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Experience with Cyclosporine in Children with Chronic Idiopathic Urticaria

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**Study performed while a fellow in the Pediatric Allergy and Pulmonary Division, University of Iowa College of Medicine; currently at Pediatric Pulmonary and Allergy/Immunology Divisions of William Beaumont Hospital, Royal Oak, Michigan, †Pediatric Allergy and Pulmonary Division, University of Iowa College of Medicine, Iowa City, Iowa*

Abstract: **Background: The identification of an autoimmune mechanism for many patients with chronic idiopathic urticaria (CIU) was used as a rational for a controlled clinical trial of cyclosporine for adults with CIU not responsive to usual measures. That randomized placebo controlled clinical trial demonstrated clinical efficacy, acceptable safety, and a suggestion of inducing remission in such patients. Objective: To report our experience with cyclosporine in pediatric patients with CIU. Methods: Fifty-four patients with CIU were referred to us during the period from 2000 through June of 2005. Seven of those, aged 9–16, failed therapy with high dose antihistamines even with the addition of alternate morning prednisone. Neoral brand of cyclosporine, 3 mg/kg/day divided b.i.d., was initiated in these patients. Cyclosporine serum concentrations, blood urea nitrogen (BUN), creatinine, and blood pressure were routinely monitored. Results: All had cessation of hives. This occurred after 1–4 weeks for six of the seven and 8 weeks for one. While some experienced relapses, all were eventually off of all medications and free of hives. None of the seven experienced any adverse effects. Conclusions: Our experience in children is consistent with a previous controlled clinical trial in adults and supports the efficacy and safety of cyclosporine for CIU. However, we recommend that it be reserved for those whose CIU that is resistant to conventional measures and that patients be carefully monitored with cyclosporine serum concentrations and measures of renal function.**

Following several case reports and open-label studies using cyclosporine for chronic idiopathic urticaria (CIU) (1–4), a randomized double-blind placebo controlled study documented the safety and efficacy of cyclosporine for CIU in adults (5). Based on that report, we subsequently began using cyclosporine in our paediatric patients with CIU resistant to conventional measures. In this report, we describe our experience using cyclosporine with seven patients referred to our tertiary care center with severe CIU who failed to respond to vigorous conventional treatment.

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METHODS

Patient Selection

Paediatric patients seen at our tertiary referral clinic with a diagnosis of CIU from 2000, the year of the first published controlled clinical trial using cyclosporine for this problem (5), through June of 2005 were identified. The diagnosis of CIU was based on daily crops of hives recurring for greater than 6 weeks with no apparent inciting cause.

Study Design

Charts were reviewed to identify demographics, criteria for diagnosis of CIU, and treatment response. All patients had detailed histories and physical exams. None had evidence for systemic disease other than the urticaria, and none of the histories were consistent with exogenous causes of the hives. For those where cyclosporine was to be used because of resistance to vigorous conventional measures, baseline blood urea nitrogen (BUN) and creatinine were measured. Initial dosage of cyclosporin was 3 mg/kg/day divided into twice daily doses, using a microemulsion formulation (Neoral) because of its more predictable absorption (6). Autologous serum skin testing was not performed in these patients since the results of such testing would not have influenced the clinical decision for a trial of cyclosporine. The in vitro test for autoantibodies to IgE or the high affinity receptor for IgE on mast cells was not available at the time these patients were seen.

Those receiving cyclosporine had cyclosporine serum concentrations, BUN, and creatinine monitored, initially weekly with decreasing frequency to monthly once all values were found to be stable. Blood pressure was performed monthly initially with decreasing frequency to 3 months intervals once stable doses were attained. Blood for cyclosporine serum concentrations were drawn prior to a morning dose when none had been missed for at least 3 days and at least 10 hours had passed since the evening dose.

While serum concentrations greater than 300 ng/mL are used for immunosuppression following organ transplant, we avoided sustained peak levels of over 200 ng/mL to minimize risk of toxicity. As symptoms were controlled, alternate-morning corticosteroids were tapered after starting cyclosporine. Once there was cessation of hives for a month, cyclosporine was tapered at 2–4 weeks intervals until completely discontinued or the lowest dose associated with prevention of hives was identified.

RESULTS

A total of 54 pediatric patients with CIU were seen at our specialty clinic from 2000 through June of 2005. All met the criteria for the diagnosis of CIU; symptoms present for ≥6 weeks duration with no identifiable cause. Specifically, lesions were urticarial in appearance, pruritic, and individual lesions would fade over the course of a day with new crops appearing daily without identifiable inciting factors. All patients were treated with antihistamines, generally hydroxyzine using high doses if necessary, as the mainstay of therapy. In patients with inadequate control or severe symptoms, short courses of oral corticosteroids were used. Longer courses of oral corticosteroids, administered on alternate mornings, were reserved for patients with severe symptoms that were not controlled on a maximum dose of antihistamines. Of the 54 patients, seven failed to experience satisfactory resolution of troublesome hives during treatment with antihistamines, even at high doses and alternate-morning prednisone. The clinical details for those seven who subsequently received cyclosporin are described below.

Case 1

SW was a 13-year-old girl (47 kg) who initially presented with a history of daily hives for 8 months. She failed therapy with hydroxyzine that had been gradually increased to 125 mg twice a day, prednisone up to 40 mg every other morning, and ranitidine. Within 2 weeks of starting therapy with cyclosporine, 75 mg twice a day (3 mg/kg/day), her symptoms markedly improved, and she was tapered off prednisone. Hydroxyzine was continued, and complete absence of urticaria was achieved within 8 weeks of starting cyclosporine. The dose of cyclosporine was gradually reduced and then stopped after 13 weeks. She then remained in remission for 16 months before experiencing the first of two relapses. Cyclosporine was re-initiated for both relapses with prompt cessation of hives. She was tapered off cyclosporine both times within 5 months. During her final remission, she was symptom free and off therapy for 2 months. She unfortunately was involved in an unrelated motor vehicle accident and died from sustained head injuries. Throughout her therapy with cyclosporine, her BUN and creatinine remained normal. Her blood pressure remained within normal limits and her cyclosporine level on the highest dose was 171 ng/mL. There were no reported adverse effects from the use of cyclosporine.

Case 2

KK was a 13-year-old girl (74 kg) who initially presented to our clinic with a history of daily hives for 11 months. She had no response from hydroxyzine 100 mg twice a day as well as prednisone 40 mg every other morning. Cyclosporine, 125 mg twice a day (3 mg/kg/day), was started. Her symptoms rapidly and completely resolved. Oral corticosteroids were tapered within 3 weeks of starting the cyclosporine. Her dose of cyclosporine was decreased to 100 mg twice a day within a month. She was slowly tapered off cyclosporine over 6 months. She remained in remission off all therapy for 6 months until she experienced her first relapse. She was again treated with cyclosporine with dramatic improvement within days and was tapered off cyclosporine within 5 weeks. She remained in remission for 37 months until her second relapse. She was again well controlled on cyclosporine (100 mg twice daily) and hydroxyzine and eventually tapered herself off of all medication. Throughout her therapy with cyclosporine, her BUN and creatinine remained normal. The cyclosporine level at the highest dose was 179 ng/mL. Her blood pressure has been normal for her age at all clinic visits. She denied any adverse effects from the medications.

Case 3

BS was a 14-year-old girl (98 kg) who initially presented to our clinic with a history of hives for 11 months duration. She had previously failed therapy with hydroxyzine 100 mg twice daily. She had minimal improvement with the addition of prednisone 40 mg every other morning. The initiation of cyclosporine 100 mg twice daily to her regimen (< 3 mg/kg/day) resulted in cessation of urticaria within 1 week. Oral prednisone therapy was tapered and she did well on cyclosporine and cetirizine. Cyclosporine was slowly tapered as tolerated. She experienced two relapses after stopping cyclosporine. Within approximately 24 months of intermittent use of cyclosporine, she achieved remission of all symptoms. She remained symptom free and off all medications including cetirizine for 26 months. Her BUN, creatinine, and blood pressure remained normal while on cyclosporine. The maximum cyclosporine level attained was 137 ng/mL. She denied any adverse effects from the use of cyclosporine.

Case 4

PV was a 14-year-old boy (62 kg) who initially presented with a history of chronic urticaria for 3 years. He had failed therapy with hydroxyzine 75 mg twice a day as well as incomplete responses to short courses of oral corticosteroids. He was started on cyclosporine, 100 mg twice a day (3 mg/kg/day), and continued on hydroxyzine. His symptoms completely resolved within 1 week of starting cyclosporine. The dose of cyclosporine was gradually reduced, and he was completely off therapy within 7 months. He then remained in remission for 6 months off all medications. He subsequently experienced two relapses. The first required varying doses of cyclosporine for 17 months as repeated attempts to incrementally reduce and stop cyclosporin resulted in return of urticaria. The second relapse required only 1 month of cyclosporine. In between the two relapses, he was symptom free and off all medications for 5 months. He is currently off of cyclosporine and is well controlled on fexofenadine alone with no hives for 7 months. Throughout his therapy with cyclosporine, his blood pressure remained within normal limits for his age. His BUN and creatinine also remained normal. The maximal cyclosporine level attained was 190 ng/mL. He denied any adverse effects from the use of cyclosporine.

Case 5

JB was a 16-year-old boy (68 kg) who initially presented to our clinic with a history of daily hives for 13 months. His symptoms persisted despite the use of high dose antihistamines and alternate-morning prednisone. He was started on cyclosporine, 125 mg twice a day (3 mg/kg/day). The alternate-morning prednisone was tapered, and he experienced complete resolution of hives within 4 weeks of therapy. Within 10 weeks of therapy while asymptomatic, he self-discontinued all medications. He then remained off all medications and remained symptom free at the time of last contact (47 months). During his short-term use of cyclosporine, he denied any adverse effects, and his vital signs including blood pressure remained normal. His BUN and creatinine also remained stable while on therapy. The maximal cyclosporine level attained was 144 ng/mL.

Case 6

AB was a 9-year-old boy (35 kg) who initially presented with a history of hives for 3 months. His previous therapy included hydroxyzine 60 mg daily, montelukast, ranitidine and alternate-morning prednisone; all of which failed to control his symptoms. He was started on cyclosporine, 50 mg twice a day (3 mg/kg/day), and hydroxyzine, while prednisone was tapered. He achieved complete resolution of urticaria within 2 weeks. He remained symptom free on cyclosporine and hydroxyzine

for 10 weeks at which time all therapy was self-discontinued. He was symptom free and off all medications for 21 months at his last contact. There were no reported adverse effects from cyclosporine, and his blood pressure remained normal while on therapy. His BUN and creatinine also remained normal while on cyclosporine. The maximal cyclosporine level attained was 140 ng/mL.

Case 7

AS was a 16-year-old girl (54 kg) who presented to our clinic with a history of hives and angioedema for 2 months. Her symptoms failed to respond to high dose hydroxyzine and ranitidine as well as a 1 month course of oral prednisone. She was started on cyclosporine, 100 mg twice a day (3 mg/kg/day) with minimal improvement in her symptoms during the first month of therapy. She was also provided with an auto-injectable epinephrine device for her recurrent episodes of angioedema. After 8 weeks of therapy, her symptoms of urticaria were controlled, although she continued to experience infrequent episodes of angioedema. She was tapered off cyclosporine after approximately 5 months of therapy. She was symptom free (without urticaria and angioedema) off all medications for 13 months at the time of last contact. She did not report any adverse effects while on cyclosporine. Her blood pressure remained within normal limits while on therapy. Her BUN and creatinine also remained normal while on therapy. The maximal cyclosporine level attained was 195 ng/mL.

DISCUSSION

All seven pediatric patients with CIU who failed therapy with traditional medications during the study period were able to achieve remission of symptoms shortly after starting therapy with low dose cyclosporine (≤3 mg/kg/day of the Neoral brand). Although several patients experienced relapses after tapering or discontinuing therapy, all seven of the patients are currently symptom free and off all medications. There were no adverse effects observed in these patients. All tolerated the medication without any changes in BUN, creatinine, or blood pressure. The results in our seven patients with CIU were therefore consistent with those of previous reports in adults (5,7). Although the use of cyclosporine to treat CIU in children has not been previously reported, low dose cyclosporine has been used with efficacy and safety for other diseases in the pediatric population (8–10).

The mechanism of benefit for calcineurin inhibitors such as cyclosporine for chronic urticaria has been examined by Marsland et al (11). Based on previous information that chronic urticaria resistant to treatment with antihistamines was often autoimmune in nature, they examined the effect of sera from urticaria patients known to have functional IgG antibodies directed against the alpha subunit of the IgE receptor. Adding sera from patients with autoimmune chronic urticaria to leukocytes from healthy donors resulted in histamine release that could be inhibited in a dose-dependent manner when the leukocytes were pre-incubated with cyclosporin or another calcineurin inhibitor, pimecrolimus. No inhibition was seen with methotrexate, diphenhydramine, or hydroxyzine (11).

As indicated from our experience that only seven of 54 children referred to our specialty clinic could not be controlled with conventional measures. Antihistamines alone are frequently quite effective in controlling chronic urticaria in the paediatric population. While so-called 2nd generation antihistamines are associated with little or no sedation with initial therapy, sedation from the much less expensive classical antihistamines is transient, even in higher than usual doses (12,13). A classic antihistamine, hydroxyzine, appears to have the most favorable pharmacodynamic effects with a greater intensity and duration of action than others (14,15). Initial sedation from hydroxyzine appears to be from about 2–6 hours after a dose while duration of suppression of histamine-induced wheal is 24 hours (16). This permits the strategy of beginning doses at bedtime to minimize even the effect of initial sedation, which will then occur during a usual sleep time. Increases can then be given if needed and most patients eventually tolerate higher doses without drowsiness (12,13). Of the second generation of antihistamines, cetirizine, an active metabolite of hydroxyzine, has been demonstrated to have greater potency than desloratadine, an active metabolite of the popular loratadine (17). While the efficacy of H_1 antihistamines is well established, the role of H_2 antihistamines is less clear. Despite some controlled clinical trials demonstrating measurable additive effect, the experience of many is that additional effectiveness is not generally apparent in clinical practice. While there has also been interest in montelukast for chronic urticaria, it has been shown to have no additive effect to even a relatively weakly potent antihistamine such as desloratadine (18).

In conclusion, low dose cyclosporin is a safe and effective alternative for the minority of pediatric patients with CIU resistant to antihistamines. While a controlled clinical trial of cyclosporine for CIU in pediatric patients would be desirable, the relative infrequency of resistant CIU in the pediatric population will make that difficult without a large multi-center study over an extended

period. This current report suggests that the efficacy and safety are at least as great in children and adolescents as in adults.

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