



Food allergy: setting the scene for tolerance induction



Aster/Science Photo Library

Published Online

December 11, 2017

[http://dx.doi.org/10.1016/S2468-1253\(17\)30391-6](http://dx.doi.org/10.1016/S2468-1253(17)30391-6)

See **Articles** page 85

IgE-mediated food allergies seem to have increased dramatically in the last few decades.^{1,2} This increase is often referred to as the second allergy wave, because it follows the observed rise of allergies of the upper and lower airways (ie, allergic rhinoconjunctivitis and asthma) that started in the 1960s. The current food allergy epidemic appears to be a perfect storm involving an increased prevalence of sensitised children, an increased severity profile, and a broadening of reactivity from fewer to more allergenic foods, although the most prevalent in infancy are still milk and egg, followed by peanut and tree nuts in young children, and fish, crustaceans, seeds, and cereals in older children and adults.

Interesting results have been obtained in the field of primary prevention of peanut allergy in infants,³ but data are less convincing for other age groups and allergenic foods,⁴ and a cure for an established food allergic disease is still not available. Pharmacological control of asthma and hayfever might reduce the risk of severe reactions upon ingestion of a culprit food in a given individual, but classic anti-allergic drugs are by no means preventive. Inspired by the relative success of allergen immunotherapy for attenuation of symptoms in inhalation allergies—induced by allergens such as grass and birch pollen and house dust mites—a similar approach has been tested in food allergies. In view of the vigorous acute response of a food allergic individual to food proteins, various strategies to eliminate allergic side-effects have been tested, such as creation of hypoallergenic molecules⁵ or use of routes of administration¹ other than the subcutaneous route that is predominantly used in allergen immunotherapy for allergic airway diseases. In this respect, an oral form of immunotherapy, in which individuals ingest daily dosages of food proteins with gradual dose increases have been described^{1,6} and shown to be efficient, safe, and patient-friendly. In spite of some success, however, oral immunotherapy is still likely to produce allergic side-effects during up-dosing, and the Achilles' heel of the treatment is its sustainability. It remains unclear whether oral immunotherapy-induced tolerance will endure when daily dosing is stopped for a period.

In *The Lancet Gastroenterology & Hepatology*, Sandra Andorf and colleagues⁷ present a clinical trial in the most vulnerable food allergic patients, namely those with not just a single, but multiple food allergies. By

including participants with a high level of sensitisation (large skin prick test areas, high levels of food-specific IgE in serum, or both) the study addresses the most severely affected and thus difficult-to-treat part of the food allergic population. The purpose of the study was to determine whether oral immunotherapy is possible in this group if given under a cover of omalizumab, a humanised antibody that neutralises circulating IgE and is assumed to gradually reduce mast cell-bound IgE and thus the allergic reactivity of the patient. In the trial, an omalizumab (or placebo) pretreatment period of 8 weeks was used before initiating the oral immunotherapy. The primary outcome was the proportion of participants who passed a titrated double-blinded, placebo-controlled food challenge to 2 g of food protein (per food)—the gold standard of food allergy diagnosis.

The good news is that the anti-IgE cover conferred a much improved safety profile on the multiple-food oral immunotherapy, and this allowed for a higher success rate in the patients who received omalizumab pretreatment compared with those who received placebo. For these individuals, failing to pass the placebo-controlled food challenge is much less of a problem than is not being able to adhere to the dosage schedule due to adverse events. The trial was a phase 2 study, and it could be argued that with a less aggressive dose-increment schedule fewer patients would have experienced side-effects and thus would have been able to reach tolerance. However, as several oral immunotherapy studies have shown, some patients might never be able to tolerate more than a specific dose of food protein. Considering the safety of the patients and the costs of this treatment to the health-care system, iterative adjustments and readjustments of dosage schedules are unlikely to lead to success in such highly vulnerable patients who are afflicted by multiple food hypersensitivities.

As discussed by the authors, the study has limitations. Whether tolerance was sustained was not addressed, and this question will require future studies. Furthermore, not all patients can be treated adequately with omalizumab due to very high levels of serum IgE, and this might in particular cause problems in the substantial subset of patients with atopic dermatitis, a condition often seen in conjunction with food allergy. On the other hand, new molecules targeting IgE are in the pipeline that might

further improve the anti-IgE cover. One might question whether cumbersome oral immunotherapy is necessary if anti-IgE does the trick. But as the study by Andorf and colleagues shows, a careful dose increase of the culprit allergenic food is still necessary to induce tolerance. This makes the situation complex, and one can only hope that this study will inspire more incremental research in the optimal dose–time relationships necessary for not only reaching temporary tolerance immediately after the treatment period, but also a sustained endurance.

Lars K Poulsen

Allergy Clinic, Copenhagen University Hospital at Gentofte,
2900 Hellerup, Denmark
lkpallgy@mail.dk

I declare no competing interests.

- 1 Tordesillas L, Berin MC, Sampson HA. Immunology of food allergy. *Immunity* 2017; **47**: 32–50.
- 2 Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014; **69**: 62–75.
- 3 Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015; **372**: 803–13.
- 4 Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016; **374**: 1733–43.
- 5 Jongejan L, van Ree R, Poulsen LK. Hypoallergenic molecules for subcutaneous immunotherapy. *Expert Rev Clin Immunol* 2016; **12**: 5–7.
- 6 Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017; **72**: 1133–47.
- 7 Andorf S, Purington N, Block WM, et al. Anti-IgE treatment with oral immunotherapy in multifoed allergic participants: a double-blind, randomised, controlled trial. *Lancet Gastroenterol Hepatol* 2017; published online Dec 11. [http://dx.doi.org/10.1016/S2468-1253\(17\)30392-8](http://dx.doi.org/10.1016/S2468-1253(17)30392-8).

Towards patient-centred and cost-effective care for patients with cirrhosis and ascites

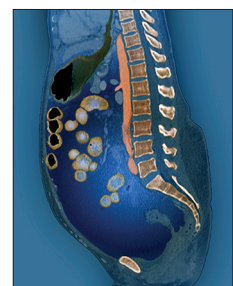


The end of life for patients with cirrhosis is marked by increased personal and financial costs, largely driven by frequent, often unrelenting, hospital admissions.^{1,2} Although resource use can be intense, it might not be matched with the patient's needs. Liver transplantation is the only definitive treatment for end-stage liver disease, but many patients are not candidates. For all patients with cirrhosis, but particularly when transplantation is not part of the plan of care, the focus must be on enhancing quality of life. This is the aim of palliative care. However, the evidence suggests that this approach is falling short. Only 11% of patients with decompensated cirrhosis are referred for palliative care.³ Efforts to re-centre the focus of care on the needs of patients with end-stage liver disease are urgently needed. Beyond palliative care consultation, there are opportunities to unburden patients by modifying the structure of care delivery to optimise symptom management.

Symptomatic ascites requiring paracentesis is the perfect test case. Patients with urgent needs are often referred for hospital admission when the capacity to provide same-day paracentesis is limited. The downstream consequences attributable to inpatient or outpatient management of symptomatic ascites are examined by Benjamin Hudson and colleagues in an Article in *The Lancet Gastroenterology & Hepatology*.⁴

The authors did a nationwide audit of outcomes over the last year of life for all patients in the UK with cirrhosis and ascites who required large-volume paracentesis. This cohort included 13 818 people, capturing 30.8% of all liver-related deaths in England between 2013 and 2015. This group of patients was particularly ill, notably with a higher-than-expected 52.5% 30-day readmission rate.^{1,5} Hudson and colleagues specifically assessed the effect of large-volume paracentesis provided by day-case units. This outpatient model provides same-day procedures as an alternative to hospital admission for patients with symptomatic ascites. Patients who attended a day-case unit for large-volume paracentesis at least once in their last year of life had significant reductions in the cost of medical care (–£4240, 95% CI –4829 to –3651; $p < 0.0001$), inpatient bed days (–16.98 days, –18.45 to –15.51; $p < 0.0001$), 30-day readmission rates (odds ratio 0.35, 95% CI 0.31 to 0.40; $p < 0.0001$), and odds of dying in hospital (0.31, 0.27 to 0.34; $p < 0.0001$).

These improved outcomes raise two major issues. First, all admissions for symptomatic ascites are unnecessary burdens on patients and payers. Given that outpatient paracentesis is an effective substitute for inpatient paracentesis, similar findings could be expected if this model was prospectively applied to all patients with ascites, before they approach the last year of their life.



Published Online
November 14, 2017
[http://dx.doi.org/10.1016/S2468-1253\(17\)30339-4](http://dx.doi.org/10.1016/S2468-1253(17)30339-4)
See **Articles** page 95