 10 mg/d; cetirizine 10 mg BID; cimetidine 400 mg BID	remitted; cetirizine 10 mg/d	no	yes	yes	lymphocytic/eosinophilic infiltrate
51	F	no	33 y	yes	cetirizine 10 mg/d; montelukast 10 mg nightly; hydroxyzine 25 mg TID	remitted; cetirizine 10 mg/d; montelukast 10 mg nightly	no	yes	no	lymphocytic infiltrate
47	M	yes	5 mo	yes	prednisone 20 mg BID; cetirizine 10 mg/d; montelukast 10 mg/d; ranitidine 150 mg BID	remitted; montelukast 10 mg/d; cetirizine 10 mg BID	no	yes	no	neutrophilic/eosinophilic infiltrate
41	F	yes	18 y	yes	levocetirizine 5 mg BID; diphenhydramine 25 mg q4h; prednisone 10 mg/d	remitted; cetirizine 10 mg/d	no	no	yes	neutrophilic/eosinophilic infiltrate
Summary	total 10 ^a		avg 66 mo	total 22	avg 3.0	avg 1.5	immunomodulator 3 ^b	prior/current 23	total 8	total with lymphocytic infiltrate 19

Q8

Abbreviations: avg, average; BID, 2 times a day; CIU, chronic idiopathic urticaria; F, female; LTA, leukotriene antagonist; M, male; NA, not available; q4h, every 4 hours; TID, 3 times a day; sulfa, sulfasalazine.

^aSteroid use longer than 30 days before initiation of sulfasalazine therapy.^bUse of other immunomodulators before initiation of sulfasalazine therapy.

dapsone, cyclosporine, and mycophenolate. Before initiating sulfasalazine, the average documented duration of CIU was 66 months (median 19 months, maximum 33 years, minimum 6 weeks). Twenty-two patients (71%) reported symptoms consistent with angioedema. Eight patients (26%) were being treated for hypothyroidism.

Duration of Sulfasalazine Therapy

The average duration of sulfasalazine treatment, including the initial escalation and any subsequent tapering periods, for all 31 patients was 74 weeks (median 64 weeks). Based on the described protocol for initiation and escalation of sulfasalazine therapy, the median time until a dose of 2,000 mg was achieved was 4.4 weeks (minimum 2 weeks, maximum 27 weeks, $n = 26$). For patients who failed sulfasalazine therapy, as previously defined ($n = 5$), the duration of therapy averaged 26.6 weeks (median 28 weeks) and 3 of these 5 patients were escalated to a sulfasalazine dose of 3,000 mg. The duration of treatment for those patients achieving remission ($n = 11$) averaged 68.6 weeks (median 75 weeks).

Measurement of Sulfasalazine Efficacy

The clinical efficacy of sulfasalazine is monitored in relation to the improvement of symptoms based on patient report and the decrease or simplification of CIU treatment regimens after initiation of sulfasalazine therapy. Overall, 83.9% of patients (26 of 31) exhibited an improvement in symptoms within the first 3 months. Approximately one third (32.3%) of patients became asymptomatic during the first 3 months of treatment with the addition of sulfasalazine to their pre-existing CIU regimens. Sixteen of the 31 treated patients (51.6%) became asymptomatic in the first 6 months after initiation of sulfasalazine therapy.

In terms of pre-existing therapies, patients were advised to maintain their pre-sulfasalazine pharmacologic regimen during the up-titration period or until the target dose was achieved. Fifteen patients were titrated up to a maintenance dose higher than the target dosage of 2,000 mg, 10 to a therapeutic dose of 3,000 mg, and 5 to a dose of 2,500 mg. As patients responded to sulfasalazine, corticosteroid and antihistamine-containing regimens were modified. Corticosteroids were tapered with the goal of complete cessation and antihistamine use was minimized. Of the 10 patients who started sulfasalazine therapy on a scheduled regimen of prednisone, 9 no longer required corticosteroids at the end of the observation period. The final patient remained on a regimen of corticosteroids owing to adrenal insufficiency and not for control of skin symptoms. Notably, of the 26 patients who responded to sulfasalazine or who achieved remission, CIU pharmacologic regimens (H_1 or H_2 blockers, leukotriene antagonists, steroids) were decreased by 50% at the end of the observation period (Table 1).

Eleven patients achieved remission, defined as no symptoms after a complete taper off sulfasalazine therapy. Notably, all patients in remission were maintained on some form of antihistamine. Demographically, this subset of patients was similar to the group as a whole, with an average age of 45 years and with women outnumbering men 3 to 2. Interestingly, these patients appeared to have more recalcitrant disease as demonstrated by a larger number of pre-sulfasalazine CIU drugs (average 3.7 vs 2.5) and as suggested by the larger percentage of corticosteroid-dependent patients included in this group (7 of the 10 corticosteroid-using patients). Within this subset of patients, all showed improvement in symptoms within the first 3 months. These patients were treated at therapeutic levels for an average of 38.2 weeks before the initiation of sulfasalazine tapering. Three of the 11 patients required an increase in maintenance dosages higher than 2,000 mg.

Overall, therapy in 5 patients failed, for an overall failure rate of 16.2%. Two of these patients actually reported an initial

improvement in symptoms within the first 4 to 6 weeks before exhibiting failed sulfasalazine therapy. Of these 5 patients, therapy failed in 1 due to an adverse drug reaction, therapy failed in 1 owing to a lack of symptom improvement, and 3 were transitioned to a different immunomodulator therapy (Table 1). These 5 patients were on therapeutic dosages of sulfasalazine for an average of 15.6 weeks.

Durability of Sulfasalazine Efficacy

The efficacy of sulfasalazine for the 26 patients who responded to sulfasalazine therapy (ie, whose therapy did not fail) was examined during an observation period, that is, the interval from the initiation of sulfasalazine to remission or the last contact with the patient before October 2012; the average duration was 83.1 weeks (median 80.9 weeks, range 9.4–192.3 weeks). The durability of sulfasalazine efficacy is demonstrated by examining the eventual outcome of patients who can achieve a completely symptom-free period while on sulfasalazine therapy and by closer scrutiny of the disease course of those patients who ultimately achieve remission. As mentioned earlier, 16 of the 31 patients (51.6%) became asymptomatic in the first 6 months after initiation of sulfasalazine therapy. Eight of these patients eventually became asymptomatic and were tapered off sulfasalazine. Of the remaining 8 patients, 5 were asymptomatic at the end of the observation period while maintained on sulfasalazine and 3 of these patients were in the process of a gradual tapering of sulfasalazine therapy.

In addition to the 16 patients who became asymptomatic in the first 6 months after starting sulfasalazine therapy, 5 additional patients were symptom free by the 52-week mark. Three of these patients ultimately achieved remission. After achieving a symptom-free period, 1 patient appeared to maintain a new level of symptom control in the remaining 39 weeks of the observed period, as evidenced by an improvement in sulfasalazine efficacy measurements (Fig 2), and 1 patient remained asymptomatic on therapeutic doses of sulfasalazine for the final 4 weeks of the observed period.

As detailed earlier, 21 patients (67.7%) were asymptomatic within the first year of sulfasalazine treatment and 11 comprised the subset that eventually achieved remission. Of those who achieved remission, the average period of asymptomatic follow-up time was 70.3 weeks ($n = 8$). Four (36.3%) of those in remission restarted sulfasalazine therapy after an average of 75.6 weeks.

Measurement of Sulfasalazine Safety

The safety of sulfasalazine is measured by the frequency and nature of laboratory abnormalities, particularly those abnormalities leading to a dose adjustment or an alteration of sulfasalazine therapy. As described, most patients were initiated on sulfasalazine using an escalation protocol. As a result, a higher frequency of laboratory draws occurred in the first 13 weeks, an average of 4.5 vs 1.7 draws at 3 to 6 months, and 1.6 draws at 6 months to 1 year. Twenty-six patients (83.9%) had an abnormal laboratory result, defined as a laboratory value outside the normal range reported by the testing laboratory. Overall, of 311 total laboratory values obtained during the observed period, 125 (40.2%) were outside the normal range, but only 7 results (2.3%), occurring in 6 patients detailed below, led to a dose change (Table 2). These percentages were mirrored in the subset of 10 patients who were maintained on a therapeutic dose of 3,000 mg. Notably, only 6 of the 26 patients with abnormal monitoring laboratory parameters exhibited liver function test aberrations, the most extreme of which was 3 times the upper limit of normal.

In total, 6 patients (19.4%) had a modified course of sulfasalazine therapy based on abnormal laboratory values. The specific abnormalities were low or decreasing white blood cell counts ($n = 2$), low or decreasing hemoglobin/hematocrit ($n = 2$), elevated

Table 2

Frequency of abnormal laboratory values

1A	abnormal CBC count leading to dose change	6 (1.9%)
1B	abnormal LFT result leading to dose change	1 (0.3%)
2	abnormal CBC count and LFT results, no dose change	0 (0.0%)
3A	abnormal CBC count, no dose change	112 (36.0%)
3B	abnormal LFT result, no dose change	13 (4.2%)
4	no CBC count or LFT abnormality	179 (57.6%)
	total laboratory draws	311 (100.0%)

Abbreviations: CBC, complete blood count; LFT, liver function test.

transaminases ($n = 1$), and elevated creatine kinase ($n = 1$). The earliest course-altering laboratory abnormality occurred 3.3 weeks into therapy and the latest abnormality occurred 41.0 weeks into sulfasalazine treatment (median 7.8 weeks). Four patients (66.7%) had abnormal laboratory values before the course-modifying laboratory result.

The manner in which sulfasalazine therapy was altered included temporary maintenance of a subtherapeutic dose lower than 2,000 mg/d ($n = 1$), reactive decrease in sulfasalazine dose ($n = 3$), and immediate cessation of therapy ($n = 2$). Of the 6 patients who had a modified treatment regimen owing to abnormal laboratory parameters, one half resumed sulfasalazine treatment and one half had full withdrawal of therapy.

Regarding serious adverse events, the experience of 2 patients is notable. One patient had sustained leukopenia and neutropenia that was considered serious and led to a full withdrawal of therapy 9.4 weeks into treatment. This patient's initial leukocyte levels were 6,100 cells/mm³ and decreased to 3,600 cells/mm³ by the third week of treatment. Leukocyte levels ultimately decreased to a nadir of 1,100 cells/mm³, with a corresponding absolute neutrophil count of 154 before returning to normal levels within 5 weeks of the cessation of sulfasalazine therapy. Despite the leukopenia and neutropenia, the patient remained clinically well and did not require hospitalization. Another patient developed symptoms of fatigue and generalized weakness within 4 weeks of starting sulfasalazine and was admitted to a local hospital, where she was diagnosed with rhabdomyolysis. It is unclear if other factors contributed to or precipitated the development of rhabdomyolysis; however, sulfasalazine therapy was discontinued in the event that it contributed to the patient's presentation. These 2 patients fully recovered from these events without any permanent or residual injury.

Discussion

The series of patients included in this study is representative of patients with refractory CIU. A skin biopsy obtained in most patients (24 of 31, 77.4%) excluded other diagnoses and the finding of lymphocytic predominant infiltrate in 19 of these 24 patients (79.2%) is suggestive of a common cellular mechanism that is responsive to sulfasalazine. In general, chronic urticaria is 2 times more prevalent in women than in men.^{12,13} Several factors suggest the presence of refractory disease, including the presence of angioedema,^{14,15} long disease duration,^{14,15} need for oral steroids,¹² and poor response to antihistamine therapy.^{16–18} In this series, most patients were women (61%), largely had angioedema-associated disease (71%), had long disease duration (median 19 months, mean 66 months, before starting sulfasalazine), and had disease that was corticosteroid dependent (32%) and/or minimally responsive to antihistamine therapy. The severity of disease included in this analysis actually exceeds prior epidemiologic estimates of severity as measured by disease duration, symptom control with H₁ antagonists, and prednisone-requiring disease.^{12,14–18} Therefore, these observations are relevant for the most refractory cases of CIU.

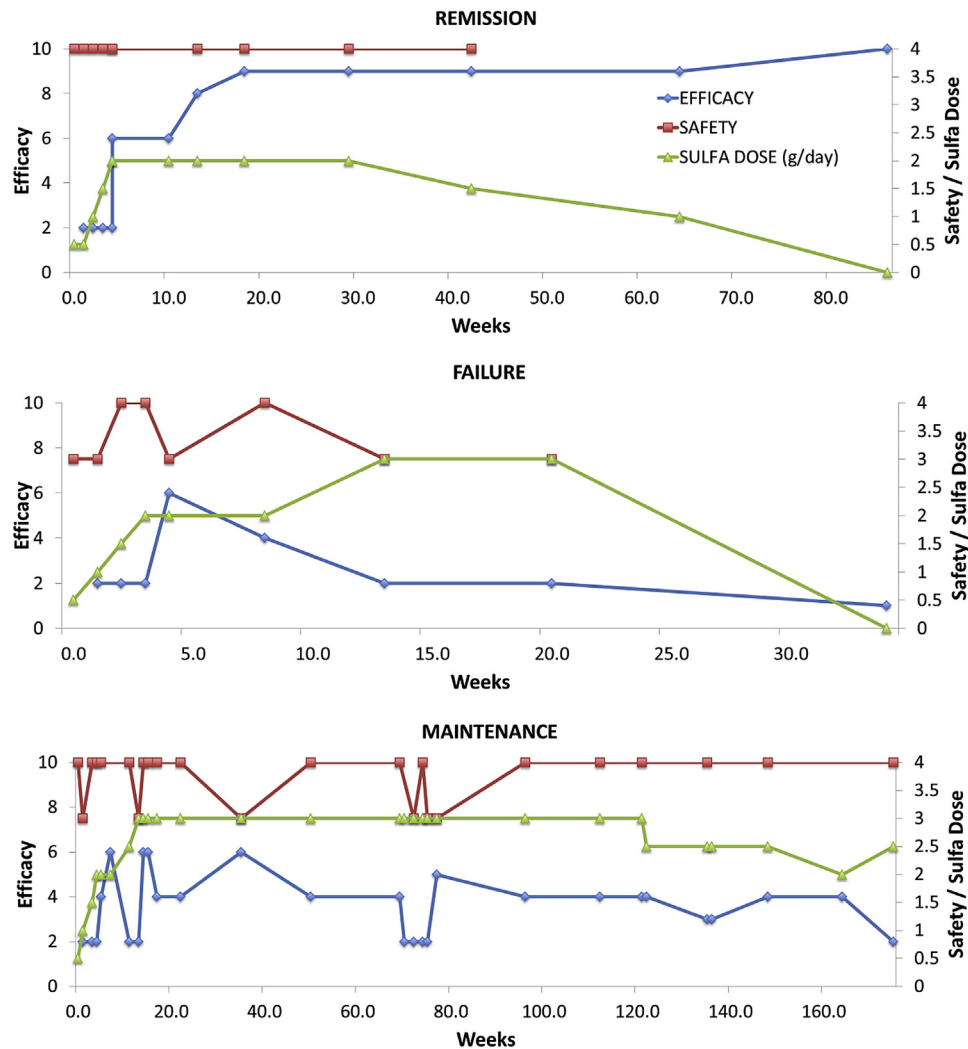


Figure 3. Graphic course of sulfasalazine therapy for 3 representative patients. Sulfa, sulfasalazine.

A limitation of this study is its retrospective, observational design and, as a result, the absence of randomization and a placebo-administered control group. Without this group, the next most appropriate population for comparison would be comprised of patients deemed suitable for inclusion in this study but who refused therapy. Unfortunately, none of the patients to whom sulfasalazine therapy was recommended declined the therapy. Arguably, the control group of a recently published randomized, placebo-controlled study investigating the efficacy and safety of omalizumab is a reasonable proxy control group for this study.¹⁹ In the trial completed by Maurer et al,¹⁹ the control group ($n = 79$) had an average age of 43 years, was maintained on an antihistamine, was comprised mostly of women (70%), and had been diagnosed with CIU for an average of 7.2 years, traits similar to the series of patients examined in this study. With respect to efficacy, 19% of patients in the proxy control group showed an improvement in disease symptoms at 3 months, as measured by an urticaria activity score. This compares with the 83.9% of patients (26 of 31) in this study who had symptom relief, 32.3% (10 of 31) of whom became asymptomatic, over the same period. This degree of disease control, although not exactly comparable, even rivals the 66% of patients on the highest dose of omalizumab (300 mg) with a significant improvement in urticaria activity score. Moreover, the incidence of serious adverse events in the omalizumab (300 mg) group approximated the rate observed in this study (approximately 6%).

Thus, sulfasalazine appears to be more efficacious than placebo, with a therapeutic and risk profile that is arguably similar to that of omalizumab.

Numerous treatments for CIU have been used to fill the medication gap between well-tolerated, nonsedating antihistamines and more toxic, highly effective corticosteroids.^{4,5} Unfortunately, research comparing these different regimens or even randomized controlled trials vs placebo is sparse. For example, case series of intravenous immunoglobulin are promising, with 30% to 80% of observed patients showing disease remission and no long-term adverse effects of treatment.^{20,21} However, these are small ($n = 10$ in the largest), uncontrolled studies and current guidelines only recommend administration at specialized centers.¹ Although most CIU remedies are supported by case reports, case series, or consensus opinion, only cyclosporine and omalizumab have been evaluated in randomized controlled trials.^{22–25} As an oral agent, cyclosporine is a natural benchmark by which to assess the efficacy and safety of sulfasalazine. In addition, research examining cyclosporine therapy described 3 discrete groups of patients: those who had remission, those whose therapy failed, and those maintained on cyclosporine for some amount of time.²⁶ A similar pattern of patients was observed in this series of patients on sulfasalazine therapy (Fig 3), enforcing the appropriateness of comparing the 2 CIU regimens.

Prior studies have reported symptom relief in approximately 60% to 70% of patients within 3 months of initiating cyclosporine

therapy.^{26,27} In this series of patients, 83.9% reported symptom relief at 3 months. Furthermore, approximately 15% to 20% of patients started on cyclosporine did not respond to the treatment,^{22,26,27} a rate that is similarly observed in this analysis of sulfasalazine therapy (16.2%). Although these rates are not exactly comparable owing to differences in research methodologies, it appears that sulfasalazine is generally as effective as cyclosporine.

The side effects of cyclosporine treatment, including gastrointestinal and peripheral neuropathy, have been reported in as many as 60% of patients receiving treatment.²³ Moreover, intolerable side effects resulting in discontinuation of therapy have been reported in approximately 8% to 17% of patients treated with cyclosporine.^{26,27} In comparison, sulfasalazine therapy was discontinued in 2 patients (6.5%) in this series owing to serious adverse events. Thus, the overall rate of therapy withdrawal for those patients on sulfasalazine appears to mirror that of those patients on cyclosporine.

Given the occurrence of 2 serious adverse events on sulfasalazine therapy, the safety monitoring of laboratory values is critical. Four of the 6 patients in whom sulfasalazine therapy was altered demonstrated abnormal laboratory values before the course-modifying laboratory result. This observation, coupled with the fact that the earliest course-modifying laboratory result occurred 3 weeks into therapy, should encourage the vigilant clinician that poor outcomes can be avoided with close initial laboratory monitoring. In addition, because these course-modifying laboratory results occurred an average of 13 weeks into sulfasalazine therapy and as late as 41 weeks into therapy, the currently described schedule of safety laboratory monitoring appears adequate.

In summary, the efficacy and safety of sulfasalazine therapy in CIU is comparable to that of cyclosporine. Dosages can be clinically effective up to 3 g/d; however, weekly escalation to an initial therapeutic dose of 2 g/d is appropriate. Without any reliable markers to detect which patients will be responsive to the existing array of therapies for refractory CIU, sulfasalazine presents a safe and effective therapeutic option.

References

- [1] Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA2LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009;64:1427–1443.
- [2] Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA2LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*. 2009;64:1417–1426.
- [3] Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy*. 2011;66:317–330.
- [4] Morgan M, Khan D. Therapeutic alternatives for chronic urticaria: an evidence-based review, part 1. *Ann Allergy Asthma Immunol*. 2008;100:403–412.
- [5] Morgan M, Khan D. Therapeutic alternatives for chronic urticaria: an evidence-based review, part 2. *Ann Allergy Asthma Immunol*. 2008;100:517–526.
- [6] Suarez-Almazor M, Belseck E, Shea B, Tugwell P, Wells G. Sulfasalazine for treating rheumatoid arthritis. *Cochrane Database Syst Rev*. 1998;2:CD000958.
- [7] Lichtenstein G, Hanauer S, Sandborn W. Management of Crohn's disease in adults. Practice Parameters Committee of American College of Gastroenterology. *Am J Gastroenterol*. 2009;104:465–483.
- [8] Kornbluth A, Sachar D. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010;105:501–523.
- [9] McGirt L, Vasagar K, Gober L, Saini S, Beck L. Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine. *Arch Dermatol*. 2006;142:1337–1342.
- [10] McConkey B, Amos RS, Durham S, Forster PJ, Hubbard S, Walsh L. Sulphasalazine in rheumatoid arthritis. *Br Med J*. 1980;280:442–444.
- [11] Lexi-Comp Online. Lexi-Drugs. Hudson, OH: Lexi-Comp; July 16, 2013. Available at http://online.lexi.com/lco/action/retrieve/docid/patch_f/7714?hl=anything. Accessed October 25, 2013.
- [12] Najib U, Bajwa Z, Ostro M, Sheikh J. A retrospective review of clinical presentation, thyroid autoimmunity, laboratory characteristics, and therapies used in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2009;103:496.
- [13] Gaig P, Olona M, Munoz-Lejarazu D, et al. Epidemiology of urticaria in Spain. *Investig Allergol Clin Immunol*. 2004;14:214.
- [14] Kozel M, Mekkes J, Bossuyt P, Bos J. Natural course of physical and chronic urticaria and angioedema in 220 patients. *J Am Acad Dermatol*. 2001;45:387–391.
- [15] Toubi E, Kessel A, Avshovich N, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy*. 2004;59:869–873.
- [16] Humphreys F, Hunter J. The characteristics of urticaria in 390 patients. *Br J Dermatol*. 1998;138:635–638.
- [17] Nettis E, Pannofino A, D'Aprile C, Ferrannini A, Tursi A. Clinical and aetiological aspects in urticaria and angio-oedema. *Br J Dermatol*. 2003;148:501–506.
- [18] Potter P, Kapp A, Maurer M, et al. Comparison of the efficacy of levocetirizine 5 mg and desloratadine 5 mg in chronic idiopathic urticaria patients. *Allergy*. 2009;64:596–604.
- [19] Maurer M, Rosen K, Hsieh H, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924–935.
- [20] O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol*. 1998;138:101–106.
- [21] Mitzel-Kaoukhov H, Staubach P, Muller-Brenne T. Effect of high-dose intravenous immunoglobulin treatment in therapy-resistant chronic spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2010;104:253–258.
- [22] Grattan C, O'Donnell B, Francis D, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol*. 2000;143:365–372.
- [23] Vena G, Cassano N, Colombo D, Peruzzi E, Pigatto P. Neo-I-30 Study Group. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol*. 2006;55:705–709.
- [24] Saini S, Rosen K, Hsieh H, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128:567–573.
- [25] Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128:202–209.
- [26] Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy*. 2010;65:1478–1482.
- [27] Toubi E, Blant A, Kessel A, Golan T. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy*. 1997;52:312–316.