

Letter to the Editor

Management of post-liver transplant-associated IgE-mediated food allergy in children

To the Editor:

New-onset posttransplantation food allergy (FA) is an established complication in children who have undergone liver transplantation (LT) that can be life-threatening because of anaphylaxis.¹ Pathogenesis of post-LT-related FA remains unclear, but tacrolimus immunosuppressive therapy, as well as host factors, are likely to play a role.^{2,3}

Both cyclosporine and tacrolimus block T-cell cytokine production. Tacrolimus, a more powerful immunosuppressive drug than cyclosporine, is now used as first-line therapy in post-LT settings.⁴ A specific tacrolimus-associated side effect is its effect on intestinal barrier function.² Tacrolimus increases intestinal permeability, which might favor transport of antigens from the intestinal lumen and exposure to the immature intestinal mucosal system of children, increasing the risk of sensitization and FA development. In children with post-LT FA undergoing a tacrolimus regimen, a switch to a cyclosporine regimen has been recommended, but the management and evolution of FA after an immunosuppressive regimen switch have not been reported.^{1,5,6} Here we report on the therapeutic management of 7 children with post-LT FA in whom a switch from tacrolimus to cyclosporine and an elimination diet induced serum specific IgE level decrease and negativization of prick skin test responses, allowing successful incriminated food reintroduction.

Seven children who underwent LT for biliary atresia at age 15 $\pm$ 5 months (mean $\pm$ SD) and had FA after LT were compared with a control group of 7 age- and tacrolimus treatment-matched children with a comparable atopic familial background who underwent LT for biliary atresia and did not have FA symptoms. These were consecutive patients within our cohort undergoing LT who had FA during a tacrolimus regimen, who were treated according to the approach reported below, and in whom follow-up after normal diet reintroduction was 6 months or longer.

After transplantation, all patients received immunosuppression based on a tacrolimus regimen (with prednisone [patients 1-2] or basiliximab [anti-CD25/IL-2 receptor α ; patients 3-7]). A family history of atopy (allergic rhinitis, eczema, asthma, and urticaria) was noted in 4 of the 7 patients. A complete clinical history was obtained in all cases. The presence of immediate symptoms of FA was validated by a senior pediatrician/allergologist (J.-L. D. or J. C.). Allergic manifestations occurred 33 $\pm$ 19 months after LT and were as follows: intense angioedema (5/7), Quincke edema (2/7), and generalized urticaria or gastrointestinal symptoms (diarrhea). Two allergens were identified in patients 1, 2, 3, and 5, and 3 allergens were identified in patients 4, 6, and 7 and were hazelnut (3/7), peanut (3/7), egg white (2/7) and yolk (3/7), lentil (2/7), fish (1/7), almond (1/7), pistachio (1/7), and mustard (1/7).

Positive skin prick test responses for food allergens were present in all cases. All patients were found to have a positive (>0.3 kU_A/L) serum specific IgE level to multiple food allergens by means of ImmunoCAP (Phadia, Uppsala, Sweden) testing (Fig 1). Initial serum IgE levels (mean $\pm$ SD) were as follows: hazelnut, 12.3 $\pm$ 13.4 kU_A/L; peanut, 9.2 $\pm$ 7.7 kU_A/L; egg white, 3.8 $\pm$ 1.1 kU_A/L; egg yolk, 17.8 $\pm$ 18 kU_A/L; fish, 15.6 $\pm$ 16.3 kU_A/L; almond, 25.4 $\pm$ 15.6 kU_A/L; soybean, 14.8 $\pm$ 11.1

kU_A/L; lentil, 48.3 $\pm$ 10.8 kU_A/L; pistachio, 16 kU_A/L; mustard, 9.6 kU_A/L; wheat, 30 kU_A/L; and sesame seed, 7 kU_A/L. The control group was tested for the same panel (16 allergens) of serum specific and total IgE at a delay after LT similar to that at which FA occurred in the 7 patients. All control children had negative specific IgE levels. In addition, the median value of total IgE levels was significantly increased in patients compared with that seen in control subjects (285 [interquartile range, 194-978] vs 23 [interquartile range, 16-100]; $P = .01$, Mann-Whitney U test), with only 1 child from the control group having an increased total IgE level (459 kU/L).

In each patient there was a concordance between incriminated food allergen species and biological data (positive specific IgE levels and skin prick test responses). In patients 6 and 7 more specific IgE species than food allergens were found. After a severe clinical manifestation of FA (angioedema or Quincke edema), a switch from tacrolimus to cyclosporine and an elimination diet of incriminated food allergens were performed systematically in all cases. Thereafter, no recurrence of symptoms of allergy and a decrease in serum specific IgE levels were observed in all patients. When serum specific IgE levels and skin prick test responses normalized, an oral challenge with each incriminated food was performed (Fig 1). In patient 7 an oral challenge was performed while the level of specific IgE was still slightly increased. The incriminated food was successfully reintroduced in all children 37 $\pm$ 27 months after immunosuppressive switch and elimination diet introduction. Importantly, during the cyclosporine regimen, no FA recurrence was observed after oral challenge and diet liberalization, with a follow-up of 27 $\pm$ 21 months. During the overall follow-up period during the cyclosporine regimen, serum liver test results remained normal, indicating the absence of liver rejection.

Pediatric IgE-dependent FA after LT is a well-known complication. Yet there are no internationally accepted guidelines regarding the reintroduction scheme of food allergen. Our report shows that IgE-mediated multiple FA after LT can be efficiently managed, allowing reintroduction of a normal diet without FA recurrence. In all cases the treatment strategy involved the association of a switch from a tacrolimus- to a cyclosporine-immunosuppressive regimen with an elimination diet. In our experience FA is observed in 4.5% and 26% of liver recipients with a cyclosporine- or tacrolimus-based regimen, respectively.⁷ Importantly, after immunosuppressive switch and an elimination diet, serum specific IgE levels normalized in all children and within 3 months in 4 cases (patients 3, 4, 5, and 7). A decrease in specific IgE levels was associated with negativization of skin prick test responses and enabled successful reintroduction of the incriminated food.

Although rare cases of a passive transfer of FA have been described, the pathogenesis of new-onset posttransplantation FA has been attributed to tacrolimus therapy.⁶ This drug is known to affect the intestinal barrier, increasing permeability for allergenic food proteins,² and has been shown to induce a shift toward a T_H2 profile of cytokine and IgE production.^{8,9} In our study increased total and specific IgE levels were observed in allergic patients but not in the control group, except in 1 control patient for total IgE. Tacrolimus-treated patients have an increased intestinal permeability and significantly higher serum LPS/endotoxin levels

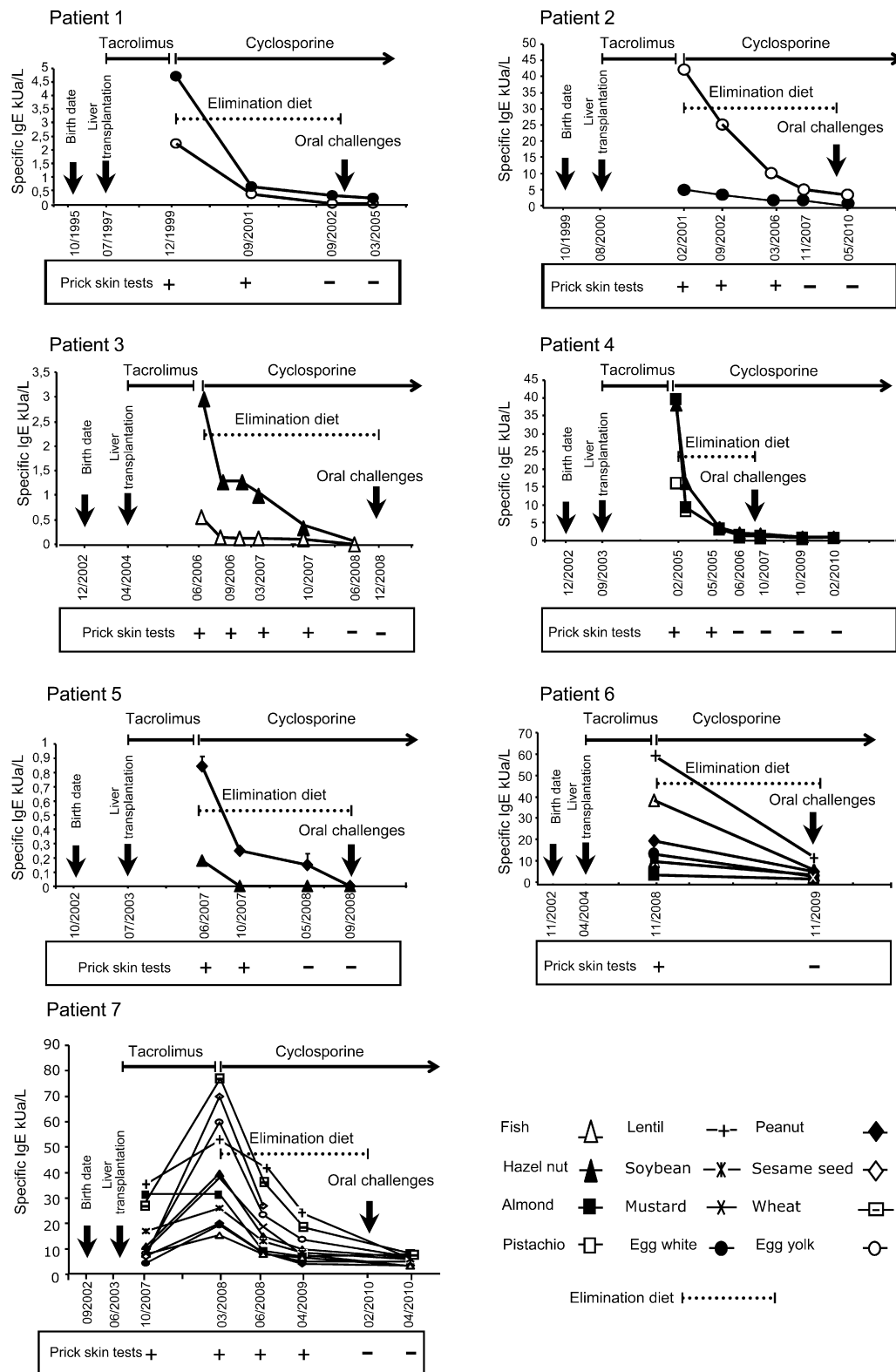


FIG 1. Cases of 7 patients with new-onset FA after LT. Treatment consisted of a switch of immunosuppressive regimen and elimination diet, allowing specific IgE decrease and food reintroduction. Follow-up of serum specific IgE levels and of skin prick test results for allergens showing clinical symptoms, date of immunosuppressive regimen switch, and elimination diet instauration and date of successful oral challenge are shown.

compared with healthy volunteers.² The intestinal barrier is a direct interface between the external and internal environment of the body that is continuously exposed to antigenic challenge from food. It plays an important role in immune system homeostasis, including a crucial role in induction and maintenance of oral tolerance. Other critical points are interactions between intestinal flora and the intestinal immune system. The establishment of a physiological “microbiome” plays a critical role in the maturation of the intestinal regional immune system, including development of its tolerance-induction capacities.³ Indeed, it was shown that intestinal commensal bacteria promote T-cell hyporesponsiveness and downregulate serum antibody responses induced by dietary antigens.¹⁰ Because children with chronic cholestasis, such as biliary atresia, receive special feeding with an artificial formula and poorly diversified diet until LT, they are likely to have highly altered microbial ecology that can affect the function of the regional immune system.

Another issue is the effect of tacrolimus treatment on the pool, function, or both of regulatory forkhead box protein 3–positive T cells. Although this issue was not addressed in this study, some studies showed the expansion of the peripheral regulatory T (Treg) cell population in tacrolimus-treated patients.¹¹ However, our group has recently reported a significantly more rapid onset of FA in children treated with tacrolimus and basiliximab compared with that seen in children receiving tacrolimus and prednisone.⁷ In children receiving basiliximab, the total pool of Treg cells did not change, but it was suggested that Treg cell function was altered in the absence of functional CD25.

Taken together, our data support the concept that after FA has occurred during a tacrolimus regimen in children undergoing LT, disappearance of clinical and biological symptoms of FA can be successfully obtained by a switch from a tacrolimus- to a cyclosporine-based immunosuppressive regimen and an elimination diet. We suggest that this therapeutic option might be suitable for selected patients presenting with severe FA symptoms and the absence of graft rejection.

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