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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

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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.

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 dapsone, 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.
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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 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).

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.

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.