

Tacrolimus-associated eosinophilic gastroenterocolitis in pediatric liver transplant recipients: Role of potential food allergies in pathogenesis

Saeed SA, Integlia MJ, Pleskow RG, Calenda KA, Rohrer RJ, Dayal Y, Grand RJ. Tacrolimus-associated eosinophilic gastroenterocolitis in pediatric liver transplant recipients: Role of potential food allergies in pathogenesis.

Pediatr Transplantation 2006; 10: 730–735. © 2006 Blackwell Munksgaard

Abstract: Tacrolimus is a macrolide agent that is now the primary immunosuppressant used in prevention of graft rejection in transplant recipients. It has been found to be superior to cyclosporine (CSA) for rescue therapy as well as for earlier weaning of steroids. Both tacrolimus and CSA share similar toxicity profiles; however, their gastrointestinal side effects have received little attention. We report three cases of eosinophilic colitis in liver transplant recipients, maintained on tacrolimus as immunosuppressive medication post-liver transplantation. These patients also had high serum immunoglobulin (Ig)E levels, eosinophilia and IgE-positive radioallergosorbent test for milk proteins. The colitis appeared to be mediated by food allergies. Each patient had symptomatic improvement following reduced immunosuppression and an appropriately restricted diet. We conclude that tacrolimus may play a role in the initiation of food allergies, leading to eosinophilic colitis. More studies are needed in a controlled setting to identify the prevalence of similar findings among other pediatric liver transplant recipients.

Shehzad A. Saeed¹, Mark J. Integlia¹, Randi G. Pleskow^{1,2}, Kathleen A. Calenda¹, Richard J. Rohrer³, Yogeshwar Dayal⁴ and Richard J. Grand^{1,2}

¹Division of Pediatric Gastroenterology and Nutrition, Department of Pediatrics, The Floating Hospital for Children, ²Division of Gastroenterology and Nutrition, Children's Hospital, Boston, ³Division of Transplant Surgery, Department of Surgery, and ⁴Department of Pathology, New England Medical Center, and Tufts University School of Medicine, Boston, MA, USA

Key words: eosinophilic gastroenterocolitis – pediatric liver transplantation – radioallergosorbent test – graft vs. host disease

Shehzad A. Saeed, Division of Pediatric Gastroenterology and Nutrition, ACC Suite 618, 1600 7th Ave South, The Children's Hospital of Alabama, University of Alabama at Birmingham, Birmingham, AL 35233, USA
Tel.: +1 205 939 9918
Fax: +1 205 939 9919
E-mail: ssaeed@peds.uab.edu

Accepted for publication 23 March 2006

Tacrolimus is an 822 kDa macrolide molecule, derived from the soil fungus *Streptomyces tsukubaensis*. Structurally it is different from CSA but exhibits similar immunosuppressive activity through inhibition of IL-2-induced T-cell activation. (1). Both tacrolimus and CSA also have inhibitory effects on the elaboration of IL-3 and

IL-4, through INF- γ , TNF-alpha and GM-CSF. Tacrolimus binds to immunophilins (proteins that bind to immunosuppressive drugs) termed FKBP-FK binding proteins. This complex then binds to and inhibits the activity of *calcineurin*, a serine–threonine phosphatase that plays a critical role in IL-2 promoter induction during T-cell activation (2). Tacrolimus also has been shown to protect rat liver against warm ischemic injury with respect to survival and lipid peroxidation (3). It facilitates hepatic regeneration after partial hepatectomy in rats and dogs; the exact mechanism remains unclear. This is in contrast to the effects of steroids and azathioprine, which are known to depress hepatic regeneration (3). Both tacrolimus and CSA have been reported to elevate serum IgE levels (4). Whether these levels

Abbreviations: CMV, cytomegalovirus; CSA, cyclosporine; CT, computed tomography; EBV, Epstein–Barr virus; GI, gastrointestinal; GM-CSF, granulocyte–macrophage colony-stimulating factor; GVHD, graft vs. host disease; HLA, human leukocyte antigen; Ig, immunoglobulin; IL, interleukin; INF- γ , interferon-gamma; LFT, liver function test; NG, nasogastric; NPO, nil per os; OLT, orthotopic liver transplantation; RAST, radioallergosorbent test; TNF-alpha, α -tumor necrosis factor; VCAM, vascular adhesion molecules.

play a role in allergic responses or in induction of local mucosal injury is not known. We undertook the present review when three patients who had undergone liver transplantation developed high serum IgE levels, bloody diarrhea (gross or occult), histologic evidence of colitis, and various food allergies, especially to milk proteins.

Materials and methods

Retrospective chart review was undertaken when three consecutively observed patients, who had received OLT, developed food allergies. These patients were identified from a total of 45 transplanted pediatric patients, who had received an OLT between 1986 and 2000 at Tufts-New England Medical Center. The three patients exhibited the following manifestations: (i) development of clinical symptoms, e.g. diarrhea with either gross or occult blood and evaluation negative for common pathogens and fecal leukocytes; (ii) evidence of food hypersensitivity with increased RASTs to food and milk proteins and peripheral eosinophilia; and (iii) histologic evidence of increased colonic mucosal eosinophilic infiltrates and focal cryptitis.

Case descriptions

Case 1 presented at two months of age with cholestasis and was diagnosed with biliary atresia (Tables 1 and 2). He underwent a Kasai porto-enterostomy at 12 wk of age and an OLT a year later. Biopsies confirmed atretic gallbladder and bile ductular atresia. Post-transplant immunosuppression was composed of tacrolimus and prednisone. He received Pregestemil® (Mead Johnson Nutritionals, Evansville, IN, USA) which was continued post-transplant and then switched to PediaSure® (Ross, Columbus, OH, USA) to optimize caloric intake. He was admitted 20 months later with diarrhea and dehydration, and noted to have guaiac-positive stools which failed to demonstrate common pathogens or fecal leukocytes. Laboratory evaluation was significant for peripheral eosinophilia (9%) and mildly elevated serum IgE level 78 IU/mL (3.2–60 IU $\neq$ mL). CMV and herpes viruses were

Table 2. Immunosuppression and LFTs at time of presentation for each case

	Case 1	Case 2	Case 3
Immunosuppressive (dose, mg/kg/day)			
Tacrolimus	0.2	0.6	0.33
Steroids	0.15	0.3	0.4
Level (ng/mL)	13.2	11	8.1
ALT (0–25 U/L)	178*	13	12
AST (0–35 U/L)	183*	19	14
Alkaline phosphatase (0–311 U/L)	207	2727	68
Total bilirubin (0.2–1.0 mg/dL)	0.2	0.2	0.6
PT (11.5–13.5 s)	12.7	11.9	12.4
Diet at time of GI presentation	Normal/regular pediaSure	Normal/regular pediaSure	Normal/regular

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; GI, gastrointestinal tract.

*Refer to text for explanation for elevated liver enzymes.

absent from the stools. Immunosuppression at the time was composed of tacrolimus 0.2 mg/kg/day, and prednisone 0.15 mg/kg/day, with a tacrolimus level of 13.2 ng/mL. Persistence of symptoms led to a proctosigmoidoscopy and biopsies revealed mild chronic inflammation with increased eosinophilic infiltrates and focal cryptitis; no viral inclusions were seen. Liver biopsy performed at the same time showed cholangitis and minimal rejection, and he was treated with three days of intravenous steroids; liver function tests normalized over the course of four months. The patient was given CSA when tacrolimus-induced renal toxicity appeared, and at the same time, IgE RASTs positive to milk protein were noted, along with peripheral eosinophilia (24%). Liver function tests were normal with CSA level of 186 μ g/mL. Biopsies obtained during colonoscopy for rectal bleeding revealed patchy acute and chronic inflammation with focal eosinophilic infiltrates. Viral cultures were negative and no inclusions were seen. He was placed on a milk

Table 1. Patient characteristics

	Case 1	Case 2	Case 3
Gender	M	M	M
Age at transplant (yr)	1.5	3	7
Age at presentation (yr)	3	4.5	8.75
Time to clinical symptoms after transplant (months)	20	24	17
Eosinophil count at presentation (%)	9	4	9
IgE level (IU/mL) at diagnosis	78 (3.2–60)	68 (3.1–35.8)	9000 (3–179)
Tacrolimus level (5–20 ng/mL)	13.2	11	8.1
RASTs allergens	Milk	Milk	Milk, eggs, wheat, oats
Histology	Focally $\uparrow$ eosinophils in cecum/left colon	$\uparrow$ eosinophils in sigmoid/rectum with acute/chronic inflammation	$\uparrow\uparrow$ eosinophils in all colon biopsies and duodenum

Ig, immunoglobulin; RAST, radioallergosorbent test.

restricted diet and has done well with no further problems with a follow up of several years.

Case 2 presented with cholestasis at two - months of age and was diagnosed with Alagille syndrome (cardiac and vertebral anomalies). Poor weight gain necessitated initiation of high calorie formula (Pregestemil® {Mead Johnson} + MCT oil ~ 32 kcal/kg) and nocturnal nasogastric tube feedings, after a normal upper endoscopy. Formula was later switched to Portagen® (Mead Johnson Nutritionals) via NG tube to ensure weight gain. He was subsequently found to have microscopic blood in stool; no pathogens were found. An upper endoscopy showed mild esophagitis and gastritis with focal eosinophilic infiltrates. A liver biopsy at 22 months of age for evaluation of elevated transaminases showed paucity of bile ducts, bile stasis and cirrhosis. He underwent an OLT at 33 months of age. Primary immunosuppression consisted of steroids, azathioprine and CSA; azathioprine was weaned after three months. He was switched to tacrolimus a month later due to an episode of rejection. He did well over the next two yr. Diet was liberalized to include age appropriate foods, with caloric supplementation via Pediasure® (Ross). Subsequently, he developed diarrhea that contained occult blood but no common pathogens or leukocytes. He was noted to be mildly anemic. Immunosuppression at the time of presentation comprised tacrolimus at 0.6 mg/kg/day (level of 11 ng/mL) and prednisone at 0.3 mg/kg/day, without peripheral eosinophilia but with elevated IgE level (Table 1). Biopsies obtained during flexible sigmoidoscopy showed acute and chronic inflammation with focally increased eosinophilic infiltrates in the lamina propria. No viral inclusions were identified. An abdominal CT scan was normal. Liver biopsy at the same time showed mild rejection and he was treated with three days of i.v. steroids, and then on prednisone dose of 2 mg/kg/day for several days; he was then weaned to maintenance dose 0.2 mg/kg/day. Two months later he developed an EBV-associated lymphoproliferative disorder. Tacrolimus was discontinued and CSA was given at 5 mg/kg/day; he was treated with acyclovir as well. Biopsies obtained at repeat colonoscopy/esophagogastroduodenoscopy showed focal colonic cryptitis with increased eosinophilic infiltrates in the transverse, sigmoid colon and rectum. The duodenal and gastric biopsies showed marked eosinophilic infiltrates, and the esophageal biopsies showed basal zone hyperplasia, papillary elongation and eosinophilic infiltrates. IgE RASTs were positive for milk proteins. The patient was placed on a

milk-free diet (Vivonex®; Novartis Nutrition, Minneapolis, MN, USA) with resolution of symptoms. A milk challenge resulted in reappearance of guaiac-positive stools. The patient is doing well with reduced immunosuppression and milk-free diet with a follow up of several years.

Case 3 presented with fulminant hepatic failure of unknown etiology and underwent an OLT at seven yr of age. His primary immunosuppression consisted of steroids (10 mg/day), azathioprine (25 mg/day) and tacrolimus (0.3–0.4 mg/kg/day). He had an episode of mild rejection two wk after transplantation that was treated with three days of i.v. steroids; peripheral eosinophil count was 1%. Four months after liver transplant, he underwent an HLA-matched bone marrow transplant for persistent aplastic anemia (5). Seventeen months later, he developed diarrhea and abdominal cramping. Stools were guaiac positive but failed to demonstrate common pathogens or leukocytes. Peripheral eosinophil count was 9%. Immunosuppression was composed of tacrolimus at 0.33 mg/kg/day and prednisone at 0.4 mg/kg/day. Lactose hydrogen breath test was abnormal. Symptoms persisted despite a lactose-free diet, and biopsies obtained at colonoscopy revealed increased mucosal eosinophilic infiltrates diffusely throughout the colon. There was no evidence of GVHD. IgE RASTs indicated allergy to milk, eggs, wheat and oats. Total serum IgE was markedly elevated at 9000 IU/mL (3–179 nL). The patient was placed on an elimination diet but symptoms of diarrhea persisted. Biopsies obtained at repeat upper and lower endoscopy revealed chronic, focal eosinophilic duodenitis, with normal antral and esophageal biopsies, as well as eosinophilic infiltrates from splenic flexure to the rectosigmoid. Stools were positive for adenovirus. Liver biopsy at the same time showed mild focal portal fibrosis without evidence of rejection or eosinophilic infiltration. The patient received a trial of cromolyn sodium (Gastrocrome®; Medeva Pharmaceuticals, Rochester, NY, USA) 100 mgs four times a day orally, but lack of response necessitated parenteral nutrition. Repeat stool cultures were negative for adenovirus. He was switched from tacrolimus to CSA 4 mg/kg/day, prednisone was continued at 0.3 mg/kg/day and he was made NPO for five months following relapse of diarrhea which occurred when diet was advanced. Elimination diet (gluten, wheat, oat and milk free) was then introduced and was tolerated. RASTs were still noted to be elevated for eggs, milk, wheat and oats. Total IgE was markedly elevated (1800 IU ≠ mL – upper normal for the laboratory – 120 IU/mL). A percu-

taneous endoscopic gastrostomy was placed for nutritional support and administration of elemental formula. Diarrhea developed when he received whey-based hydrolyzed formula (Peptamen Jr®; Clintec, Deerfield, IL, USA) but stopped when a free amino acid-based formula (Neocate One Plus®; SHS America, Gaithersburg, MD, USA) was used. A serum D-xylose test was abnormal, indicating small bowel dysfunction. Repeat colonic biopsies showed improvement in eosinophilic infiltrates on the elemental diet. Liver biopsies failed to show any rejection but did show cholestasis secondary to a biliary stricture which was treated by stent placement with subsequent normalization of LFTs on antibiotics. The patient has been doing well on CSA and restricted diet, although he did have a relapse of bloody diarrhea when he ate french fries dipped in milk (see Figs 1 and 2).

Summary of clinical data

Of the 45 children who received OLT during the study period (1986–2000), 16 (35%) were treated

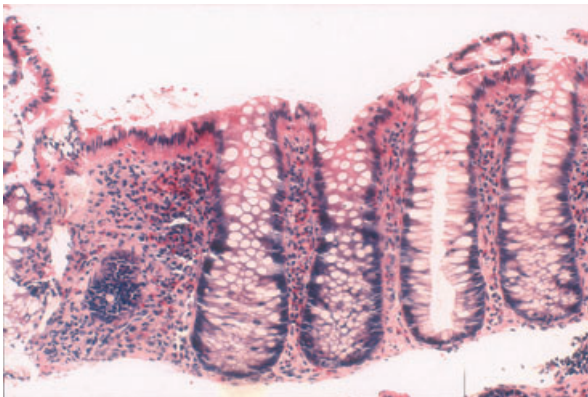


Fig. 1. Case 3: colonic biopsy with increased eosinophilic infiltration of lamina propria; hematoxylin and eosin stain.



Fig. 2. Case 3: colonic biopsy with eosinophilic colitis, cryptitis, crypt abscess and increased eosinophilic infiltration of lamia propria; hematoxylin and eosin stain.

with tacrolimus. Three patients (19%) developed eosinophilic enterocolitis. Most of the symptoms developed in patients who were clinically well, several months post transplantation. The trough tacrolimus levels were not noted to be high in these patients at the time of their clinical presentation (Table 1). Two of three patients had evidence of peripheral eosinophilia and all had elevated serum IgE levels, coupled with IgE RAST evidence of food or dairy hypersensitivity. Two of three patients had a relapse of symptoms upon diet challenge, and resolution after reimplementation of food restriction, even though they continued to receive immunosuppressive therapy.

Discussion

Although tacrolimus-associated food allergic (primarily respiratory) symptoms have been previously reported (6–8), our case series is one of the few observing tacrolimus-associated GI allergic symptoms with peripheral eosinophilia, elevated serum IgE levels, eosinophilia of the GI tract, and relapse of symptoms upon dietary challenge (two of three patients, Table 3). Case 3 especially illustrates that the trial of elimination diet alone did not produce clinical or histologic improvement; it was only after immunosuppression was reduced (by switching to CSA) that symptoms of diarrhea improved, confirmed by improved mucosal eosinophilia. Also, two of three cases had either no evidence of eosinophilic gastroenteropathy prior to tacrolimus exposure (case 2) or had improvement after switching, as noted above for case 3. This implies a critical role of tacrolimus in the pathogenesis of this clinical association.

Eosinophilic gastroenteritis in the setting of pediatric liver transplantation was first reported in 1997 (9). Dhawan et al. noted heme-positive stools, diarrhea, and protein losing enteropathy in two liver transplant recipients 4–6 wk after receiving a single bolus of high-dose intravenous solumedrol for presumed graft rejection. Peripheral eosinophilia was noted in one patient. GI biopsies were consistent with eosinophilic gastroenterocolitis. An association with development of food allergies was not reported.

Life threatening food allergy in liver transplant recipients on tacrolimus has also been observed (6, 7). The authors of these reports speculated that a tacrolimus-induced imbalance between Th1 and Th2 cells played a major role in the development of the allergic diathesis. Another report of eosinophilic gastroenteritis in pediatric liver transplant recipients noted the development

Table 3. Comparison of studies reporting gastrointestinal or respiratory symptoms attributed to food allergy in pediatric liver transplant recipients

Study	Age at transplant (mean, yr)	Immunosuppressant	PE (% patients available for study)	IgE	Tacrolimus level (CSA level)	Food allergy	EGID	Treatment
Romero et al. (10)	3.7	Tacro	28	↑	NR	Milk	26%	NR
Lacaille et al. (6)	0.7	Tacro	NR	↑	Not elevated	Milk, eggs, peanuts	NR	Neocate® elimination, tapered tacrolimus ketotifen, cromolyn steroid bolus
Inui et al. (7)	2.5	Tacro	NR	↑	NR	Seafood	NR	Elimination, tapered tacrolimus
Dhawan et al. (9)	6	CSA	50	NR	CSA-500–600	NR	100%	Steroids
This study	3.8	Tacro	19	↑	Not elevated	Milk, eggs, wheat	100%	Elimination diet switch to CSA

PE, peripheral eosinophilia; EGID, eosinophilic gastrointestinal disease in patients with peripheral eosinophilia; NR, not reported; Tacro, tacrolimus; CSA, cyclosporine.

of peripheral eosinophilia in 28% of patients and evidence of eosinophilic gastroenteritis in 26% (10). Fifty percent of these patients had elevated IgE levels and positive RASTs for milk proteins. Patients were more likely to have been treated with tacrolimus and to have an EBV load associated with eosinophilic GI disease, similar to one of our cases (case 2).

Angioedema has been found in 10% of tacrolimus-treated liver transplant recipients compared to only 0.2% receiving CSA (11). Interestingly, none of these patients had a previous history of allergy or atopy. There was a delay in onset of symptoms post-transplant (mean 28 months). Eight of 12 patients (66%) were switched to CSA, along with dietary restriction, with resolution of symptoms. Of those who continued on tacrolimus therapy, symptoms persisted, with elevated eosinophil counts and IgE levels. Patients had episodic diarrhea, although evaluation for that was not reported. Our cases share features in common with this report, including development of symptoms of food allergy, peripheral eosinophilia, and elevated serum IgE levels in the absence of previous atopy, a lag time to the development of symptoms after transplantation, and response to dietary restriction and reduced immunosuppression. Interestingly, our patients tended to be older when food allergy is not a commonly encountered phenomenon.

We believe that GI eosinophilia in the setting of tacrolimus treatment could be explained by two mechanisms. Tacrolimus is known to induce increased intestinal/colonic permeability (12–14). This may lead to exaggerated transepithelial transport of antigens, predisposing to allergy. A second intriguing mechanism could be altered cytokine production leading to eosinophilia (15, 16). Both tacrolimus and CSA paradoxically increase serum IgE levels (4). We speculate that the increased intestinal permeability, coupled

with increased IgE levels, can potentially lead to mucosal injury producing clinical symptoms of diarrhea, hematochezia and food intolerance. Furthermore, differential inhibition of cytokine elaboration by tacrolimus and CSA might alter the balance between Th1 and Th2 T-cell subsets and thereby produce an altered pattern of reaction to an antigenic challenge or exposure. Indeed, Wilhelm and Kirchner (17) observed increased IgE synthesis by Th2 cells, and atopic patients were noted to have a predominance of Th2 cells with resultant increased IgE levels. IL-4 plays varied roles in the allergic response cascade including increased IgE production, increased T-cell proliferation, activation of mast cells and basophils (major effector cells of allergic response) and increased expression of VCAM. The latter promote migration of mononuclear cells and eosinophils to the site of allergic inflammation. Hence, IL-4 regulates both acute and late phases of the allergic response. IL-4 also inhibits INF- γ (18). As opposed to proinflammatory cytokines, INF- γ has been shown to inhibit allergen induced responses (19, 20), and reduction of peripheral eosinophilia in atopic patients (21).

The data presented reflect a single center experience based on retrospective chart review. Despite these limitations, we feel that the association of eosinophilic GI disease in the setting of liver transplantation is an important observation and needs to be considered in the evaluation of diarrhea in such patients. The value of RASTs as surrogate markers of the allergenic response needs to be determined by further study, but the role of skin testing in chronically immunosuppressed patients is also problematic.

Pretransplant evaluation would need to include a careful history to rule out a pre-existing allergic diathesis, and measurement of serum IgE levels and RASTs. This will not alter the outcome of post-transplant immunosuppression

but may guide dietary/nutritional recommendations. Future studies may also need to address the role of targeted anti-IgE therapy (e.g. Omalizumab) in this particular setting. These issues raise the need for a prospective multicenter study to assess the prevalence of eosinophilic gastroenteropathy in pediatric liver transplant patients.

Acknowledgments

The authors gratefully acknowledge John T. Boyle, MD, for critical review of the manuscript and Susan E. Fitzmaurice, RN, MPA, for help in data retrieval. This work was supported in part by NIH Research Training Grant T32DK07471.

References

1. HOOKS MA. Tacrolimus, a new immunosuppressant—a review of the literature. *Ann Pharmacother* 1994; 28: 501–511.
2. McDIARMID SV. The use of tacrolimus in pediatric liver transplantation. *J Pediatr Gastroenterol Nutr* 1998; 26: 90–102.
3. WALLEMACQ PE, REDING R. FK506 (tacrolimus), a novel immunosuppressant in organ transplantation: clinical, biomedical and analytical aspects. *Clin Chem* 1993; 39: 2219–2228.
4. KAWAMURA N, FURUTA H, TAME A, et al. Extremely high serum level of IgE during immunosuppressive therapy: paradoxical effect of cyclosporine and tacrolimus. *Int Arch Allergy Immunol* 1997; 112: 422–424.
5. TREDE NS, WARWICK AB, ROSOFF PM, et al. Tacrolimus (FK506) in allogeneic bone marrow transplantation for severe anemia following orthotopic liver transplantation. *Bone Marrow Transplant* 1997; 20: 257–260.
6. LACAILLE F, LAURENT J, BOUSQUET J, et al. Life threatening food allergy in a child treated with FK506. *J Pediatr Gastroenterol Nutr* 1997; 25: 228–229.
7. INUI A, KOMATSU H, FUGISAWA T, et al. Food allergy and tacrolimus. *J Pediatr Gastroenterol Nutr* 1999; 28: 355–356.
8. NOWAK-WEGREZYN AH, SICHERER SH, CONOVER-WALKER MK, et al. Food allergy after pediatric organ transplantation with tacrolimus immunosuppression. *J Allergy Clin Immunol* 2001; 108: 146–147.
9. DHAWAN A, SEEMAYER TA, PINSISKI C, et al. Post transplant eosinophilic gastroenteritis in children. *Liver Transpl Surg* 1997; 3: 591–593.
10. ROMERO R, ABRAMOWSKY CR, PILLEN T, et al. Peripheral eosinophilia and eosinophilic gastroenteritis after pediatric liver transplantation. *Pediatr Transplant* 2003; 7: 484–488.
11. LYKAVIERIS P, FRAUGER E, HABES D, et al. Angioedema in pediatric liver transplant recipients under tacrolimus immunosuppression. *Transplantation* 2003; 75: 152–165.
12. MADSEN K, YANCHAR NL, SIGALET DL, et al. FK506 increases permeability in rat intestine by inhibiting mitochondrial function. *Gastroenterology* 1995; 109: 107–114.
13. GABE SM, BJARNASON I, TOLON-GHAMARI Z, et al. The effect of tacrolimus (FK506) on intestinal barrier function and cellular energy production in humans. *Gastroenterology* 1998; 115: 67–74.
14. YANCHAR NL, RIEGEL TL, MARTIN G, et al. Tacrolimus (FK506) – its effects on intestinal glucose transport. *Transplantation* 1996; 61: 630–634.
15. RENZ H. The central role of T-cells in allergic sensitization and IgE regulation. *Exp Dermatol* 1995; 4: 173–182.
16. WANG SC, ZEEVI A, JORDAN ML, et al. Fk506, rapamycin and cyclosporine: effects on IL-4 and IL-10 mRNA levels in a T-helper 2 cell line. *Transplant Proc* 1991; 23: 2920–2922.
17. WILHELM D, KIRCHNER H. T cells and their role in allergies. *Exp Clin Immunogenet* 1993; 10: 208–218.
18. VERCELLI D, JABARA HF, LAUENER RP, et al. IL-4 inhibits the synthesis of IFN- γ and induces the synthesis of IgE in human mixed lymphocyte cultures. *J Immunol* 1990; 144: 570–573.
19. RENZ H, LACK G, SALOGA J, et al. Inhibition of IgE production and normalization of airways responsiveness by sensitized CD8 T cells in a mouse model of allergen-induced sensitization. *J Immunol* 1994; 152: 351–360.
20. DIAZ-SANCHEZ D, NOBLE A, STAYNOV DZ, et al. Elimination of IgE regulatory rat CD8+ T cells in vivo differentially modulates interleukin-4 and interferon- γ but not interleukin-2 production by splenic T cells. *Immunology* 1993; 78: 513–519.
21. HANIFIN JM, SCHNEIDER LC, LEUNG DYM, et al. Recombinant interferon gamma therapy for atopic dermatitis. *J Am Acad Dermatol* 1993; 28: 189–197.