Original Article

Treatment of Chronic Urticaria in Children with Antihistamines and Cyclosporine

Lisa Neverman, MD, and Miles Weinberger, MD *Iowa City, Iowa*

What is already known about this topic? Controlled clinical trials of cyclosporine have demonstrated efficacy and relative safety for cyclosporine for adults.

What does this article add to our knowledge? This report demonstrates that cyclosporine appears to be effective and safe for pediatric patients with chronic idiopathic urticaria resistant to antihistamines and that antihistamine resistance is not explained by the presence of autoantibodies as currently determined.

How does this study impact current management guidelines? Other agents proposed for antihistamine resistant chronic idiopathic urticaria include H2 antagonists, leukotriene modifiers, prednisone, doxepin, sulfasalazine, and omalizumab. The apparent relative efficacy and safety of cyclosporine justify considering cyclosporine an option for children with antihistamine resistant chronic idiopathic urticaria.

BACKGROUND: Chronic idiopathic urticaria, daily hives that last >6 weeks, can be resistant to antihistamines, even when higher than conventional doses are used. Other pharmacologic agents have been associated with inconsistent benefit.
OBJECTIVE: We examined the relationship of clinical characteristics and the presence of autoimmune antibodies to antihistamine resistance in children. We further examined the efficacy and safety of cyclosporine in children whose urticaria was resistant to antihistamine.
METHODS: Patients referred to the pediatric allergy and pulmonary specialty clinic at the University of Iowa Children's Hospital and diagnosed as having chronic idiopathic urticaria were identified during the period from August 2008 to July 2013. A retrospective examination of treatment and outcome was performed.
RESULTS: Forty-six patients, 26 female patients and 20 male patients, with chronic idiopathic urticaria were identified. The ages of 16 patients who were antihistamine resistant ranged from 9 to 18 years (median, 12.5 years). Those patients who were antihistamine responsive had a median age of 6 years, significantly lower than those who were antihistamine resistant ($P = .0001$). There was no significant association between autoimmune antibodies and antihistamine resistance. All the patients who were antihistamine resistant were treated with cyclosporine; all experienced complete resolution of urticaria at times that ranged from 2 days to 3 months (median, 7 days). Relapses responsive to repeated cyclosporine occurred in 5 of the patients after 1 week to 15 months (median, 6 months). Adverse effects were not seen in these patients.
CONCLUSION: Our data were consistent with efficacy and safety of cyclosporine for chronic urticaria in children when even high doses of antihistamines are ineffective. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)**

Key words: *Urticaria; Hives; Cyclosporine; Autoantibodies; Immunoglobulin E; Antihistamines; Cetirizine; Hydroxyzine*

Urticaria is commonly thought of as an acute response to allergic reactions. However, idiopathic acute urticaria is common, with 10% to 20% of the population experiencing transient hives once or twice in their lifetime.[1] Chronic urticaria (CU) is generally defined as daily hives that last 6 weeks or longer. Although acute urticaria and CU are both commonly responsive to antihistamines, CU can be resistant to antihistamines, even when higher than conventional doses are used. Additional pharmacologic agents, referred to as second-line measures, have been associated with inconsistent benefit.[2,3]

The identification of autoimmune antibodies to the high affinity receptor for IgE on mast cells and to IgE itself led to trials of immunosuppressant therapy. After several case reports and open-label studies that used cyclosporine for chronic idiopathic urticaria (CIU),[4-7] a randomized double-blind placebo-controlled trial documented the efficacy and relative safety of cyclosporine for CIU in adults.[8] Based on that study, we subsequently began using cyclosporine for our pediatric patients with CIU resistant to antihistamines. We previously reported our initial experience with 7 patients.[9] The current study examined

Department of Pediatrics, University of Iowa Children's Hospital, Iowa City, Iowa
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Corresponding author: Miles M. Weinberger, MD, Department of Pediatrics University of Iowa Children's Hospital, 200 Hawkins Drive, Iowa City, IA 52242-1083. E-mail: miles-weinberger@uiowa.edu.
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Abbreviations used
CIU- Chronic idiopathic urticaria
CU- Chronic urticaria

the clinical characteristics associated with response to therapy and the relationship of autoimmune antibodies to antihistamine resistance in children. We further examined the efficacy and safety of cyclosporine in the pediatric population.

METHODS

Patients with a diagnosis of CIU referred to the pediatric allergy and pulmonary specialty clinic at the University of Iowa Children's Hospital were identified from August 2008 to July 2013 from our electronic medical record. Approval was obtained from our institutional review board for this retrospective examination of treatment and outcome of these patients. Clinical evaluation had excluded allergic and physical urticaria. Our protocol for treating patients with CIU was to use gradually increasing doses of either cetirizine or hydroxyzine, a prodrug of cetirizine.[10,11] Doses were administered twice daily, consistent with the pharmacodynamic and pharmacokinetic characteristics of these antihistamines.[12-14] Patients whose urticaria was completely suppressed by antihistamines were defined as antihistamine responsive. Antihistamine resistance was defined as failure to effectively suppress urticaria to the extent that the patient was no longer troubled by daily hives when using hydroxyzine or cetirizine at doses of at least 75 mg hydroxyzine or 20 mg cetirizine twice daily for adolescents (scaled down for smaller children). If the patient was found to be antihistamine resistant, then low-dose cyclosporine was begun as the microemulsion formulation (Neoral, Novartis, Basel, Switzerland and generic equivalents) because of its more reliable absorption than the original formulation (Sandimmune, Novartis, Basel, Switzerland and generic equivalents).[15] The initial dosage of cyclosporine was approximately 3 mg/kg/d with half given morning and evening.

To maximize the safety of the cyclosporine, cyclosporine serum concentrations prior to the morning dose were monitored when no doses were missed for at least 3 days. This was done approximately 2 weeks after initiation of cyclosporine. If serum concentrations were lower than 125 ng/mL and urticaria persisted, then doses were adjusted up in 25-mg twice-daily increments but were kept below 200 ng/mL (serum concentrations to suppress transplantation rejections are generally >300 ng/mL). Serum urea nitrogen and creatinine levels also were monitored at regular intervals, at least every 4 weeks and more often after a dose increase. Blood pressures were measured at each clinic visit, at least every 3 months. Cyclosporine would be reduced once urticaria was effectively suppressed for a period of 1 to 3 months, depending on the prior duration of CU. For example, reduction would begin after 1 month of being hive free if the prior duration had been 4 months or less and 3 months if the prior duration had been for longer periods. Reductions would be done in 25-mg twice-daily increments at 2-week intervals as tolerated without prompt return of hives.

A measure of autoantibodies using the commercial CU index (IBT Laboratories, Lenexa, Kan)[16] was obtained for many but not all of the patients at the discretion of the clinician, generally influenced by the duration and severity of the CU. This test reports values ≥10 as indicating the presence of autoantibodies. The relationships among age, sex, CU index, and antihistamine resistance that requires cyclosporine were analyzed by the Fisher exact test.

RESULTS

From August 2008 to July 2013, 46 patients seen in the Pediatric Allergy Clinic were diagnosed with CIU. Of these 46 patients, the age range was 1 to 22 years, with a median of 9.5 years at the time of initial diagnosis (Table I). The sex distribution was 26 female patients (56.5%) and 20 male patients (43.5%). Twenty-two had CU index values obtained; 8 of the 22 had CU index values ≥10 (median, 42.5), consistent with the presence of autoantibodies. The ages of those with positive indices ranged from 5.5 to 22 years, with a median of 13.5 years. Six of the 8 were female patients ($P = .399$). The duration of hives before being seen in our clinic ranged from 1.5 to 72 months (median, 7.5 months).

Sixteen of the 46 (34.8%), 12 female patients and 4 male patients, were determined to be antihistamine resistant and were started on cyclosporine (Table I). There was little difference in the median prior duration of symptoms of patients who were antihistamine responsive or antihistamine resistant. The ages of the patients who were antihistamine resistant ranged from 9 to 18 years, with a median of 12.5 years. Those patients who were antihistamine responsive had a median age of 6 years, significantly lower than those who were antihistamine resistant ($P = .0001$). Of the 16 patients who were antihistamine resistant, a CU index had been obtained in 12, with only 5 (42%) having values ≥10 (range, 10 to >50; median, 17.6). There was no significant association between the CU index and antihistamine resistance ($P = .67$).

Once started on cyclosporine, each of the 16 patients experienced complete resolution of urticaria. The time to resolution for these 16 patients ranged from 2 days to 3 months, with a median time to initial resolution of 7 days based on patient report and earliest available clinic documentation. Serum cyclosporine levels measured at the time of resolution ranged from 66 to 227 ng/mL, with a median level of 94.5 ng/mL. After resolution of urticaria was documented, all the patients eventually underwent a gradual taper of cyclosporine. If urticaria recurred during that gradual reduction of dosage, the lowest 5 of the dose effective at complete urticarial suppression was resumed and maintained for a time. The total duration of cyclosporine treatment ranged from 2 to 17 months, with a median duration of 5.5 months.

Five of the 16 patients treated with cyclosporine (31.3%) experienced a relapse of urticaria after cyclosporine was discontinued. The time to urticarial relapse after cyclosporine discontinuation ranged from 1 week to 15 months, with a median of 6 months. All 5 of the patients responded to resumption of cyclosporine. No adverse effects attributable to the cyclosporine were identified based on either patient-initiated concerns or routine querying at scheduled clinic visits. None had elevated blood pressure, serum urea nitrogen, or serum creatinine levels.

Of the 46 patients enrolled, 3 had been previously diagnosed with other autoimmune disorders at the time of initial evaluation. One patient, age 22 years, with type 1 diabetes mellitus, did not have antihistamine resistant CIU but did have a CU index value >50. Juvenile idiopathic arthritis was a known diagnosis