

New-onset post-transplantation food allergy in children – Is it attributable only to the immunosuppressive protocol?

Levy Y, Davidovits M, Cleper R, Shapiro R. New-onset post-transplantation food allergy in children – Is it attributable only to the immunosuppressive protocol?

Pediatr Transplantation 2009; 13: 63–69. © 2007 Wiley Periodicals, Inc.

Abstract: New-onset post-transplantation food allergy has been described mainly after liver transplantation, and its pathogenesis was attributed to the immunomodulatory effects of tacrolimus therapy. The aim of the present study was to evaluate the association of food allergy with solid organ transplantation in our center. The medical records of children who underwent kidney transplantation and children who underwent liver or liver and kidney transplantation from 1986 to 2005 were reviewed. A total of 189 children (124 after kidney transplantation, 65 after liver or liver and kidney transplantation) received tacrolimus as part of the immunosuppressive regimen. New-onset post-transplantation food allergy was documented in four of them: two with liver transplants and two with combined kidney and liver transplants. The absence of new-onset food allergy in the children with isolated kidney transplants is compatible with other reports in the literature. This study supports the concept that the functioning liver itself, and not only tacrolimus immunosuppression, is a main contributor to food allergy in this patient population.

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Key words: food allergy – transplantation – liver – kidney – children – tacrolimus

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Accepted for publication 14 November 2007

New-onset food allergy, whether immediate hypersensitivity type or eosinophilic gastroenteropathy, is an infrequent but potentially serious complication of organ transplantation. It has been described mainly after liver transplantation (1–14), but also after small bowel (3, 15) and heart (10) transplantations. Three reports in adults with liver transplants attributed the development of food allergy to passive transfer of food (peanuts and nuts)-specific IgE antibodies from the allergic donors to the recipients (16–18). However, in cases of pediatric transplantation in which the donors were not food allergic, the allergy in the recipients was attributed to the immunomodulatory effects of tacrolimus, together with its known effect on the gastrointestinal mucosa in small children (19, 20).

Our search of the literature yielded only one report of food allergy in a child after kidney transplantation receiving tacrolimus therapy (21). The possible role of the liver in the

pathogenesis of post-transplantation food allergy was recently supported by the study of Watanabe et al. (22) in a mouse model, wherein the liver was found to be one of the sites at which Th₂ lymphocytes specific to a food antigen develop.

The paucity of reports on new-onset food allergy in kidney transplant children treated with tacrolimus prompted us to evaluate the association of food allergy with solid organ transplantation in our center.

Patients and methods

The databases of the Department of Nephrology and Dialysis Unit and of the Institute of Gastroenterology, Hepatology and Nutrition of a major pediatric tertiary medical center were searched for transplant recipients with post-operative new-onset food allergy.

From 1986 to 2005, 232 children underwent 262 kidney transplantations (86 live donors, 176 cadaveric). Their mean age was 10.8 yr (range: 2–18 yr). Up to 1997, the immunosuppressive protocol included a combination of

cyclosporin A (target blood trough level, 200 ng/mL) and azathioprine. Thereafter, cyclosporin A was replaced by tacrolimus, 0.3 mg/kg/day (target blood trough level, 3–5 ng/mL at six-months post-transplantation). In 1999, azathioprine was replaced by mycophenolate mofetil, 600 mg/m²/day for two wk and then 300–400 mg/m²/day. Corticosteroids were given perioperatively at a dose of 300 mg/m²/day intravenously, and then continued orally in a tapering dose of 60–10 mg/m²/day for six months after transplantation.

From 1995 (when liver transplants were first performed in our institute) to 2005, 65 children underwent liver transplantation (14 live donors, 51 cadaveric). Their mean age was 5.5 yr (range: 0.5–17.5 yr). Thirteen of them had a combined liver and kidney transplantation. The immunosuppressive protocol included tacrolimus 0.2–0.4 mg/kg/day (target blood trough level, 5–7 ng/mL at six-months post-transplantation) or cyclosporin A 5–8 mg/kg/day (target blood trough level, 100–120 ng/mL), and prednisone 0.1–0.2 mg/kg/day, up to 6–12 months after transplantation.

The diagnosis of food allergy was based on the presence of clinical symptoms of immediate hypersensitivity-type reactions (urticaria/angioedema with or without respiratory and/or gastrointestinal system involvement) and evidence of specific IgE antibodies against the suspected foods, either by skin prick test (ALK Abello, Port Washington, NY, USA) performed at the allergy clinic and/or serum measurements by the Immulite 2000 method (DPC, Los Angeles, CA, USA, positive: ≥ 0.35 kU/mL).

The following data were documented: sex and age at transplantation, underlying disease, time to appearance of food allergy, immunosuppressive protocol at time of appearance of food allergy, allergenic foods, presence of eosinophilia ($> 500/\text{mm}^3$), symptoms of allergic reactions, and treatment. The same data, where available, were extracted from the reports in the literature on post-transplantation food allergy. The literature search was performed using the PubMed database.

Results

None of the 232 children who underwent kidney transplantation, including the 124 who received tacrolimus-based immunosuppression, acquired a food allergy. Four of the 65 children (6%) who

underwent liver ($n = 2$) or liver and kidney ($n = 2$) transplantation acquired a new-onset food allergy postoperatively. Eight other patients had an eosinophil count of 500–2800/mm³, but they did not display any symptoms of food allergy (data not shown). All had received tacrolimus as the main immunosuppressive therapy.

The characteristics of the food-allergic children are presented in Table 1. Three children were aged 1–1.5 yr at transplantation, and one was aged seven yr; there were two boys and two girls. Time from transplantation to development of the food allergy was 1.5–6 yr. Two children had extrahepatic biliary atresia; one, primary hyperoxaluria type 1 and the other, Alagille syndrome. All four had food-induced angioedema or urticaria and angioedema, and one patient also had respiratory involvement (stridor). Peripheral eosinophilia was documented in all four patients. Tacrolimus therapy was switched to cyclosporin A in two patients, but no change in the food-induced allergic reactions was noted. All the patients were instructed to eliminate the allergenic foods from their diet, which resulted in resolution of their symptoms. No attempt was made to reintroduce the allergenic foods in the children's diet during the follow-up period (2–4 yr). All patients consulted a dietician to ensure a balanced diet.

The results of our literature search on post-transplantation food allergy are summarized in Table 2. Seventy children with new-onset post-transplantation food allergy were reported (1–11, 13–15). The organs transplanted included the liver in 64 children (91%) because of biliary atresia in 41 of them, intestines in three, liver and intestines in one, and heart and kidney in one

Table 1. Data of children with food allergy after organ transplantation

Patient	Sex/age (years) at transplantation	Diagnosis	Organ(s) transplanted	Time to food allergy (years)	Immunosuppressive treatment	Allergenic foods	Total IgE (IU/mL)	Eosinophils/mm ³	Clinical presentation
1	M/1	EHBA	Liver	2	Tacrolimus, switched to cyclosporin A*	Fish, egg, sesame, peanut, soybean	224	800	Urticaria and angioedema, stridor
2	F/1	EHBA	Liver	2.5	Tacrolimus	Milk, sesame, soybean, peanuts, nuts	155	800	Urticaria
3	F/7	PH1	Liver, kidney	6	Tacrolimus, prednisone	Egg	3900	4500	Angioedema
4	M/1.5	Alagille syndrome	Liver, kidney	1.5	Tacrolimus, switched to cyclosporin A*, mycophenolate mofetil, prednisone	Milk, nuts, apple	ND	820	Urticaria, angioedema

EHBA, extrahepatic biliary atresia; PH1, primary hyperoxaluria type 1; ND, not done.

*Due to food allergy.

patient each. The rate of food allergy in the children after transplantation was documented in six studies and ranged between 6% and 57%. The male/female ratio was equal (38 reported patients). Mycophenolate mofetil was added to the tacrolimus immunosuppressive regimen in three cases of liver transplantation. Forty-seven patients (67%) had immediate food-induced hypersensitivity reactions with involvement of the skin and respiratory and gastrointestinal tracts; 21 of them were also diagnosed with eosinophilic gastrointestinal disease. Twenty-three patients had eosinophilic gastrointestinal disease only. Treatment consisted of elimination of the allergenic foods, administration of hypoallergenic formula, antihistaminic medications, and epinephrine for anaphylactic reactions. In two studies, a switch from tacrolimus to cyclosporin A immunosuppressive therapy was the preferred treatment.

Discussion

The present study, of 232 children who underwent kidney transplantation over a 19-yr period and 65 children who underwent liver transplantation over a 10-yr period yielded only four patients with new-onset food allergy after surgery. All were liver transplant recipients (liver only or liver and kidney). None of the 124 recipients of isolated kidney transplants who were treated with tacrolimus acquired a food allergy.

Our 6% rate of new-onset food allergy in children after liver transplantation is similar to the findings in another recent study (6). Also, as in other studies, there was no sex predominance in our food-allergic patients, and biliary atresia was the primary disease in half of them. Of our other two patients, one had Alagille syndrome, previously reported as the primary disease in two patients with post-transplantation food allergy (4, 11), and the other had primary hyperoxaluria type 1, which has never before been documented as the primary disease in this context. The latter finding may be explained by the higher prevalence of hyperoxaluria type 1 in the Israeli Arab population, which has a high rate of consanguineous marriages (23).

The pathogenesis of new-onset post-transplantation food allergy may involve several factors: the status of the donor, the organ transplanted, and the immunosuppressive protocol.

Passive transfer of food allergy has been described in association with bone marrow transplants (24) and solid organ (liver, liver, and kidney) transplants, all in adult patients (16–

18). The findings were explained by the presence of specific IgE-producing B cells in the donor bone marrow (24) and by the presence of IgE-producing B cells and specific IgE antibodies (16) or sensitized mast cells with peanut-specific IgE in the donor liver (25). It is noteworthy that in one case, another recipient of a kidney and pancreas from the same liver donor (16) did not develop food allergy.

We do not have data on the status of the donors in our four food-allergic patients. However, the time interval between transplantation and the clinical presentation of the food allergy (1.5–6 yr) does not support the theory that the donors were food allergic: food-specific IgE antibodies persist in the circulation only for a few days (26), and engraftment of specific IgE-producing B lymphocytes should have led to clinical manifestations after a shorter interval (27).

Regarding the transplanted organ – the second important contributing factor in the development of food allergy – there is only one report in the literature of food allergy in a child after isolated kidney transplantation (21). This patient presented with angioedema after peanut ingestion (21). However, it remained unclear if the symptom first developed during therapy or if it was present before (21). In adults, food allergy has been reported in two renal transplant recipients receiving sirolimus. The angioedema in these cases occurred following walnut and mango ingestion (28). One of the patients also received tacrolimus, but both received other drugs known to induce angioedema (enalapril, salicylic acid) (28).

There are two reports (total four children, one with combined liver and intestinal transplantation) of food allergy after small bowel transplantation (3, 15), and one report of a patient with food allergy after heart transplantation (10). All the remaining reported patients were liver transplant recipients (1–11, 13, 14). Interestingly, the heart transplant recipient was a one-month-old baby treated with prednisone and tacrolimus in whom multiple food allergies developed at the age of 12 months (10). In this case, the authors could not unequivocally attribute the allergy solely to the organ transplantation because the procedure was performed before the child was exposed to allergenic foods.

A previous study of 49 children with heart transplants treated with tacrolimus reported that eosinophilia occurred in 19 (39%), 11 of whom manifested allergic symptoms such as eczema, allergic rhinitis, asthma, and eosinophilic

Year (reference no.)

2003 (6)						
2003 (5)						
2003 (4)						
2003 (3)						
2003 (2)						
2003 (1)						
No. patients	1	11/64 (17%)	7	12/21 (57%)	1	3/50 (6%)
Sex	F			7-M, 5-F		
Age at transplantation	7 months	Mean 13.4 months	6:4.8–15.5 months	0.5–3.3 yr	6 months	5–13 yr
Primary disease	Biliary atresia		1:8.6 yr 6-biliary atresia, 1-multiple anomalies	10-biliary atresia, 1-mitochondrial myopathy, 1-Alagille syndrome	Biliary atresia	Cirrhosis, fulminant hepatitis, glycogen storage disease
Organ(s) transplanted	Liver	Liver	6-liver, 1-small bowel	Liver	Liver	Liver
Immunosuppression	Tac, prednisone, azathioprine	Tac, methylprednisone, CsA, MMF	Tac, prednisone, MMF	Tac	Tac	2-Tac+ prednisone, 1-CsA+ prednisone
Time to onset of allergy (months)	5	Mean 6	0.5–21	13–45	2	4–9
Allergenic foods	Milk, eggs, peanuts	Milk, eggs, nuts, fish, wheat, soy, potato	Eggs, peanuts, chicken, milk, wheat, soy, rice	Almonds, beef, cod, chicken, eggs, hazelnuts, peanuts, soy, wheat	Milk	Peanuts, eggs, soy, wheat, chicken, banana
Clinical presentation	Urticaria, angioedema, wheezing, diarrhea	Eczema, rash, facial swelling, wheezing, vomiting, diarrhea, itching	Anaphylaxis, angioedema, diarrhea, rash, 3-EGID	Anaphylaxis, angioedema, diarrhea	Urticaria, wheezing, diarrhea	Angioedema, wheezing
Lab data/diagnostic methods						
Treatment	Hypoaallergenic formula	Hypoaallergenic diet, epinephrine, antihistamines	Eosinophilia: 9–25%, SPT, serum specific IgE Abs Hypoaallergenic diet	Eosinophilia: 320–1200/mm ³ , SPT, specific IgE Abs Switch to CsA in 8	Specific IgE Abs Hypoaallergenic formula	Eosinophilia: 16–18%, SPT, specific IgE Abs Hypoaallergenic diet
2006 (11)						
2006 (10)						
2006 (9)						
2006 (8)						
2006 (7)						
2006 (15)						
No. patients	6	3	1	1	2	3
Sex		2-F, 1-M	M	F	1-M, 1-F	M
Age at transplantation	3.7 ± 5.5 yr	3.5–8.5 yr	19 months	8 months	1, 18 months	1.5–3 yr
Primary disease	Biliary atresia	2-intestinal pseudo-obstruction 1-cholestasis + short bowel syndrome	Biliary atresia	EHBA	Hypoplastic left heart, argininosuccinic aciduria	Biliary atresia, Alagille syndrome, fulminant hepatic failure
Organ(s) transplanted	Liver	2-intestine, 1-liver + intestine	Liver	Liver	Heart, liver	Liver

Table 2. Continued

	Year (reference no.)					
	2003 (7)	2004 (15)	2005 (8)	2005 (9)	2006 (10)	2006 (11)
Immunosuppression	Tac, prednisone, MFV, dacluzimab, CsA	Tac, prednisone	Tac, methyl-prednisone, azathioprine	Tac, prednisone	Tac, prednisone Tac, MFV, prednisone	Tac, prednisone, CsA, azathioprine
Time to onset of allergy		4 months–2 yr	1 months	8 months	12, 7 months	17–24 months
Allergenic foods		Peanuts, eggs, clam, milk, mustard, pork	Eggs, peanuts, cashew	Banana	Milk, eggs, peanuts	Milk, eggs, wheat, oats
Clinical presentation	EGID	Angioedema, hives, pruritus, vomiting, 1-EGID	Urticaria	Angioedema	Rash, angioedema, diarrhea, 1-EGID	Diarrhea, EGID, eosinophilic colitis
Lab data/diagnostic methods	Eosinophilia: >350/mm ³	SPT, specific IgE Abs	SPT, specific IgE Abs	Specific IgE Abs	Eosinophilia: 10–23%, specific IgE Abs	Specific IgE Abs, endoscopy with biopsy
Treatment		Elimination diet, epinephrine, benadryl	Antihistamines	Switch to CsA	Elimination diet	Elimination diet

	Year (reference no.)		
	2006 (12)	2006 (21)	2007 (13)
No. patients	3/30 (10%)	1	14/38 (37%)
Sex		M	5-M, 9-F
Age at transplantation		7 yr	5–33 months
Primary disease			14-biliary atresia, 1-hepatoblastoma
Organ(s) transplanted	Liver	Kidney	Liver
Immunosuppression	Tac	Tac, prednisone, azathioprine	Tac, steroids
Time to onset of allergy			1–7 months
Allergenic foods	Milk, eggs, peanuts, sesame nuts, soy, wheat	Peanuts	Soy, eggs, milk, wheat
Clinical presentation	Angioedema, stridor, wheezing, rash, diarrhea, EGID	Angioedema	Rash, diarrhea, EGID
Lab data/diagnostic methods	Endoscopy with biopsy, specific IgE Abs, eosinophilia: ↑ total IgE	SPT, specific IgE Abs	Specific IgE, endoscopy with biopsy, eosinophilia
Treatment		Elimination diet	Elimination diet

Tac, tacrolimus; CsA, cyclosporin A; EGID, eosinophilic gastrointestinal disease; MFV, mycophenolate mofetil; SPT, skin prick tests; Abs, antibodies; EHBA, extrahepatic biliary atresia.

enteritis. However, food allergies were not documented in this study (29).

The finding that only liver and small bowel transplantations seem to be associated with new-onset food allergy suggests that the hematopoietic tissue and dendritic cells play a role in this phenomenon. T-cell activation by antigens migrating through the portal vein occurs in the liver (30), and some liver-resident dendritic cells and sinusoidal endothelial cells direct naive CD4⁺ T cells preferentially to Th₂ differentiation (31, 32). Furthermore, it was recently shown in a mouse model that helper CD4⁺ T cells in the liver induced an IgE response to a food antigen (22).

The third potential factor involved in post-transplant food allergy is the immunosuppressive protocol. Both tacrolimus and cyclosporin A inhibit the production of IL-2, thereby causing an imbalance in the Th₁/Th₂ ratio and facilitating IgE production (33). Tacrolimus, however, is more potent than cyclosporin A (34) and, in addition, augments the production of IL-5 and IL-13 – eosinophil- and IgE-promoting cytokines (35). It is also known to increase intestinal permeability, which may lead to increased exposure to allergenic proteins and a further shift toward Th₂ cytokines and IgE production against these proteins (20). Nevertheless, in our study, none of the 124 kidney-only recipients treated with tacrolimus, at a dose similar to that of the liver transplant recipients, acquired a post-transplant food allergy. At the same time, it could be argued that children with kidney transplants receive more prednisone than children with liver transplants, which may downregulate mast cell degranulation in response to exposure to allergenic foods. Furthermore, unlike children with liver transplants, they receive mycophenolate mofetil, which also suppresses humoral immunity (36), and, thereby, IgE production. Of interest are three reported children with food allergy after liver transplantation who also received mycophenolate mofetil, which did not ultimately change their course (2, 3, 10). The role of tacrolimus immunosuppression in inducing peripheral eosinophilia is highlighted by the presence of peripheral eosinophilia in 12 of the 65 tacrolimus-treated children (18%) in our study, in addition to pediatric transplant recipients in eight studies published in the literature (3, 4, 6, 7, 10, 13, 29). However, whereas six of the eight studies documented eosinophilic gastrointestinal disease in the children with peripheral eosinophilia (3, 7, 10, 13, 29), the 12 children with peripheral eosinophilia in our series, including the four with immediate food-induced

allergic reactions, did not have eosinophilic gastrointestinal disease. The pathogenesis of eosinophilic gastrointestinal disorders involves both IgE and non-IgE-mediated mechanisms, with a contributory role for IL-5 and eotaxin (37). Therefore, it should be borne in mind that tacrolimus immunosuppression might affect the gastrointestinal tract through different pathways and in the absence of evidence of IgE-mediated food allergy. Further support for the effect of tacrolimus compared to cyclosporin immunosuppression was provided by the study of Granot et al. (12), wherein peripheral eosinophilia developed in 11 of 20 pediatric liver transplant recipients (50%) being treated with tacrolimus immunosuppression (four symptomatic) but in only 10% of the cyclosporin-treated children, who remained asymptomatic.

Food allergy itself might influence the immunosuppressive regimen in the children after organ transplantation. A recent study has shown that food-allergic patients need higher doses of tacrolimus and cyclosporin A than non-allergic patients to ensure serum concentrations in the therapeutic range. With an appropriate elimination diet, the doses of the drugs – and their adverse side-effects – can be reduced (14). It is also noteworthy that in our series, the children who underwent liver transplantation were younger than those who underwent kidney transplantation, making them more vulnerable to food allergy.

In conclusion, our findings for children after solid organ transplantation are compatible with the data in the literature. Our study highlights the absence of food allergy in tacrolimus-treated kidney transplant recipients compared to liver-transplant recipients, suggesting that the main contributor to new-onset post-transplantation food allergy is immunocompetence of the transplanted organ, mainly the liver. Recent studies in animal models indicate that the immunologic function of the grafted liver itself and the renewal of the enterohepatic circulation are crucial to the development of food allergy. However, further studies are needed to clarify the effect of the different immunosuppressive protocols (i.e., tacrolimus alone or tacrolimus with mycophenolate mofetil) in pediatric transplant recipients.

References

1. LACAILLE F, LAURENT J, BOUSQUET J. Life-threatening food allergy in a child treated with FK506. *J Pediatr Gastroenterol Nutr* 1997; 25: 228–229.
2. PRABHAKARAN K, LAU HT, WISE B, SCHWARZ K, COLOMBANI PM. Incidence of allergic symptoms in pediatric liver transplant

- recipient treated with tacrolimus-based immunosuppression. *Pediatrics* 1999; 104(Suppl): 786.
3. NOWAK-WEGRZYN AH, SICHERER SH, CONOVER-WALKER MK, WOOD RA. Food allergy after pediatric organ transplantation with tacrolimus immunosuppression. *J Allergy Clin Immunol* 2001; 108: 146–147.
4. LYKAVIERIS P, FRAUGER E, HABES D, BERNARD O, DEBRAY D. Angioedema in pediatric liver transplant recipients under tacrolimus immunosuppression. *Transplantation* 2003; 75: 152–155.
5. PACIFICO L, FREDIANI T, SIMONETTI A, CHIESA C, CUCCHIRARA S. Tacrolimus and food allergy. *Transplantation* 2003; 76: 1778.
6. ARIKAN C, KILIC M, TOKAT Y, AVDOGDU S. Allergic disease after pediatric liver transplantation with systemic tacrolimus and cyclosporin A therapy. *Transplant Proc* 2003; 35: 3039–3041.
7. ROMERO R, ABRAMOWSKY CR, PILLEN T, SMALLWOOD GA, HEFFRON TG. Peripheral eosinophilia and eosinophilic gastroenteritis after pediatric liver transplantation. *Pediatr Transplant* 2003; 7: 484–488.
8. BOYLE RJ, HARDIKAR W, TANG ML. The development of food allergy after liver transplantation. *Liver Transplant* 2005; 11: 326–330.
9. YILMAZ A, ARTAN R, UGUZ A, ARSLAN G, AKCAM M. Severe angioedema caused by banana allergy under tacrolimus immunosuppression. *Transplant Proc* 2005; 37: 4251–4253.
10. OZDEMIR O, ARREV-MENSAH A, SORENSEN RU. Development of multiple food allergies in children taking tacrolimus after heart and liver transplantation. *Pediatr Transplant* 2006; 10: 38–383.
11. SAEED SA, INTEGLIA MJ, PLESKOW RG, et al. Tacrolimus-associated eosinophilic gastroenterocolitis in pediatric liver transplant recipients: Role of potential food allergies in pathogenesis. *Pediatr Transplant* 2006; 10: 730–735.
12. GRANOT E, YAKABOVICH E, BARDENSTEIN R. Tacrolimus immunosuppression – An association with asymptomatic eosinophilia and elevated total and specific IgE levels. *Pediatr Transplant* 2006; 10: 690–693.
13. LEE JH, PARK HY, CHOE YH, LEE SK, LEE SI. The development of eosinophilic colitis after liver transplantation in children. *Pediatr Transplant* 2007; 11: 518–523.
14. GUIDI R, NOBILI V, MARCELLINI M. Food allergy in pediatric liver transplant recipients: Harmful or harmless? *Pediatr Transplant* 2007; 11: 1–2.
15. CHEHADE M, NOWAK-WEGRZYN A, KAUFMAN SS, FISHBEIN TM, TSCHERNIA A, LELEIKO NS. De novo food allergy after intestinal transplantation: A report of three cases. *J Pediatr Gastroenterol Nutr* 2004; 38: 545–547.
16. LEGENDRE C, CAILLAT-ZUCMAN S, SAMUEL D, et al. Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney transplant. *N Engl J Med* 1997; 337: 822–824.
17. TROTTER JR, EVERSON GT, BOCK SA, WACHS M, BAK T, KAM I. Transference of peanut allergy through liver transplantation. *Liver Transplant* 2001; 7: 1088–1089.
18. PHAN TG, STRASSER SI, KOOREY D, et al. Passive transfer of nut allergy after liver transplantation. *Arch Intern Med* 2003; 163: 237–239.
19. PERRY I, NEUBERGER J. Immunosuppression: Towards a logical approach in liver transplantation. *Clin Exp Immunol* 2005; 139: 2–10.
20. GABE SN, BJARNASON I, TOLOU-GHAMARI Z, et al. The effect of tacrolimus (FK-506) on intestinal barrier function and cellular energy production in humans. *Gastroenterology* 1998; 115: 67–74.
21. DEHLINK E, GRUBER S, EIWEGER J, et al. Immunosuppressive therapy does not prevent the occurrence of immunoglobulin-mediated allergies in children and adolescents with organ transplants. *Pediatrics* 2006; 118: e764–e770.
22. WATANABE T, KATSUKURA H, SHIRAI Y, et al. Helper CD4+ T cells for IgE response to a dietary antigen develop in the liver. *J Allergy Clin Immunol* 2003; 111: 1375–1385.
23. RINAT C, WANDERS RJ, DRUKKER A, HALLE D, FRISHBERG Y. Primary hyperoxaluria type I: A model for multiple mutations in a monogenic disease within a distinct ethnic group. *J Am Soc Nephrol* 1999; 10: 2352–2358.
24. BELLOU A, KANNY G, FREMONT S, MONERET-VAUTRIN DA. Transfer of atopy following bone marrow transplantation. *Ann Allergy Asthma Immunol* 1997; 78: 513–516.
25. CASTELLS M, BOYCE J. Transfer of peanut allergy by a liver allograft. *N Engl J Med* 1998; 338: 202–203.
26. JOHANSSON SG, NOPP A, VAN HAGE M, et al. Passive IgE-sensitization by blood transfusion. *Allergy* 2005; 60: 1192–1199.
27. MACHATSCHKE J, DUDA J, MATTHAY K, COWAN M, HORN B. Immune reconstitution, infectious complications and post-transplant supportive care measures after autologous blood and marrow transplantation in children. *Bone Marrow Transplant* 2003; 32: 687–693.
28. MAHE E, MORELONE E, LECHATON S, KREIS H, DE PROST Y, BODEMER C. Angioedema in renal transplant recipients on sirolimus. *Dermatology* 2007; 214: 205–209.
29. ASANTE-KORANG A, BOYLE GJ, WEBBER SA, MILLER SA, FRICKER FJ. Experience of FK506 immune suppression in pediatric heart transplantation: A study of long-term adverse effects. *J Heart Lung Transplant* 1996; 15: 415–422.
30. WATANABE T, YOSHIDA M, SHIRAI Y, et al. Administration of an antigen at a high dose generates regulatory CD4+ T cells expressing CD95 ligand and secreting IL-4 in the liver. *J Immunol* 2002; 168: 2188–2199.
31. KHANNA A, MORELLI AE, ZHONG G, TAKAYAMA T, LU L, THOMSON AW. Effects of liver-derived dendritic cell progenitors on Th₁- and Th₂-like cytokine responses in vitro and in vivo. *J Immunol* 2000; 164: 1346–1354.
32. KNOLLE PA, SCHMITT E, JIN S, et al. Induction of cytokine production in naive CD4(+) T cells by antigen-presenting murine liver sinusoidal endothelial cells but failure to induce differentiation toward Th1 cells. *Gastroenterology* 1999; 116: 1428–1440.
33. KAWAMURA N, FURUTA H, TAME A, et al. Extremely high serum level of IgE during immunosuppressive therapy: Paradoxical effect of cyclosporin A and tacrolimus. *Int Arch Allergy Immunol* 1997; 112: 422–424.
34. HENDERSON DJ, NAYA I, BUNDICK RV, SMITH GM, SCHMIDT JA. Comparison of the effects of FK-506, cyclosporin A and rapamycin on IL-2 production. *Immunology* 1991; 73: 316–321.
35. DUMONT FJ, STARUCH MJ, FISCHER P, DASILVA C, CAMACHO R. Inhibition of T cell activation by pharmacologic disruption of the MEK1/ERK MAP kinase or calcineurin signaling pathways results in differential modulation of cytokine production. *J Immunol* 1998; 160: 2579–2589.
36. RENTENAAR RJ, VAN DIEPEN FN, MEIJER RT, et al. Immune responsiveness in renal transplant recipients: Mycophenolic acid severely depresses humoral immunity in vivo. *Kidney Int* 2002; 62: 319–328.
37. ROTHENBERG ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004; 113: 11–28.