



Letter

Tacrolimus use in renal and cardiac pediatric transplantation: no increased risk of food allergies

Food allergies have been shown to occur in increased prevalence in children after orthotopic liver transplantation from nonatopic donors.^{1–8} Immunosuppression with tacrolimus (TAC) and young age at transplantation have been identified as important risk factors for the development of transplant-acquired food allergy (TAFA), although the pathophysiology remains unclear.^{1–8} The objective of this study was to establish whether TAFA was observed after renal and cardiac transplantations and to determine whether the type of solid organ transplanted and/or immunosuppression protocol played a role in the development of TAFA.

We performed a retrospective cohort study by reviewing charts of children hospitalized for heart or renal transplantation at the Sainte-Justine University Hospital Center (Montreal, Quebec, Canada). The project was approved by the ethics committee. The study population consisted of 56 renal transplants and 45 cardiac transplants ($n = 101$). Patients included in the study were exposed to cyclosporine or to TAC as part of their main immunosuppressive therapy for at least 6 months after transplantation. The median age at combined renal and cardiac transplantation was 11 years. Data collected included age at transplantation, indication for transplantation, immunosuppression protocol, history of food allergies, atopic background (asthma, allergic rhinitis, eczema), and blood eosinophil count (Table 1).

A total of 253 patients 1 month to 19 years old received 315 renal transplants from June 1974 through February 2013. Of these patients, we randomly selected a sample of 65. Nine were excluded: 1 died within 6 months after transplantation, 1 was transferred back to his primary center and lost to follow-up 2 months after transplantation, and 7 had acute transplant rejections and were put back on dialysis after a total immunosuppression shorter than 6 months. Of the remaining 56 patients included in the study, 29 patients were treated with cyclosporine and 27 with TAC. No TAFAs were observed in either group. Furthermore, our hospital systematically refers transplant recipients to the allergy department when a food or drug allergy is suspected and where parallel charts are kept. Of the remaining 188 charts that were not reviewed, only 2 had parallel charts in the allergy department and were evaluated for suspected latex allergy (no TAFA), strongly suggesting that these patients did not have any significant food allergies.

A total of 63 patients underwent cardiac transplantations from July 1984 through September 2011. Of these patients, 18 were excluded: 9 died within 6 months of transplantation and 9 charts

were unavailable. Of the remaining 45 patients, 12 patients received TAC and 33 received cyclosporine. One new-onset egg allergy (8.3%) was observed in a patient in the TAC group transplanted at 1 month of age and appeared approximately 1 year after transplantation. This female patient had positive cutaneous test reactions and rash after the ingestion of eggs, and her parents were told to avoid egg products all together. No anaphylaxis was reported. At her last follow-up in the allergy clinic at 4 years 4 months of age, the patient was still strictly avoiding eggs in her diet and cutaneous tests to egg white elicited wheals of 19 mm. The patient eventually died of post-transplantation lymphoproliferative disease at 6 years of age.

Our study supports the fact that TAC is not a risk factor for TAFA after pediatric kidney or heart transplantation. No TAFAs were seen in kidney transplant recipients, even in the subgroup of transplant recipients younger than 5 years ($n = 11$). Only 1 case of new-onset food allergy (8.3%) was observed after cardiac transplantation, this being similar to the prevalence of allergies in the general population.⁹ This is the third case of new-onset food allergy observed after cardiac transplantation, with the first 2 cases reported in patients undergoing transplantation at a very young age also receiving TAC immunosuppression.^{5,8} We could not solely attribute the new allergy to transplantation, because the allergen was not introduced before cardiac transplantation and could have been a natural allergic evolution for this child.

The pathophysiology of TAFA is probably multifactorial; local hematopoietic cells and immunoregulatory processes unique to the liver most likely play an important role,⁷ which could explain why so few TAFAs were seen after renal and cardiac transplantation. TAC has a cytotoxic effect on the gastrointestinal system and could increase intestinal barrier permeability to allergenic food proteins, especially in susceptible hosts after liver transplantation who are at greater risk of infection and medication-induced gut toxicity. In addition, TAC inhibition of interleukin-2 and suppression of T-regulatory cells¹⁰ could direct the immune response toward a T-helper cell type 2 phenotype, which is more important in young transplant recipients with immature immune systems; indeed, most TAFAs in the literature were described in patients who underwent transplantation at a very young age (generally <1 year^{6–8}). Thus, another reason for the very few TAFAs in cardiac and kidney transplant recipients could be attributed to the older age at transplantation (median age 11 years in the present cohort) and already established immune tolerance to dietary antigens.

Our data seems to indicate that TAC can be safely used in pediatric cardiac and renal transplant recipients without significantly increasing the risk of TAFA. Prospective multicentric studies are needed to confirm these findings.

Disclosures: Mr Racicot has received grants from the Allergy Service of CHU Sainte-Justine.

<http://dx.doi.org/10.1016/j.anai.2015.05.021>

1081-1206/© 2015 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Table 1
Patient characteristics

	Renal transplant recipients	Cardiac transplant recipients
Total patients (after exclusion)	56	45
Boys, n (%)	36 (65)	24 (53)
Indications for transplantation (n)	Congenital nephron-uropathy (20) Hemolytic uremic syndrome (5) Cystinosis (4) Nephronophthisis (4) Focal segmental glomerulosclerosis (3) Renal cortical necrosis (3) Renal hypoplasia (3) Polycystic kidney disease (3) Alport syndrome (2) Others (9) ^a	Dilated CMP (19) Hypertrophic CMP (6) Transposition of great vessels (5) Cyanotic heart disease (5) Restrictive CMP (2) Aortic stenosis (2) Single ventricle (2) Endocardial fibroelastosis (1) Coarctation of aorta (1) Ischemic CMP (1) Doxorubicin-induced CMP (1)
Age at transplantation (y), median (range)	13.2 (2.6–18.6)	9.7 (0.08–18.1)
Immunosuppression protocol, n (%)		
Tacrolimus	27 (48)	12 (27)
Cyclosporine	29 (52)	33 (73)
Food allergies before transplantation, n (%)		
Tacrolimus	3 (11)	0 (0)
Cyclosporine	2 (6.9)	1 (3)
History of atopy (asthma, allergic rhinitis, eczema), n (%)		
Tacrolimus	7 (26)	1 (8.3)
Cyclosporine	7 (24)	9 (27)
Eosinophilia after transplantation (defined as eosinophils $\geq 0.5 \times 10^9/L$), n (%)		
Tacrolimus	3/27 (11.1)	3/12 (25)
Cyclosporine	2/27 (7.4)	4/29 (13.8)
Transplant-acquired food allergy	0	1 (tacrolimus)

Abbreviation: CMP, cardiomyopathy.

^aGlomerulonephritis (1), Bardet-Biedl syndrome (1), Renal osteodystrophy (1), McKusick-Kaufman syndrome (1), Denys-Drash syndrome (1), familial idiopathic steroid-resistant nephrotic syndrome (1), Henoch-Schönlein nephritis (1), congenital nephrotic syndrome of the Finish type (1), and type 4 renal tubular acidosis (1).François Graham, MD, MSc^{*,†}Frédéric Racicot, MD[†]Luminita Jamali, MD[†]Véronique Phan Cong, MD[‡]Marie-Josée Raboisson, MD[§]Jean Paradis, MD^{*,†}Louis Paradis, MD^{*,†}Anne Des Roches, MD[†]^{*}Allergy and Immunology

Centre Hospitalier de l'Université de Montréal

[†]Allergy and Immunology[‡]Nephrology[§]Cardiology

Centre Hospitalier Universitaire Sainte-Justine

Montreal, Quebec, Canada

a.des.roches@umontreal.ca

References

- [1] Lebel MJ, Chapdelaine H, Paradis L, Des Roches A, Alvarez F. Increase in de novo food allergies after pediatric liver transplantation: tacrolimus

vs. cyclosporine immunosuppression. *Pediatr Transplant.* 2014;18:733–739.

- [2] Nowak-Węgrzyn 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.
- [3] 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 Transplant.* 2009;13:63–69.
- [4] De Bruyne R, Dullaers M, Van Biervliet S, et al. Post-transplant food allergy in children is associated with liver and not with renal transplantation: a monocentric comparative study. *Eur J Pediatr.* 2013;172:1069–1075.
- [5] Ozdemir O, Arrey-Mensah A, Sorensen RU. Development of multiple food allergies in children taking tacrolimus after heart and liver transplantation. *Pediatr Transplant.* 2006;10:380–383.
- [6] Brown C, Haringman N, Davies C, et al. High prevalence of food sensitisation in young children with liver disease: a clue to food allergy pathogenesis. *Pediatr Allergy Immunol.* 2012;23:771–778.
- [7] Wisniewski J, Lieberman J, Nowak-Węgrzyn A, et al. De novo food sensitization and eosinophilic gastrointestinal disease in children post liver transplantation. *Clin Transplant.* 2012;26:E365–E371.
- [8] Frischmeyer-Guerrero PA, Wisniewski J, Wood RA, Nowak-Węgrzyn A. Manifestations and long-term outcome of food allergy in children after solid organ transplantation. *J Allergy Clin Immunol.* 2008;122:1031–1033.
- [9] Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity and distribution of childhood food allergy in the United States. *Pediatrics.* 2011;128:e9–e17.
- [10] Eiwegger T, Gruber S, Geiger C, et al. Impact of systemic immuno-suppression after solid organ transplantation on allergen-specific responses. *Allergy.* 2011;66:271–278.