
Cyclosporin A in hyperimmunoglobulin E syndrome

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Background: The hyperimmunoglobulinemia E syndrome is a serious disorder of an unknown etiology without effective treatment. Cyclosporin A has immunosuppressive properties. Its effect in a patient with hyperimmunoglobulinemia E syndrome was evaluated.

Methods: We report a 3-year-old boy with severe hyperimmunoglobulinemia E syndrome in whom various therapeutic modalities were ineffective. He was started on cyclosporin A 3 mg/kg/d for 6 months. We examined several humoral and cellular immune functions during the treatment period and monitored his clinical condition.

Results: Marked improvement in his clinical condition was observed during therapy with cyclosporin A. There was a significant decrease in serum IgE and significant increase in neutrophil chemotactic function. No change in CD40 ligand expression was observed. Cyclosporin A blood level did not exceed 150 ng/mL during the study.

Conclusions: A small dose of cyclosporin A (3 to 5 mg/kg/d) is beneficial in patients with hyperimmunoglobulinemia E syndrome. It should be considered in severe cases where other therapeutic modalities have failed.

Ann Allergy Asthma Immunol 1997;78:413-4.

INTRODUCTION

The hyperimmunoglobulinemia E syndrome is a rare immunodeficiency disorder characterized by recurrent severe staphylococcal abscesses of the skin, lung infections with pneumatocele formation, chronic eczematoid dermatitis, and coarse facial features. Despite extensive investigation, the only consistent laboratory abnormalities in these patients are extremely high serum IgE levels and elevation in the number of eosinophils in the blood.¹ The etiology of this syndrome is still unknown, but recent studies suggest an important role for Th2 lymphocytes associated with increased levels of interleukin 4.² The most successful treatment is life-long, continuous antistaphylococcal antibiotic therapy,³ but no definite

therapy is available. In this report we describe the beneficial effect of treatment with low dose cyclosporin A in a patient with hyperimmunoglobulinemia E syndrome, and discuss the possible mechanisms of action.

CASE REPORT

This 3-year-old boy suffered from recurrent skin abscesses, from which *Staphylococcus* was cultured many times, with coarse facial appearance from early infancy and at age 2 had an episode of pneumococcal pneumonia with pneumatocele formation. He never experienced any fungal infections. The results of the relevant laboratory tests are summarized in Table 1. The clinical picture with the very high serum IgE levels (31,500 IU/mL), confirmed the diagnosis of the hyperimmunoglobulinemia E syndrome. The patient was treated intravenously with antibiotics and his condition improved but no change in his skin lesions was observed. After obtaining an informed consent from his parents, we started

therapy with cyclosporin A, 3 mg/kg/day. Serum cyclosporin A trough levels were around 50 ng/mL on various occasions. A gradual decrease in IgE was noted at approximately 500 IU. An improvement in chemotactic function was also seen. No change in the expression of CD40 ligand on activated CD4 cells was found. The clinical condition of the child improved dramatically and after 3 weeks of cyclosporin A treatment his skin lesions cleared completely and remained clear for the next 6 months. At that point cyclosporin A therapy was discontinued and after several weeks the skin condition deteriorated. Another episode of pneumonia followed by pneumatocele formation occurred. We resumed cyclosporin A (3 mg/kg/d) administration and again observed a rapid and dramatic improvement. Monitoring cyclosporin A side effects, such as renal function, did not reveal any abnormalities during the followup period. The child is currently in very good general condition and continues to receive cyclosporin A.

DISCUSSION

Cyclosporin A is a known immunoregulatory agent that exerts its main effect on the cellular immune response primarily by decreasing interleukin-2 production by T cells. Its main clinical use is in preventing graft rejection and it was found beneficial also in several autoimmune disorders. While various side effects have been described, low blood levels of cyclosporin A as found in our case, were never associated with any serious side effect.

Recently cyclosporin A was found to inhibit CD40 ligand expression on activated T lymphocytes.⁴ CD40 ligand has a crucial role in the switching of B lymphocytes to IgE-producing

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Received for publication August 5, 1996.

Accepted for publication in revised form October 7, 1996.

Table 1. Immunological Variables Before and During Cyclosporin A Therapy

	Before	During
Eosinophils, %	11	4
Absolute Eosinophil count (per mm ³)	1650	400
IgG, mg/dL	850	825
IgA, mg/dL	28	33
IgM, mg/dL	98	85
IgE, IU/mL	31,500	500
CD4, %	43	39
CD8, %	24	29
CD40 ligand, %	27	34
Chemotaxis, % of control	62	87

plasma cells. We therefore investigated its expression in the patient's CD4⁺ lymphocytes before and after therapy, but were unable to show any change in its expression.

It is well established that the balance between Th1 cells, which produce interleukin-2 and interferon- γ , and Th2 cells, which produce interleukin-4, 6 and 10, is important for controlling IgE production. Indeed, Del Prete et al⁵ found that patients with hyperimmunoglobulinemia E syndrome had a lower proportion of circulating T cells able to produce interferon γ , and that T cell clones from these patients support more IgE synthesis than did those derived from normal healthy controls. Cyclosporin A may alter the balance between Th1 and Th2 response. Indeed, cyclosporin A can switch the immune response from a humoral to a cell-mediated one.⁶ For example, cyclosporin A markedly enhanced delayed type hypersensitivity responses to *Leishmania major* in BALB/c mice which usually produce high levels of

IgE.⁷ Furthermore, cyclosporin A increases in vivo circulating levels of interferon γ in atopic patients.⁸

We suggest that the beneficial effect of cyclosporin A observed in our patient with hyperimmunoglobulinemia E syndrome is due to its ability to shift the immune response from a predominance of Th2 to Th1.

Several anecdotal reports of favorable results of cyclosporin A in hyperimmunoglobulinemia E syndrome have been described;⁹ a multicenter, double-blind controlled study should be initiated to investigate the clinical and laboratory effect of cyclosporin A in this severe syndrome.

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