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Letters

Another look at cyclosporine for treating antihistamine-resistant chronic spontaneous urticaria

There are only two treatments with demonstrated efficacy in randomized placebo controlled clinical trials for antihistamine-resistant chronic spontaneous urticaria (CSU), cyclosporine[1] and omalizumab.[2] The latter is a commercial product that was well studied to obtain FDA approval for marketing as a treatment for CSU within the past 5 years. Cyclosporine is a generic drug that was first demonstrated in a randomized placebo controlled trial to be an effective treatment for CSU almost 20 years ago.[1]

My experience with cyclosporine began following that first controlled clinical trial of cyclosporine for CSU.[1] At the time, I was caring for seven adolescents, ages 9 to 16, 3 boys and 4 girls, who were completely resistant to vigorous treatment with antihistamines at 4 times usual doses, other second-line medications, and oral corticosteroids.[3] Their previous duration of urticaria ranged from 2 to 36 months (median 11 months).

Before undertaking treatment of pediatric patients with a drug for which I had no prior experience, I first set about learning more about the pharmacokinetics and pharmacodynamics of cyclosporine in order to ensure that I would do no harm with this potentially potent immunosuppressant. I learned there were two distinct formulations of cyclosporine, an original formulation known as non-modified (original brand name Sandimmune) and a subsequently introduced modified microemulsion formulation (original brand name Neoral). The newer modified formulation is more reliably absorbed[4] and had not been available for use in the earlier study of cyclosporine for CSU.[1] There are currently FDA approved generics for both formulations but they are not interchangeable.[5] I also learned that efficacy and toxicity of cyclosporine were related to serum concentration with a narrow therapeutic index. Rates of elimination and consequently dosage could vary among patients. Serum concentrations over 300 ng/ml were needed for sufficient immunosuppressant effect in transplant rejection, and the risk of adverse effects on renal function also increased with increasing blood levels.

Armed with this knowledge, I undertook the treatment of those 7 teenagers with frustratingly antihistamine-resistant CSU. I began with 3 mg/kg/day administered as twice daily divided doses. A predose morning blood sample after one week of treatment and then monthly was used to keep serum concentrations below 200 ng/ml, chosen as a concentration less likely to be associated with adverse effects. Care was taken to ensure that there were no missed doses during the 3 days prior to the blood drawing based on a mean half-life of greater than 8 hours (range up to 18 hours). If hives were persisting and initial serum concentrations were under 100 ng/ml, a dose increase was made to attain blood concentration between 100 and 200 ng/ml. Unlike in previously published studies of cyclosporine for CIU,[6] no adverse effects were clinically apparent in the 7 patients, and monthly monitoring found no increase in blood pressure or creatinine.[3] Cessation of urticaria occurred in all after a median duration of 2 weeks of treatment with cyclosporine. Relapses that occurred in 3 of the 7 patients were only after many months following cessation of treatment during which time they had been free of urticaria.[3]

Encouraged by the response to cyclosporine in those 7 patients, the same pharmacokinetically based protocol was continued and eventually applied to 16 subsequent children and adolescents with chronic antihistamine-resistant spontaneous urticaria.[7] Ages and results were similar to the first 7 patients treated. The median time to cessation of urticaria was 7 days and the median total duration of cyclosporine administration including very slow tapering was 5 months. Adverse effects were again not seen; blood pressure and renal function were not affected. Relapses occurred in only 5 of the 16, again only after many months of being symptom-free without any medication.

In contrast to complete resolution of hives and pruritus from cyclosporine in all of our patients treated with cyclosporine, a major publication on the use of omalizumab for CSU reported only 53% of patients receiving omalizumab had resolution of hives and only 44% had complete resolution of both hives and pruritus.[2] In contrast to the return of hives when omalizumab was discontinued, extended periods of remission continued following cessation of treatment with cyclosporine. Although relapses eventually occurred in 8 of the 23 patients in the 2 reports, they occurred only after prolonged symptom-free periods following cessation of all treatment.[3,7] Treatment with cyclosporine for the relapse would then again provide relief of the hives and result again in prolonged remission following subsequent cessation of medication.

An extensive review of the treatment of urticaria that included cyclosporine was included in a practice parameter of the major allergy organizations.[6] That review provided additional references supporting the clinical efficacy of cyclosporine for CSU and acknowledged that observational studies indicated that cyclosporine was capable of inducing sustained remission following cessation of medication. Adverse effects of cyclosporine were described in that review that were not seen in our observational reports.[3,7] However, the studies referenced in the practice parameter did not utilize dose guidance by therapeutic drug monitoring. Moreover, the doses used were generally 4 to 5 mg/kg/day[6] in contrast to the initial dose in our reports of 3 mg/kg/day with half

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given morning and evening.[3,7] An estimated whole sale price of $650 per month was included in the review for the original brand name of the modified cyclosporine formulation, Neoral,[6] but the retail price at CVS pharmacy on-line of FDA designated therapeutically equivalent generics[5] was $103 for sixty 100 mg tablets,[8] which would have been a month's supply at about 3 mg/kg/day for a 70 kg patient.

Monitoring with monthly blood drawing for cyclosporine blood levels and renal function creates a degree of complexity to treatment, but the cost of omalizumab will be substantially greater, and treatment will be longer. Duration of treatment with omalizumab will be necessary until natural remission occurs, Natural remission rates for children are reported to be 19, 54, and 68% at 1, 3, and 5 years, respectively.[9] For adults, natural remission rates are somewhat longer.[10] Treatment with cyclosporine is likely to be associated with much earlier sustained remission following cessation of medication.

In summary, the evidence suggests that cyclosporine, used as the microemulsion modified formulation with appropriate clinical and therapeutic drug monitoring, has greater efficacy and will be associated with much earlier complete medication-free remission of CSU than omalizumab and at much lower cost. Experience and data to date are promising in children and adolescents with antihistamine-resistant CSU. Further controlled clinical trials are indicated for all ages using the modified microemulsion cyclosporine formulation with dosage guided by therapeutic drug monitoring.

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