

Tacrolimus immunosuppression – An association with asymptomatic eosinophilia and elevated total and specific IgE levels

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Abstract: *De novo* development of food allergy is an infrequent but potentially serious complication of transplantation. An increased prevalence of food allergy noted specifically in children receiving tacrolimus immunosuppression supports the hypothesis that selective suppression of Th1 lymphocytes by the IL-2 inhibitor immunosuppressants CsA, and the more potent drug, tacrolimus, promotes Th2 lymphocytes and an allergic immune response. This study was undertaken to characterize the IgE-mediated immune response, in CsA and tacrolimus-treated, post-OLT children. Thirty children and adolescents aged 1.9–21 yr, mean: 10.6 yr, (6.4 yr post-tx.) were studied. Immunosuppression-CsA: 10 patients, tacrolimus; 20 patients. Blood eosinophils, total IgE levels and specific IgE antibodies (Immulite 2000 Allergy; Diagnostic Products Corp., Los Angeles, CA, USA) to a panel of food and inhaled allergens were measured and correlated with clinical symptoms of allergy. Eosinophilia ($> 500/\text{mm}^3$) range: 599–3125, mean: 1294, was present in 10/20 of patients treated with tacrolimus and 1/10 treated with CsA. IgE levels were elevated in eight of these 10 tacrolimus-treated patients and in two CsA patients; five were < 3 yr of age and IgE levels ranged from 54 to 111 IU/mL (mean: 83), normal for age < 45 IU/mL and five were ≥ 9 yr and IgE levels ranged from 134 to 1606 IU/mL (mean: 557), normal for age < 87 IU/mL. Specific IgE levels to a wide panel of food allergens were positive in five tacrolimus-treated patients and to both food and inhaled allergens in three patients (two tacrolimus-treated, one CsA). Four children (tacrolimus-treated) had symptoms of food allergy. None had a family history of allergy. Eosinophilia is present in up to 50% of children and adolescents receiving tacrolimus immunosuppression. The majority of these patients also have elevated levels of total and specific (mainly to food allergens) IgE antibodies. Most patients are asymptomatic and do not manifest food allergy or asthma.

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De novo development of food allergy is an infrequent but potentially serious complication of transplantation, described after both bone marrow and solid organ transplants (1–8). Initially, allergy was thought to result from passive transfer of donor lymphocytes contained in the transplanted organ (1–3). The increased prevalence of food allergy noted in patients receiving

tacrolimus supports the hypothesis that selective suppression of Th1 lymphocytes by calcineurin inhibitors, CsA and the more potent drug tacrolimus, promotes Th2 lymphocytes and an allergic immune response (4, 5).

Post-transplant allergic reactions have been observed predominantly in the pediatric age group. In most of these patients timing of food related allergic reactions was consistent with an IgE-mediated process and they have manifested high eosinophil counts and elevated total and specific IgE levels.

Abbreviations: CsA, cyclosporin A; IgE, immunoglobulin E; OLT, orthotopic liver transplant.

Little data are available regarding eosinophil count and IgE levels in post-transplant patients who do not exhibit any allergic symptoms. The following study was therefore performed in order to further characterize the IgE-mediated immune response in post-liver transplant children treated with CsA or tacrolimus.

Methods and patients

Patients

Thirty children and adolescents (16 boys, 14 girls), aged 1.9–21 yr, mean age: 10.6 yr (median: 10.75) were studied. They had undergone an orthotopic liver transplant 1–17 yr (mean time post-transplant 6.4 yr, median: 5.75) earlier. The indication for liver transplantation was biliary atresia in 17, fulminant liver failure because of hepatitis A in three and of undetermined etiology in four, autoimmune hepatitis in two, acetaminophen toxicity in one, glycogen storage disease type III in one. Immunosuppressive therapy was based on CsA in 10 of the patients (trough levels 60–80 ng/mL) and in 20 on tacrolimus (trough levels 3–6 ng/mL). Six patients in the CsA group were also maintained on prednisone at a dose of ~0.1 mg/kg/day. Three patients in the tacrolimus group received mycophenolate mofetil at a dose of 15–25 mg/kg/day. In all patients liver function tests were normal.

Methods

Blood eosinophils were calculated from the mean of three consecutive routine follow-up tests. Total IgE levels and specific IgE antibodies to a wide panel of food and inhaled allergens were measured using commercial kits (Immulite 2000 Allergy, Diagnostic Products Corporation, Los Angeles, CA, USA).

Results

Eosinophilia

Eosinophilia (considered present when the eosinophil count was $> 500/\text{mm}^3$) was noted in 10/20 patients treated with tacrolimus; range: 544–3125/ mm^3 (mean: 1294) but in only one of the 10 CsA-treated patients (599/ mm^3).

IgE levels

The following were considered as normal for children aged: < 5 yr: ≤ 45 IU/mL, 5–9 yr: ≤ 52 IU/mL, > 9 yr: ≤ 87 IU/mL.

IgE levels were elevated in 10 children; eight were on tacrolimus therapy and two patients were on CsA therapy. These eight tacrolimus-treated patients also had eosinophilia. Of the 10 patients with elevated IgE levels five were younger than age three and their mean IgE level was 83 IU/mL (range: 54–111) and in the five older patients mean IgE level was 557 IU/mL with a range of 134–1607 IU/mL.

Specific IgE

Specific IgE levels to a wide range of food allergens were positive (considered positive if > 0.35 IU/mL) in five tacrolimus-treated patients and to both food and inhaled allergens in another three patients (two on tacrolimus and one on CsA.) None of the patients had a family history of allergy. Food allergens to which IgE antibodies were detected included alpha lactalbumin, beta lactoglobulin, egg white, peanuts, sesame, nuts, chickpeas, soy, wheat, corn, tomato, avocado, carrot, peaches, oranges, apple, banana, mustard. Inhaled allergens: grass, weeds, olive and pecan trees.

In all, of 20 tacrolimus-treated patients 11 manifested either eosinophilia, elevated total IgE or specific IgE antibodies and in eight of these all three parameters were present (Table 1). Of the 11 patients seven were asymptomatic and only four had symptoms, three of food allergy and one of food allergy and mild asthma. Symptoms included angioedema, stridor, wheezing, perioral rash, diarrhea and anemia associated with occult blood in stool and eosinophilic infiltration of intestinal mucosa. It is noteworthy that in one of these patients the symptoms of cow's milk protein allergy were already present prior to liver transplant. In contrast, in the CsA-treated group one patient had eosinophilia and another elevated total and specific IgE levels. These two patients were asymptomatic. Of subjects with elevated IgE levels, in the four symptomatic patients IgE levels did not differ from levels in asymptomatic subjects.

Eosinophil counts in two of the four symptomatic patients were markedly higher than mean eosinophil counts observed in asymptomatic patients with eosinophilia; 2327/ mm^3 and 3125/ mm^3 , respectively, vs. 1294/ mm^3 .

Table 1. Eosinophilia, total and specific IgE levels in cyclosporin A and tacrolimus-treated patients

	Cyclosporin A (n = 10)	Tacrolimus (n = 20)
Eosinophilia ($> 500/\text{mm}^3$)	1	10
Elevated IgE levels	2	8
Specific IgE	1	7
Food allergens	–	(5)
Food and inhaled allergens	(1)	(2)
Symptoms	–	4
Eosinophilia/total IgE/specific IgE		
One of above present	2	11
Two of above present	1	9
Three of above present	–	8

Discussion

An association between tacrolimus therapy after liver transplantation and development of food allergy was first suggested by Lacaille et al. in 1997 (4). Since then symptoms related to food allergy have been described in a significant number of pediatric recipients of liver transplants while on tacrolimus immunosuppression. Prabhakartan et al. noted a prevalence of allergic symptoms in up to 17% of their patients (5). In the cases reported by Lykavieris et al. (6) 12 children, constituting 10% of a series of 121 children, presented with angioedema at a mean age of 1.3 yr. In four of them symptoms necessitated a decrease in tacrolimus dosage, whereas, in eight only the switching to CsA resolved the allergic manifestations. Peripheral blood eosinophilia and increased levels of IgE globulins were noted in the majority of these children.

Among our 30 patients four manifested allergic symptoms related to food allergens. Yet, in one of these patients symptoms had already been present prior to transplant so in effect only three of our patients showed evidence of *de novo* food allergy. In two of these patients symptoms were also respiratory with mild recurrent asthmatic attacks. All four patients were on tacrolimus therapy and no symptomatic allergic disease was observed among the CsA-treated group.

Although most pediatric series have noted food allergy predominantly in very young children there are reports of *de novo* food allergy in older children. Two of the post-liver transplant patients described by Arikan et al. (7) were aged nine and 13, respectively.

De novo food allergy following transplantation is not organ specific. *De novo* food allergy has been described following intestinal transplantation in young children (8) and in pediatric heart transplant recipients. Among the 49 heart transplant patients reported by Asante-Korang et al., eosinophilia was present in 19 patients and 11 of them manifested allergic symptoms (9).

Allergic symptoms in patients receiving tacrolimus have been attributed to inhibition of IL-2 activation of T cells with resultant skewing of the immune response towards a Th2 response. The Th2 cytokines IL4 and IL5 promote production of IgE-secreting B cells and eosinophilia. This effect seems to be less apparent in patients treated with the considerably less potent calcineurin inhibitor CsA. Peripheral blood eosinophilia, elevated IgE globulins and positive selective IgE antibodies have been frequently observed in

patients with post-transplant food allergy. We questioned whether asymptomatic post-liver transplant patients receiving either CsA or tacrolimus would similarly manifest eosinophilia, and/or increased IgE levels. Our finding that up to 50% of patients on tacrolimus immunosuppression who are free of allergic symptoms do have eosinophilia is thus of interest. Furthermore, among our patients five of the eight patients with elevated total IgE levels and four of the seven of patients with positive IgE antibodies to selected allergens are asymptomatic. Among the CsA-treated group there were no patients with symptoms of food allergy. Two patients did have eosinophilia and one of them also had high IgE levels. The high prevalence of eosinophilia and high total and specific IgE levels in tacrolimus-treated patients when compared with CsA-treated patients lends further support to the hypothesis that these cases of new onset food allergy are a result of calcineurin inhibitor-induced imbalance between Th1 and Th2 helper cells and not a result of passive transfer of sensitized donor lymphocytes in the transplanted organ. Yet, we cannot preclude that steroid therapy, albeit at low doses of 0.1–0.2 mg/kg/day, in some of the CsA-treated patients, may abrogate an eosinophilic response.

Age at transplant had previously been noted to be a risk factor for development of *de novo* post-transplant food allergy. Although our four symptomatic patients had undergone transplantation at the young age of 0.5–3 yr, this age range did not differ from age at transplantation of our asymptomatic patients with eosinophilia and elevated IgE levels.

To date, published studies have focused on pediatric transplant recipients. Further studies will determine whether in patients undergoing transplants in adulthood tacrolimus immunosuppression is accompanied by similar findings. The alleged effects of tacrolimus on gut permeability and the thereby concomitant increase in antigenic exposure (10) may be of consequence only in a setting of relatively immature gastrointestinal and immune systems.

The observed high rate of eosinophilia is also of significance in view of the previously suggested predictive value of blood eosinophil counts in diagnosis of acute rejection. In a cohort of liver transplant patients an elevated eosinophil count was noted by Barnes et al. (11) to have a high positive predictive value of rejection. Based on our findings we believe that the role of eosinophilia in diagnosis of rejection, in pediatric patients, is at best, limited.

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