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Addition of mycophenolate mofetil to tacrolimus is associated with decreases in food-specific IgE levels in a pediatric patient with liver transplantation-associated food allergy

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TO THE EDITOR

Transplantation-associated food allergy (TAFA) refers to the *de novo* development of food-specific serum IgE (sIgE) after solid organ transplantation, associated in many instances with clinical reactivity to those foods. It is primarily observed in pediatric patients who have received a liver transplant and are receiving immunosuppression with tacrolimus (Tac).^{1–3} Tac may be implicated in TAFA through possible effects on gut permeability, which could alter intestinal antigen presentation.⁴ It may also preferentially suppress T-regulatory cells,⁵ facilitating T_H2-type inflammation. Substitution of cyclosporine A (CsA) for Tac can decrease food sIgE levels and may be appropriate management of TAFA.^{3,6} However, no consensus guidelines are available for the management of this condition, and CsA may not provide sufficient immunosuppression and may also have intolerable side effects or limited availability. Here, we report the case of a girl who developed TAFA with attendant eosinophilic gastrointestinal disease (EGID) and atopic dermatitis (AD) after liver transplantation and whose food-specific IgE values dramatically declined in association with a decreasing Tac dosage and the addition of mycophenolate mofetil (MMF) to her immunosuppressive regimen, along with marked clinical improvement.

The patient underwent orthotopic liver transplantation at the age of 5 months after a failed Kasai procedure for the treatment of biliary atresia. The food allergy (FA) status of the liver donor was not known. Her diet consisted of breast milk and milk-based formula, and her initial immunosuppressive regimen consisted of CsA plus prednisone. At the age of 14 months and coinciding with the introduction of solid foods into her diet, she developed mild AD. At about this same time she developed generalized hives on touching an eggshell, and over the next 2 years she developed similar reactions with egg ingestion, soy, and peanuts. Skin prick tests (SPTs) were positive to peanuts, tree nuts, eggs, and sesame seeds; avoidance of these foods was recommended. At age 5 years, CsA was discontinued because of signs of liver rejection and the development of hirsutism, and Tac was initiated at a dosage of 0.2 mg/kg per day. Over the next 2 years she developed aversion to multiple foods, daily abdominal pain, frequent episodes of nausea, and occasional vomiting. When

evaluated at age 7 years 8 months, her height and weight were 123 cm and 24 kg (30th and 15th percentiles, respectively), and her AD had become severe. sIgE testing performed with the CAP test (Phadia, Sweden) was positive to egg white and yolk, peanut, wheat, beef, cow milk, soy, chickpea (Figure 1), red kidney bean, sesame, lentil, potato, rice, rye, casein, cheddar cheese, whey, alpha lactalbumin, mustard, yeast, and avocado (not shown). EGID was diagnosed on endoscopy at this time, which showed diffuse mildly increased eosinophils in the gastrointestinal lamina propria, with signs of degranulation. A repeat endoscopy done in May 2007 was described as having similar eosinophil counts, although numbers were not reported by the pathologist. By our counts, eosinophilic infiltration of the lamina propria was as follows in October 2004 and May 2007, respectively: the mid esophagus had 17 eosinophils per hpf and then 10/hpf; distal esophagus had 37/hpf and then 16/hpf; gastric antrum had 10/hpf and then 8/hpf; the terminal ileum was sampled only in May 2007 and had 42/hpf; right colon had 32/hpf and then 14/hpf; rectum had 18/hpf and then 7/hpf (the upper limit of normal number of eosinophils in the lamina propria per hpf for the esophagus is 0, antrum, 8; ileum, 28; ascending colon, 50; and rectum, 32).⁷ Because of the severity of her AD and EGID, her diet was further restricted to chicken, turkey, pork, and some fruits and vegetables, without discernible symptomatic improvement. At age 10 years, her height and weight were 136 cm and 30 kg (15th and 30th percentiles, respectively), and all of her previously identified food allergen sIgE levels had increased substantially despite avoidance and notwithstanding a proportional decrease in Tac dosage in respect to body weight, down to 0.13 mg/kg per day (Figure 1). Two healthy younger siblings share some food sIgEs and clinical sensitivities with our patient, but neither one of them developed EGID, AD, food aversions, or failure to thrive. One of the siblings developed gastrointestinal and respiratory symptoms on exposure to peanuts at age 2 years; was found positive on SPT to soy, peanut, tree nuts, mustard, sesame, and shellfish; and continues avoiding these foods at age 11 years. The other sibling developed immediate-type contact urticaria to eggs at age 2 years; was found positive on SPT to eggs, soy, peanuts, tree nuts, mustard, sesame, and shellfish; is 8 years old; and also still avoids all of these foods. Other than the aforementioned foods, neither one has developed SPT positivity to the range of foods our patient has. At 10 years 8 months of age, MMF (31 mg/kg per day) was introduced because of renal toxicity attributed to Tac. Over the subsequent 28 months, all food sIgE levels declined dramatically (< 40 kU/L; Figure 1). Tac was discontinued September 2010 because of its presumed association with TAFA in and EGID, followed by further decreases in food-specific IgEs. Wheat was reintroduced into her diet and was well tolerated. Her AD also improved markedly after the discontinuation of Tac, and her symptoms of gastrointestinal discomfort resolved. Food aversions decreased, and her weight increased to the 71st percentile. She has not undergone a repeat endoscopy or food challenges for clinical and logistical limitations and ethical reasons. Importantly, she has not shown signs of liver transplant rejection on MMF as a single immunosuppressive agent.

The development of multiple elevated food sIgEs in patients who received a transplant and taking Tac is now widely recognized. Although no studies have formally verified clinical reactivity (and therefore “FA” according to the practice guidelines⁸), the term TAFA has been widely adopted to refer to this phenomenon. In our patient, evidence of sensitization to foods occurred concomitantly with AD, EGID, food aversions, and growth failure. The

dramatic and rapid decrease in food-specific sIgE after a change in her immunosuppressive regimen from Tac to MMF, along with concomitant resolution of AD, symptoms of EGID, and growth failure, suggest a causal link to true FA and also suggest a direct role for MMF and/or reduction in the dose of Tac in the resolution. However, it is difficult to ascribe causality to many of this patient's positive sIgEs, given that many were measured on the account of EGID symptoms and not immediate-type hypersensitivity reactions. In addition, given that the atopic status of the liver donor is not known, the possibility that some of our patient's food sensitivities were transferred from her transplanted liver cannot be discounted, because this condition has been described in the medical literature.⁹

Nonetheless, the magnitude and rate of decline in sIgE to egg white, egg yolk, and soy proteins (53, 45, and 61 kU/L, respectively) observed over a 2.5-year period in our patient after the addition of MMF markedly exceeds the rates of decline in these values in atopic children with either transient or persistent egg or soy allergy reported by Savage et al^{10,11} (16 kU/L in a span of 14 to 18 years for those with transient egg allergy, and 13 kU/L in that same time frame for those with persistent egg allergy). Because neither the rate nor the magnitude of decreases in levels of food-specific IgE in our patient's case is typical of a natural trend toward tolerance observed in atopic children without TAFAs, it more likely reflects the introduction of MMF plus a proportional decrease in Tac.

Data are limited on pediatric patients with liver TAFAs treated with MMF. Six of 7 patients in the cohort studied by Nowak-Węgrzyn et al² developed TAFAs while on a regimen that consisted of Tac plus MMF, but the dosage of MMF was not specified. Similarly, Prabhakaran et al¹² described 11 patients on Tac plus MMF who developed TAFAs, but, again, the dose for MMF is not available, and the nature of the apparent clinical reactions to the foods are not reported. Granot et al¹³ report on 10 pediatric recipients of a liver transplant who developed asymptomatic eosinophilia and elevated IgEs while treated with Tac, 3 of whom were concomitantly treated with MMF at 15 to 25 mg/kg per day. However, they did not clarify whether the 3 patients treated with Tac plus MMF developed FA.¹³ Ozdemir et al¹⁴ mention that 1 of 2 patients in their report developed FAs on Tac plus MMF for primary immunosuppression, but the average dose of MMF was 20 mg/kg per day, which is less than the dose taken by our patient (31 mg/kg per day). Finally, Levy et al¹⁵ report on 1 of 4 patients who developed TAFAs while on Tac and was switched to CsA plus MMF at a dose of 600 mg/m² per day for 2 weeks, then 300 to 400 mg/m² per day (our patient's dose was 788 mg/m² per day). Although they reported that TAFAs persisted in this patient, the length of follow-up was not reported. The rapid and broad decline in food sIgEs, occurring concomitantly with clinical improvement in AD, and nutritional status in our patient strongly support causality between Tac and the development of TAFAs and suggest that MMF as an alternative reagent may hasten the resolution of TAFAs. Dose-ranging studies would be needed to determine whether an optimized dose of MMF could both provide adequate immunosuppression and facilitate resolution of, or protection from, TAFAs.

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Clinical Implications

- Transplantation-associated food allergy is most commonly seen in pediatric liver transplant recipients on tacrolimus and may be associated with atopic dermatitis, eosinophilic gastrointestinal disease, poor weight gain, and clinical reactivity to multiple foods.
- Reducing the dose of tacrolimus and adding mycophenolate mofetil to the immunosuppressive regimen may lead to resolution of this condition.
- Clinical trials should investigate whether mycophenolate mofetil facilitates resolution or confers protection from transplantation-associated food allergy.

FIGURE 1.

Decrease in total and food-specific sIgE levels and growth parameters after changes to immunosuppressive regimen. Changes in this patient's total and food-specific sIgE levels over time are presented, in addition to height and weight percentiles. The dates and time points of adjustments in her immunosuppressive regimen are noted.