



Use of biologics in severe food allergies

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Purpose of review

Severe cases of food allergy account for the majority of the burden in terms of risks, quality of life, and resource expenditure. The traditional approach to these forms has been strict avoidance. More recently, Oral ImmunoTherapy (OIT) has gained a role in their management. However, in severe food allergies OIT is often infeasible.

Recent findings

Case reports, observational, and prospective studies have recently proposed different approaches to severe food allergy. The majority of them include the use of biologics. Omalizumab has been the most studied drug for severe food allergies, and its role as adjuvant treatment to OIT is well established. Interest has been raised on other biologics, as dupilumab, reslizumab, and mepolizumab. Toll-like receptor agonists, and gene therapy using adeno-associated virus coding for Omalizumab are promising alternatives.

Summary

The recent studies are deeply influencing the clinical practice. We review the modifications of the clinical approach to severe food allergies so far available. We indicate the possible evolutions of treatment with biologics in severe food allergies.

Keywords

dupilumab, food allergy, Omalizumab, severe food allergy

INTRODUCTION

Definitions of allergy are very clear [1], but the scoring of their severity varies across the allergic manifestations. For rhinitis, the severity assessment relies mainly on symptom scores, visual analogue scales (VAS), and quality of life (QoL), but objective measures as measurements of nasal obstruction, measurements of inflammation, reactivity measurements, and measurements of the sense of smell are available [2]. Asthma severity is indicated by the level of treatment required to control symptoms and exacerbations. Patients with asthma requiring Step 4 or 5 treatment, e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite these treatments, are considered severe [3]. Rhinitis and asthma definitions of severity are not static features and may change over months or years. In asthma, a clear difference has been established among patients with 'difficult to treat asthma' and the truly severe conditions. Patients with inadequate or inappropriate treatment, lack of adherence, comorbidities such as chronic rhinosinusitis or obesity, have not a severe form, but a 'difficult to treat' asthma. The definition of severe asthma should be reserved for patients with refractory asthma and those in whom

response to treatment of comorbidities is incomplete [4]. 'Severe' is often also used to describe the intensity of asthma symptoms, the magnitude of airflow limitation, or the nature of an exacerbation.

A similar classification has not been adopted in food allergy, where a shared definition of severity does not exist. The U.S. NIAID guidelines allude in many points to the severity of gastrointestinal, dermatological, respiratory manifestations, and in particular to the severity of immediate anaphylactic reactions. It is stated that 'no tests are available to predict severity of IgE-mediated reactions'. It is reported that food allergy is associated with severe asthma [5]. However, the severity of food allergy in general is not defined. Similar considerations apply to the EAACI food allergy guidelines [6].

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KEY POINTS

- The current approach to severe food allergy treatment is passive (food avoidance) or reactive (epinephrine).
- Active treatments (OIT) are risky and often unfeasible in severe food allergy.
- The anti-IgE Mab Omalizumab has proven effective in reducing the risk of reactions in patients with food allergies.
- It can be used as door-opener for OIT, but the risk of nonimmediate side effects of OIT (EoE) is not eliminated.
- Studies on the pathogenesis of food allergy are identifying new targets for possible biologic treatments in the future.

One of the difficulties in defining severe food allergy is that this condition has many faces, and severity should be indicated for each of them. For instance, every anaphylactic reaction is a severe event by definition ('a serious, life-threatening, generalized hypersensitivity reaction' [7]), but risk factors for the very severe, near-fatal reactions are known, varying age by age. In infancy, they include under-recognition and under-diagnosis of anaphylaxis. In adolescence, lack of compliance with asthma preventer medications and dietary advice, exercise, fasting, denial of symptoms, and delay in seeking help. In adult age, treatment with β -blockers and ACE inhibitors, in particular when combined with cardiovascular disease and/or chronic obstructive pulmonary disease. In all age classes, the risk of severe anaphylaxis is increased by food-dependent, exercise-induced forms, by acetylsalicylic acid plus alcohol consumption, and by systemic mastocytosis [8]. Some of these criteria are similar to the criteria for 'difficult to treat' asthma.

In absence of a shared definition, what is a severe food allergy may vary across studies. As an example, in a study on the association among food allergy and celiac diseases, 'very severe' food allergy has been defined as 'a positive history of at least one severe allergic reaction (i.e., a reaction defined as classes 4 and 5 according to Clark's classification)' with 'elevated IgE levels against food proteins (IgE values > 85 kU/l) [9]. Another possible criterion is the type of reaction to diagnostic challenges. For instance, a food reaction failing to improve after receiving intramuscular adrenaline (plus supporting measures) or presenting a severe rebound after initial improvement is indubitably a severe reaction. In a German experience, severe anaphylactic reactions requiring ICU transferal account for a 0.2% of

Oral food Challenge (OFCs). Such severe reactions are more frequent in older children with peanut allergy [10], but also hen's egg, cow's milk, and hazelnut may lead to severe anaphylactic reactions [11].

Even more difficult is to give a definition of severity for non-IgE-mediated food allergies. For FPIES, severity stands in the definition ('a non-IgE, cell-mediated food allergic disorder that can be severe and lead to shock' [12]), but it appears that there are different degrees of severity in the number of offending foods and the characteristics of the reaction. A severe FPIES reaction is defined by 'repetitive, projectile emesis with or without diarrhea, pallor, lethargy, dehydration, hypotension, shock, methemoglobinemia, metabolic acidosis'. In pathologies as eosinophilic esophagitis (EoE), Atopic dermatitis (AD), or allergic enterocolitis, the evaluation of severity must rely upon disparate subjective and objective parameters, so that probably the best definition of a severe food allergy is the evaluation of QoL [13].

A definition of severe food allergy will be needed to establish a common approach to the treatment of these forms with biologics. Similar to severe asthma, associated with the greatest share of asthma morbidity and economic burden [14], severe food allergies probably are responsible for the highest expenditure in terms of office and emergency visits, inpatient hospitalizations, ambulance runs, epinephrine devices [15], and death [16]. The new treatments must focus on the most vulnerable fraction of patients, taking in account their risks, the pathogenesis of the specific forms, and the efficacy of single therapies.

WHAT CAN BIOLOGICS ADD TO THE TREATMENT OF SEVERE FOOD ALLERGY

By definition, biological products include a wide range of products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins [17]. The allergist is very familiar with such products: our speciality was born with the identification of the allergy mechanisms, and we use since 100+ years biological treatments as specific immunotherapy. In the recent years, however, gene-based and cellular biologics, produced at the forefront of biomedical research, have irrupted in our speciality.

BIOLOGICS FOR SEVERE IMMEDIATE FOOD ALLERGY

Food avoidance plays a role in curtailing the QoL of food allergy sufferers. To establish alternative strategies, some of the most prominent groups in the

field of food allergy re-assessed in the last 15 years the original idea of Giampiero Patriarca [18] of oral immunotherapy (OIT) [19,20]. In the majority of cases, this method is able to reduce the risk of reactions to food traces. However, it is debated if it is able to produce desensitization more than sustained unresponsiveness [21,22]. If they are desensitized, the treated patients will be able to ingest a food without reaction while continuing to ingest regular doses of that food (e.g. continuing on OIT). This means that OIT did not get a modulation of underlying pathogenic immune mechanism, and the effect is mediated by changes in mast cells, basophils or other effector cells. In this case, the ingestion of the food after a period of elimination (discontinuation of OIT) would result in an acute allergic reaction. By contrast, sustained unresponsiveness is the ability to tolerate a food after a period of time of OIT discontinuation, usually at least 4 weeks. The acquisition of sustained unresponsiveness is believed to reflect reprogramming of the immune response to allergen, involving regulatory T cells or other T-cell subsets and/or allergen-specific anergy and clonal selection. Sustained unresponsiveness is expected to persist for at least months or years after the food therapy has been discontinued [23].

Early studies shown that OIT was no more effective than elimination diet in the induction of tolerance [24]. To date, with the possible exception of OIT administered with probiotics [25], the immunological changes determined appear to be more a consequence of allergen exposure than an active factor able to modify the natural history of food allergy [26]. Sustained unresponsiveness occurs in a small fraction of desensitized patients, generally those with lower baseline food-specific IgE levels. [23,27]. OIT is less likely to be successful in patients with higher baseline food-specific IgE levels [23,28], precisely those with severe food allergies. Local adverse effects and systemic, potentially serious reactions during the course of OIT are common. These effects are multiplied in children with severe food allergy, who also are those for which the risks of OIT are highest: severe reactions requiring injection of epinephrine, refractariety to the treatment, and insurgence of EoE after the exposure to allergen [29,30]. These patients are also likely to have multiple food allergies, whereas OIT is strictly food specific [31]. The rates of reaction may be increased in patients with food allergy undergoing OIT compared with continued avoidance [32²²].

As OIT may not be a satisfactory treatment in severe food allergy, the support of therapies is being considered. Among them, the ability of humanized monoclonal antibody against IgE (Omalizumab) to

reduce the side effects of OIT and the effect of adjuvants (immune response modifiers) in enhancing tolerogenic responses associated with it.

Omalizumab, a recombinant humanized monoclonal antibody antifree circulating IgE, has been suggested as approach to reduce allergic reactions during the rush and up dosing phases of OIT. Omalizumab, binding to the CH₃ region of IgE, prevents binding of IgE to FcεRI and FcεRII receptors on the surface of mast cell and basophils, blocking their activation [33]. Omalizumab also prevents IgE from binding to FcεRI on dendritic cells by greatly reducing the level of circulating free IgE (although levels of circulating bound IgE increases). The reduced expression of FcεRI on dendritic cells is thought to reduce allergen presentation to T cells, followed by a reduction in Th2 cell activation, and a consequent decreased production of Th2 cytokines during the effector phases of allergic diseases [34].

Omalizumab is approved as treatment for moderate to severe asthma not responsive to other conventional treatments and for chronic spontaneous urticaria. It is precluded to patients with severe asthma with serum IgE levels greater than 1500 kUI/l, in absence of specific studies, for the risk of potentially dangerous immune complexes in excess of IgE. Its mode of action proposes Omalizumab as a promising therapeutic option for other allergic conditions, including allergic rhinitis, insect hypersensitivity and atopic dermatitis. In food allergy, it has been shown able to temporarily increase the tolerance to peanut [35–37].

After small open studies, showing improved tolerability of OIT with peanut and cow's milk and reduction of the likelihood of anaphylaxis on accidental food ingestion under Omalizumab treatment [38], several clinical trials have successfully its effect as an adjunctive therapy to food allergen OIT [39–41].

In the first study, children with high-risk, significant milk allergy and high milk-specific IgE (median 50 kU/l) were pretreated with Omalizumab for 9 weeks, then exposed to increasing doses of milk in rush mode [42]. Ninety-two percentage of them reached the target dose of 1000 mg milk protein, 84% the top dose of 2000 mg. After discontinuation of Omalizumab, tolerance was maintained in all the patients upon continuous administration of milk.

In a second trial of Omalizumab as door-opening in milk OIT, patients tolerating less than 2 mg milk protein at OFC were treated for 4 months, then exposed to a slow milk OIT protocol [43²²]. After 16 months, 71.4% of placebo-treated and 89% of Omalizumab-treated patients passed a 10 mg oral food challenge, consistent with previous studies showing that slow persistent OIT up dosing without

Omalizumab can be successful. The addition of Omalizumab to OIT in this case led to marked improvements in safety, but no significant change in the rate of sustained unresponsiveness. In the case of milk, for the use in general practice one must notice that – as CMA disappears spontaneously in practically all patients – the effects of OIT are difficult to assess without a placebo group, in particular when children reacting at higher doses are included.

In a third study, children with severe peanut reactions after a median of 50 mg peanut protein (< 1/4 peanut; median peanut-specific IgE of 229 kU/l) were treated with Omalizumab for 12 weeks, then exposed to up to 250 mg peanut protein. They could tolerate 1 peanut on day one, 8–10 peanuts in 8 weeks in 93% of cases, and 16–20 peanuts in 20 weeks in 86%. In this study, several mild to moderate – but not severe – reactions to peanuts were recorded during the drug administration. After Omalizumab discontinuation, 14% of the patients experienced severe reactions, mainly associated with exercise, infection, stress, NSAID ingestion or menstrual periods [44].

As follow-up of this pilot study, the placebo-controlled study of Omalizumab in patients with significant peanut allergy Peanut Reactivity Reduced by Oral Tolerance in an anti-IgE Clinical Trial (PRROTECT) involved patients severely allergic to peanuts. Their median peanut-specific IgE levels were 91 kUA/l; the patients could tolerate at basal OFC 50 mg peanut protein or less. After a preliminary course of Omalizumab for 12 weeks, the patients developed a 10-fold peanut protein tolerance versus placebo (250 vs. 22.5 mg). Tolerance to a daily dose of 2000 mg peanut protein was assessed 6 weeks after withdrawal of study drug, and a further challenge with 4000 mg peanut protein was administered 12 weeks after their last dose of study drug. The OIT was successful in 79% of treated group vs. 12% of placebo, with desensitization persistent upon continuous peanut administration even after the discontinuation of Omalizumab [32]. This trial shows that Omalizumab allows subjects with peanut allergy to be rapidly desensitized over as little as 8 weeks of peanut oral immunotherapy, and that the effect of OIT is maintained even after Omalizumab treatment is discontinued. Remarkably, however, three on 37 treated patients (two in the Omalizumab and one in the placebo group) developed EoE, indicating that the drug is not able to prevent such allergic manifestation.

In summary, Omalizumab pretreatment is highly effective in reducing the risks of OIT in patients with severe food allergies. However, these risks are not completely eliminated, and EoE

remains a significant obstacle to a successful use of OIT [45].

An alternative approach is to use Omalizumab not together, but instead of OIT. The pilot experiences, establishing the proof of concept of the effectiveness of Omalizumab, show that this approach is effective.

A boy with severe asthma and food anaphylaxis, with very high IgE levels and positive OFCs (or reactions to tiny amounts) to several foods including milk, hazelnuts, and soy, was treated with Omalizumab after preparatory selective IgE apheresis [Dahdah *et al.* (227–231)]. Forty days after the start of Omalizumab, baked milk, hazelnuts, and soy were completely tolerated at challenge. Pursuing therapy with omalizumab, the boy became tolerant to all the offending foods without necessity of progressive dose increases as in OIT [46^{***}].

A report from Sweden, describing a clinical experience with five multiallergic children suffering from a severe IgE-mediated milk allergy with anaphylaxis, indicates that this remains a possibility, and suggests the use of basophil allergen threshold sensitivity (CD-sens) test to avoid risky food challenges [47,48]. They also indicate that CD-sens can be used to individualize the dosages of Omalizumab [49].

Peanut-allergic adolescents were treated with Omalizumab for 8 weeks, and CD-sens was analyzed before and after therapy. Based on the CD-sens results, the patients underwent a peanut challenge or received eight more weeks with increased dose of Omalizumab, followed by peanut challenge or another 8-week cycle of Omalizumab. This individualized treatment obtained good tolerance to peanut in all patients. Those who required elevated Omalizumab dose to suppress CD-sens displayed significantly higher Ara h 2 IgE-ab/IgE.

BIOLOGICS FOR SEVERE MIXED FOOD ALLERGIES AND SEVERE NON IgE-MEDIATED FOOD ALLERGIES

In the allergy nomenclature, non-IgE-mediated reactions, which are poorly defined both clinically and biologically, are believed to be generally T-cell-mediated. They are typically delayed in onset, occurring 4 to 28 h after ingestion of the offending food(s).

Mixed IgE and non-IgE-mediated food reactions include delayed food-allergy-associated AD (6–48 h post exposure [50]), and eosinophilic gastrointestinal disorders, such as EoE, often triggered by milk and other food allergens [51]. In these allergic diseases, the role of food allergy is not exclusive, but they are often responsive to the food allergen elimination [52–54]. Three type 2 cytokines play a role in the pathogenesis of these conditions:

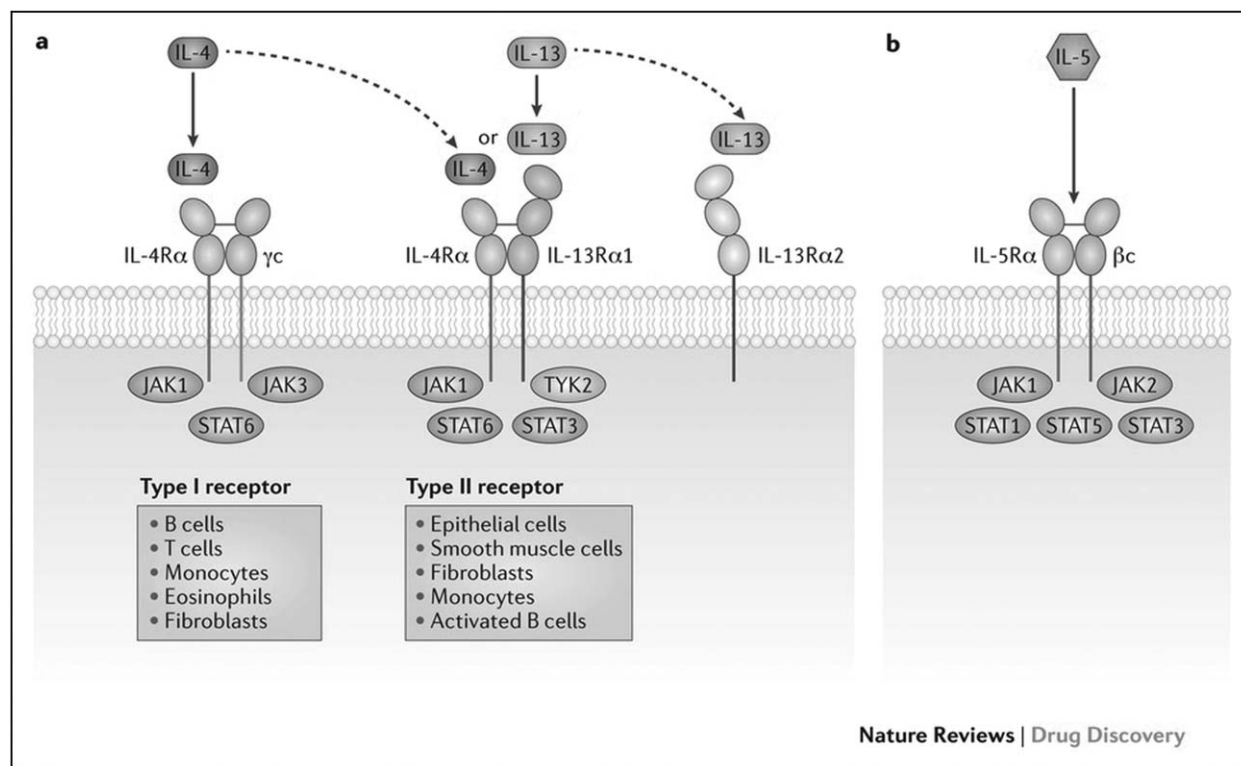


FIGURE 1. Receptor systems for IL-4, IL-13, and IL-5. IL-4 and IL-13 shared a receptor moiety, IL-4 receptor subunit alpha (IL-4Rα). The former activates lymphocytes, monocytes, eosinophils, and fibroblasts. IL-4 is the central mediator of TH2 cell differentiation, growth of B cells, initiation of isotype class switching (especially to IgE) and recruitment of eosinophils. IL-13 has some redundancy in these pro-inflammatory processes, plus additional roles in mediating goblet cell hyperplasia and smooth muscle contractility. IL-4 and IL-13 both mediate aspects of IgE production through activity on B cells. IL-5 (binding specifically to IL-5Rα) is the main mediator of eosinophil differentiation and their trafficking to tissues. Together, IL-4, IL-5, and IL-13 do orchestrate the type 2 immune response towards IgE production and eosinophilia. (reproduced with permission from 56).

interleukin-5 (IL-5) and the sister cytokines IL-4 and IL-13, which share a common receptor (Fig. 1) [55]. As mutations in the α-subunit of the IL-4 receptor (IL-4Rα) [56] and in IL-13 [57] have been associated with an increased risk of food allergy, they have been considered a target for biologic antiallergic treatments. Possible interventions include the IL-5-specific humanized monoclonal antibodies mepolizumab (GSK) and reslizumab (Teva), effective in a subset of patients with asthma and chronic sinusitis with nasal polyps (CSwNP) [58], and the fully human IL-4 receptor subunit alpha (IL-4Rα)-blocking antibody Dupilumab (Regeneron/Sanofi), able to simultaneously block IL-4 and IL-13 signaling, also effective in CSwNP and asthma.

In EoE, three monthly antibody infusions of mepolizumab resulted in a decrease in esophageal eosinophil counts (peak count decreased from 122.5 to 40.2 eosinophils per high-powered field; mean decreased from 39.1 to 9.3) [59]. In another study, 226 patients with EoE received four monthly antibody infusions of reslizumab, getting an approximately 60% reduction in the median esophageal

eosinophil count compared with a 24% reduction for the placebo group [60]. In these studies, there is a poor correspondence among the clinical evaluation (physician and patient's assessment of EoE severity) and the histologic recovery. A pilot study with Omalizumab in EoE found an histologic and clinical improvement in 33% of the patients, characterized by low peripheral blood absolute eosinophil counts [61]. Dupilumab is currently being tested in patients with EoE [62]. This monoclonal antibody has been found to be effective for the treatment of AD in adults [63,64], and is waited with interest in pediatrics [65].

In the genesis of allergic reactions, a growingly explored role is that of epithelial cells. In the gut, they produce cytokines and chemokines promoting TH2 skewing by Dendritic Cells (DCs), in particular thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. This same mechanism acts at the respiratory and cutaneous epithelial level. These cytokines target the innate lymphoid cells (ILCs), a first-line lymphoid system able to selectively dialogue with TH1 (ILC1), Th2 (ILC2), and T^{reg} (ILC3). TSLP, IL-25,

and IL-33 are particularly active in stimulating ILC2. It is conceivable that food allergy arises from these interactions not only at the gut level, but also at cutaneous and respiratory interfaces. So far, the only tentative approach in this direction are the phase I and phase II studies with AMG-157, an anti-TSLP produced by Amgen [66].

The other emerging protagonist of the food allergic sensitization is DC, whose role as antigen-presenting cell has been largely clarified. At mucosal surfaces, DCs sample luminal contents through the epithelium, receive and manipulate antigens delivered by goblet cells, and sample the lymphoid tissues [67]. After antigen recognition, DCs migrate to lymph nodes and promote tolerance presenting the antigen to T cells. They are activated mainly by their innate immunity receptors, the Toll-like receptors (TLRs) [68], who are sensitive to intestinal bacterial proteins (mainly LPS), and in turn are conceivable targets for biologic therapies. TLRs may be stimulated by specific agonists as the TLR7 agonist R848, the TLR9 agonist CpG oligodeoxynucleotides, the TLR4 agonist monophosphoryl lipid A [69], or bacterial wall preparates used in other contexts [70]. So far, none of these approaches has been evaluated in the context of food allergy.

GENE THERAPY FOR SEVERE FOOD ALLERGIES?

The protection provided by a single administration of Omalizumab is short, estimated at 2 to 4 weeks, requiring at least monthly parenteral administration of the mAb to maintain persistent effective therapy. A possible strategy to circumvent the requirement for repeated anti-IgE mAb administration is the single administration of an adeno-associated virus (AAV) coding for Omalizumab. This would provide long-term expression of anti-IgE, protecting against food-induced allergic reactions on a persistent basis. This hypothesis has been evaluated using a mouse model of human IgE-mediated peanut anaphylaxis. It was shown that, when treated with a single administration of a serotype rh.10AAVvector coding for Omalizumab, a persistent prevention of peanut-induced severe allergy arises [71]. In mice, this proved effective both in primary (i.e. it can be administered as prophylaxis before peanut sensitization) or secondary (i.e. given as therapy after the mice exhibit the peanut anaphylaxis-related symptomatology) prevention.

CONCLUSION

It is likely that the introduction of biologics will revolution the paradigms of treatment of severe food allergy. So far, the only possibilities are

avoidance of the provoking foods and a strategy of 'damage reduction' as OIT. New treatment options, as the use of Omalizumab with OIT, could improve the clinical approach for patients with high-risk food allergy. In the future, new strategies will be explored. Among them the use of Omalizumab instead of OIT, the use of Dupilumab and the use of Anti-IL-5 biologics are the most promising.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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This study opens the way to gene therapy in the treatment of severe food allergies. In a humanized mouse model of severe, anaphylactic peanut allergy, a single intravenous injection of a gene encoding for Omalizumab, vehiculated by an Adeno-associated virus, obtained the development of circulating anti-IgE antibodies able to prevent experimental peanut sensitization and treat experimental peanut anaphylaxis.