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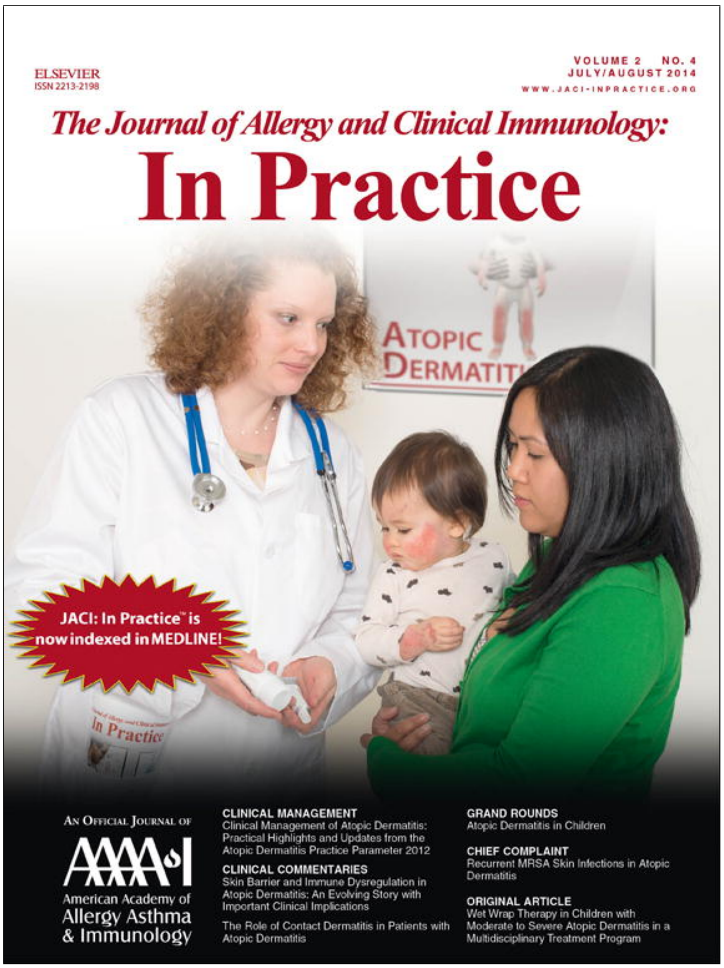

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Original Article

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;2:434-8)**

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 $\geq$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 $\geq$10 (median, 42.5), consistent with the presence of autoantibodies. The ages of those with positive indices ranged from 5.5 to 22 years, with a median of 13.5 years. Six of the 8 were female patients ($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 $\geq$10 (range, 10 to >50; median, 17.6). There was no significant association between the CU index and antihistamine resistance ($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 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 for a 14-year-old girl. Her CU index was 2, and her urticaria was

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TABLE I. Relationship between a positive CU index and antihistamine resistant urticaria by age group

	No. female patients					No. male patients					
	+Index		−Index			+Index		−Index			
Age (yrs)	AHres	AHrsv	AHres	AHrsv	No index*	AHres	AHrsv	AHres	AHrsv	No index*	No. all patients
<5	0	0	0	0	6	0	0	0	0	5	11
6-10	0	1	0	1	4	0	0	0	3	4	13
11-15	2	0	3	1	3	2	0	3	1	2	17
16-22	2	1	2	0	0	0	0	0	0	0	5
Total	4	2	5	2	13	2	0	3	4	11	46

+Index, Positive CU index (≥10); *−Index,* negative CU index (<10); *AHres,* antihistamine resistant (no suppression from maximal dose of antihistamine); *AHrsv,* antihistamine responsive.
*CU index was not performed.

found to be antihistamine responsive. Autoimmune thyroiditis was present in a 12-year-old boy who was found to have a CU index higher than 50 but whose symptoms and urticaria were controlled with antihistamines. Antinuclear antibodies were present in 3 of 16 patients from whom the data were obtained. All 3 of them were antihistamine resistant and were started on cyclosporine ($P = .06$). The CU index was 14 in one of these patients, 3.9 in another, and not performed in one.

DISCUSSION

Analysis of our data supports the effectiveness and safety of cyclosporine for the treatment of children with CIU unresponsive to high doses of hydroxyzine or cetirizine. Moreover, cyclosporine was associated not just with improvement but typically resulted in complete cessation and apparent extended remissions for 11 of the 16 patients. The 5 patients who relapsed had cessation of urticaria upon re-treatment with cyclosporine. Characterization of the patients we saw found significant differences in the ages of children who were antihistamine resistant and those who were antihistamine responsive. Those patients who did not respond to antihistamines were significantly older; none were younger than age 9 years (Table I). Although an antihistamine regimen was universally effective in younger preadolescent children, this therapy was only effective in 5 of the 22 adolescents in our study. These results also are consistent with the results previously published of our initial experience with CIU in children.[9] In that series, 7 of 54 children were found to be antihistamine resistant and responsive to cyclosporine therapy. The ages ranged from 9 to 16 years, with 4 of the 7 being female patients. Those patients all achieved extended periods of apparent remission of urticaria as well, with no adverse events reported.[9]

Many patients with CIU were found to have autoantibodies to the high affinity receptor for IgE on mast cells or to IgE itself. Although an elevated CU index ≥10 and antihistamine resistance were both more common in female patients and adolescents, we did not find an association between the autoantibodies, as measured by the commercial CU index, and antihistamine resistance. A report by Cho et al[17] found that CU index values occurred among patients with other autoimmune conditions in the absence of urticaria. Although most frequently in CIU, values did not correlate with the presence or severity of urticaria.[17] However, Biagtan et al[16] found significantly higher antihistamine resistance in those patients with positive urticaria indices in their study of adults with CIU. Sabroe et al[18] identified autoantibodies to the high affinity receptor for IgE on mast cells with and without histamine-releasing activity. They reported more severe urticaria in patients with serum histamine-releasing activity. Kaplan and Joseph[19] found 55 of 104 patients with CIU to be positive for evidence of autoantibodies, with none in 35 controls.

Other pharmacologic agents have been described for use in patients whose urticaria is not adequately controlled with an H1 antihistamine. These medications have included the addition of H2 antagonists, leukotriene modifiers, prednisone, doxepin, sulfasalazine, dapsone, hydroxychloroquine, and omalizumab. While, anecdotally, some patients may exhibit additive benefit from the addition of an H2 to an H1 antagonist, the overall data are unconvincing for more than a minimal effect in an occasional patient.[20] The role of leukotriene modifiers in CU has been associated with variable results. There are case reports that have suggested symptom improvement for CIU, [21,22] but blinded, placebo-controlled trials failed to demonstrate efficacy compared with antihistamines.[23-26] A systematic review by Di Lorenzo et al[27] concluded that leukotriene receptor antagonists were not advantageous for CIU when administered either as monotherapy or in combination with antihistamines.

Prednisone is often, although not always, effective in suppressing CU but is undesirable because of its well-recognized adverse effects when used for more than short periods. Doxepin, a tricyclic antidepressant, was shown to provide clinical improvement in CU but not complete cessation of urticaria or remission and was associated with lethargy, dry mouth, and constipation.[28] In a retrospective study of sulfasalazine in adults with CIU, 5 of 31 were reported to have complete relief of symptoms within 6 months, but there was no control group, and 2 patients had serious adverse effects[29] Data related to dapsone and hydrochloroquine were analyzed in a recent review of alternative agents for refractory CIU.[30] There has been some limited clinical benefit reported for dapsone, but adverse effects are concerning. Hydroxychloroquine is not associated with convincing data to justify its use. Although there have been case reports of benefit for CIU from other immunosuppressive agents, none, other than cyclosporine, have been subjected to controlled clinical trials.

A controlled clinical trial of omalizumab for CU demonstrated significant decrease in hives.[31] However, complete resolution of symptoms, both urticaria and pruritus, was only achieved in 44% with the maximum dose used, and symptoms of pruritus and the number of hives increasingly returned after discontinuation of the monthly injections. In contrast, analysis of our data in both this and our previous study demonstrated complete suppression, not just a symptomatic decrease, in all the patients. Moreover,

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remission appeared to occur both in our patients and in adult patients in the initial controlled clinical trial,[8] although longer-term controlled clinical trials are needed to confirm those clinical impressions. Relapses that did occur after varying periods of remission in 5 of our patients again responded to cyclosporine with complete suppression of urticaria.

A limitation of this report is its retrospective nature. Although there is the suggestion that remission is induced by cyclosporine, it would take a placebo-controlled trial to definitely distinguish drug induced from spontaneous remission. While there was no significant association of autoimmunity, as measured by the commercial CU index, and antihistamine resistance, it might be that larger numbers of patients could identify a statistically significant association. Nonetheless, a sufficient association for reliable predictive purposes appears unlikely based on our data. Although the children in our study were followed closely and queried regarding adverse effects, it also may be that minor adverse effects were not recorded in this retrospective review. The controlled clinical trial of Grattan et al[8] of adults indicated that adverse effects were common in the patients who received cyclosporine but were not sufficiently severe to require cessation of the medication. Because the researchers did not compare the presence of similar symptoms in the patients who received placebo, it cannot be determined if these were actually drug-related adverse effects.

This examination of the outcome of children with CIU indicates that treatment should initially be with a dose of cetirizine or hydroxyzine at doses progressively increased, as needed and tolerated, to at least 75 mg hydroxyzine or 20 mg cetirizine given twice daily, scaled down for smaller children. Most children with CIU can be effectively controlled with these medications. The potential therapeutic merit of a progressively increasing dose as needed and tolerated has been previously described.[2,32] Of the various antihistamines, cetirizine and hydroxyzine (a prodrug of cetirizine) appear to be the best choices for initial therapy, based on pharmacodynamic studies that examined the ability to suppress a histamine-induced wheal.[10-14] Levocetirizine, the active optical isomer of cetirizine, has been studied at up to 4 times the usual dose with impressive dose-response effect.[32] Much lesser effect was apparent with desloratadine, the major active metabolite of loratadine, which has been shown to have a lesser antihistaminic effect than other antihistamines.[14] Because the major active metabolite of hydroxyzine is cetirizine, an equivalency of 25 mg hydroxyzine and 10 mg cetirizine has been demonstrated.[33] Despite the long-outdated package insert of hydroxyzine that indicates 4 times daily dosing, suppression of a histamine-induced wheal is of sufficient duration to justify twice daily dosing.[10]

Our practice in the use of cyclosporine has involved careful monitoring of blood pressure and the reversible renal function that can be associated with use of this medication. We also have carefully maintained serum concentrations well below the levels used for transplantation rejection by keeping morning predose concentrations at steady state, generally lower than 200 ng/mL. These serum concentrations and serum urea nitrogen and creatinine levels have been obtained at regular intervals, initially at 2-week intervals and at 4-week intervals once stability was seen.

We were generally able to identify unresponsiveness to antihistamines within approximately 2 weeks and thereby identify patients for whom cyclosporine should be started. CU can interfere with sleep because of the pruritus and can cause discomfort and embarrassment because of the variable rash and occasional angioedema. There is little to be gained by spending time on other antihistamines whose pharmacodynamics do not match that of hydroxyzine or cetirizine.[14] Analysis of our data demonstrated the merit of rapidly assessing benefit from increasing doses of an effective antihistamine and moving on to cyclosporine when high doses of antihistamines are ineffective. In choosing a second-line agent when antihistamine resistance is observed, omalizumab and cyclosporine are the best choices based on current data. Commercial motivation has resulted in a large multicenter study that supported the value of omalizumab.[31] Cyclosporine, a generic medication, has the potential for efficacy and safety at considerable lower cost, although based on more limited data. Nonetheless, cyclosporine has been used in doses similar to those in our study extensively for other autoimmune diseases, and serious adverse effects appear unlikely. If our clinical impression of inducing remission is supported, then this may further influence the choice.

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