OMALIZUMAB AS AN OPPORTUNITY IN THE TREATMENT OF IGE-MEDIATED PEANUT PROTEIN ALLERGY

Thomas Niewenstein[1]

[1]Master's student Biomedical Sciences, Radboud university medical center, Nijmegen, the Netherlands

Abstract

Immunoglobulin-E-mediated peanut allergy is one of the most severe and well-known food allergies in the western world. Current treatment consists of allergen avoidance and pharmacological intervention in case of accidental exposure to the culprit allergen. Patients with severe peanut allergies can receive additional allergen immunotherapy. While this therapy is generally effective at reducing the severity of allergic reactions, it takes a long time to reach effective levels. Additionally, its effects – while impressive – leave something to be desired as the level of tolerance is merely enough to prevent an allergic reaction from a small accidental exposure. Omalizumab, a biological used to treat other immunoglobulin-E-related diseases such as allergic asthma and spontaneous urticaria, could be used in the treatment of peanut allergy as well. While the theoretical background of omalizumab efficacy against peanut allergy is sound, few studies have looked into this opportunity. Three phase I/II studies and three phase II studies have thus far been performed, examining omalizumab as monotherapy, or as an add-on for peanut oral immunotherapy. Omalizumab as monotherapy appears to induce an estimated 50-fold increase in the maximum tolerated dose of peanuts with minimal adverse events. Omalizumab as an add-on for oral immunotherapy appears to be even more impressively effective. Using omalizumab as add-on therapy for oral immunotherapy, subjects were able to reach peanut protein maintenance doses up to six times higher in only one-third of the time compared to conventional oral immunotherapy. Whether this effect persists after omalizumab discontinuation is not fully clear. Thus far, the studies have included few participants and interstudy heterogeneity is high. As such, risk of bias in the data is high. However, omalizumab poses a hopeful opportunity for severely allergic patients, but more and larger studies need to be performed before clinical implementation for this indication can be considered.

Background

Food allergy

The prevalence of food allergies has been increasing steadily in the western world during the past century. Current estimates of prevalence range from 2 - 4% in adults, and up to 8% in children [1, 2]. While the epidemiological mechanisms responsible for the increase in prevalence are not fully clear, theories such as the hygiene hypothesis - the idea that reduced exposure to pathogens due to increased sanitary conditions in the western world results in the immune system recognising food proteins as dangerous - attempt to elucidate this effect [3]. Food allergies can be described as a collection of disorders in which the immune system reacts to a food component [4]. Food allergies are distinctly different from food intolerances, as the latter is caused by metabolic insufficiencies and generally does not include an immune component, while the former is dependent on the involvement of the immune system [4].

Food allergies can crudely be divided into three categories (Figure 1): immunoglobulin E (IgE)-mediated, non-IgE-mediated, and mixed. This review will only cover IgE-mediated food allergies. IgE-mediated food allergies are type I hypersensitivity reactions. As such, these reactions can develop quickly following contact with the allergen. During a reaction, patients can experience symptoms in multiple organs, including the skin, gastrointestinal tract, lungs, and circulatory system, as well as severe systemic conditions such as anaphylaxis. Food-induced anaphylaxis is a serious, life-threatening reaction, which requires immediate administration of intramuscular adrenaline as life-saving medication. Next to this, an IgE-mediated food allergic reaction can exacerbate other IgE-mediated diseases, such as allergic asthma.

Peanut protein allergy is perhaps the most widely known form of IgE-mediated food allergy. IgE-mediated peanut protein allergy (IMPA) is a serious allergy, in which small exposures often lead to severe reactions, including anaphylaxis, in a matter of seconds to minutes after exposure. Due to its strict IgE-linked mechanism and societal infamy, IMPA is the most suitable form of IgE-mediated allergy to study for new discoveries.

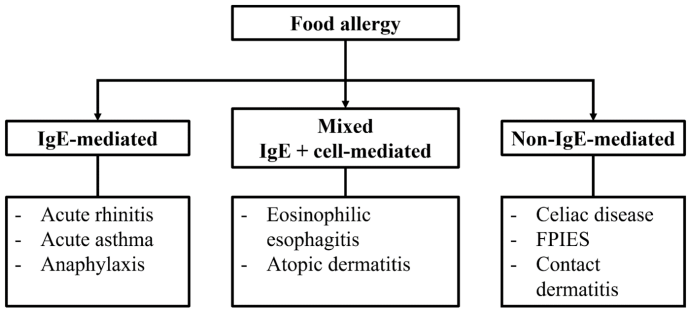

Figure 1: *Overview including examples of IgE-mediated, mixed, and non-IgE-mediated forms of food allergy. IgE - Immunoglobulin E; FPIES – Food-Protein Induced Enterocolitis Syndrome.*

Immunological processes in IgE-mediated food allergy

IgE-mediated food allergies are closely associated with other diseases in which IgE commonly plays a role, such as allergic asthma, atopic dermatitis, and allergic rhinitis. These diseases are frequently found together, as they employ a similar mechanism of action [5]. Type 2 helper T-cells (Th2) are significantly involved in all atopic diseases and form the basis for later reactions. Food allergy consists of a sensitisation phase and an effector phase. During the sensitisation phase, the subject first encounters the allergen (Figure 2) [4]. While it is not fully clear why only some exposures will lead to food allergies, it is suggested that barrier dysfunction (e.g., lung/gut epithelium) is likely involved [4]. The skin-gut axis also plays an important role, as sensitisation to an allergen in the skin can cause symptoms upon allergen challenge in the gastrointestinal tract [6].

In a healthy gut, macrophages sample food allergens and transport these across the gut membrane. Here, the sampled allergens are presented to dendritic cells, which present the allergen to naïve T-cells in the context of anti-inflammatory factors. The naïve T-cells differentiate into allergen-specific regulatory T-cells. Regulatory T-cells promote allergen tolerance. In the case of disrupted barrier function, food allergens can pass the gut membrane without being cleaved or sampled and are instead found by dendritic cells directly. Additionally, the damaged epithelium releases pro-inflammatory cytokines which expand and activate type 2 innate lymphoid cells and promote the polarisation of naïve T-cells towards a Th2 response [4]. Innate lymphoid cells and Th2 cells subsequently secrete cytokines promoting the recruitment and proliferation of basophils and eosinophils. Furthermore, B-cells are recruited and differentiated to produce food-allergen-specific IgE [4, 7].

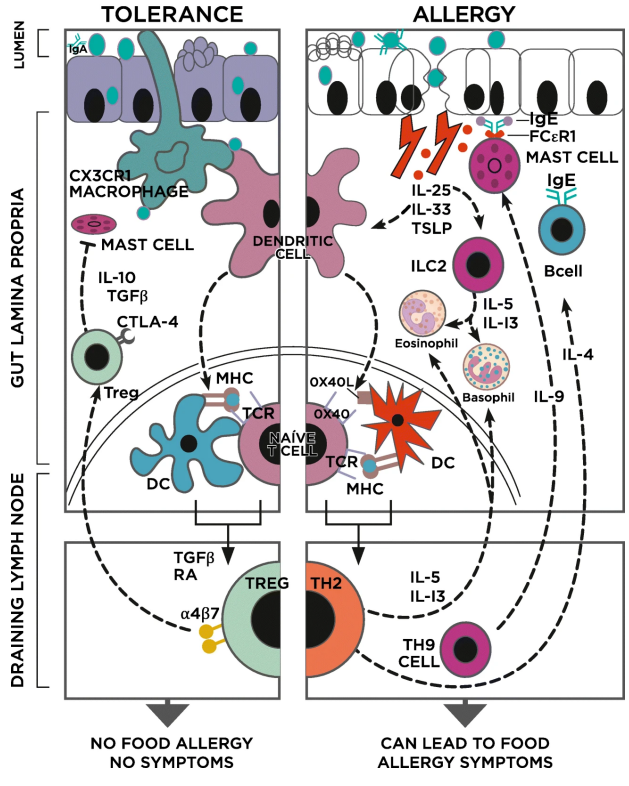

Figure 2: *Comparative overview of the mechanisms of tolerance and allergy in the gut. Figure adapted from Anvari et al. (2018) [4]. On the left, the normal (tolerant) situation is depicted. The immune system promotes tolerance towards sampled food allergens through a series of anti-inflammatory events. On the right, a damaged epithelium induces the allergenic sensitisation process. Through a host of pro-inflammatory events, tolerance to the food allergen is lost and allergen-specific IgE is formed. This allergen-specific IgE is found free in the circulation, as well as bound to the FcεRI receptors on mast cells, ready to induce an allergic reaction upon exposure to the food allergen. Abbreviations: IL – Interleukin; MHC – Major Histocompatibility Complex; TCR – T-cell receptor; DC – Dendritic Cell; Treg – T regulatory cell; IgE – Immunoglobulin E; TGF-β – Transforming growth factor β; TSLP – Thymic Stromal Lymphopoietin.*

Following sensitisation, allergen-specific IgE can be found in the circulation. Upon exposure, IgE will bind the allergen and cross-link FcεRI - high-affinity IgE-receptors - on the surface of mast cells and basophils, causing degranulation and release of mediators into the circulation [4]. These mediators act on various organ systems and will lead to symptoms in a patient. Histamine release is one of the most important mediators in this process, causing vasodilation, increased heart rate, and glandular secretion. Other mediators, such as tryptase, leukotrienes, and prostaglandins, are involved in bronchoconstriction and increased vascular permeability, among others [4]. By doing this, they form a positive feedback loop to enhance the reaction. At sufficient concentrations, these mediators can cause a cardiovascular crash, close the trachea through swelling, or reduce lung flow, all of which can have a deadly outcome.

Current treatment

Effective treatment of IgE-mediated food allergies is currently lacking for all patients, but most notably for severely allergic patients. The mainstay of treatment consists of allergen avoidance. In addition to dietary intervention, allergy treatment can include pharmacological intervention (e.g., oral antihistamines) in case of a reaction. These two pillars of treatment are not sufficient for patients with severe IMPA. These patients would benefit most from a therapy that would reduce the allergic sensitivity or decrease the potency of allergic responses.

As a final pillar of allergy treatment, allergen immunotherapy can be used to reduce the severity or impact of the food allergy in patients with severe food allergies. Allergen immunotherapy involves exposing the patient to doses of allergen lower than their reaction threshold [8]. This process will slowly build up tolerance to the culprit allergen and increase the threshold dose for an allergic reaction to occur. Allergen immunotherapy can be given through various routes of exposure, such as oral (OIT), sublingual, and epicutaneous exposures, as well as subcutaneous injections. In the case of peanut allergy, OIT has shown the most impressive increases in sustained tolerance doses [9]. However, allergic reactions and adrenaline use as rescue medication are common during OIT [8]. OIT consists of a slow dose-escalation phase in which the patient is exposed daily to increasing concentrations of their allergen over the course of months, followed by an indefinite daily maintenance phase. While the goal of reducing the sensitivity to the culprit allergen may be achieved through OIT, the treatment will not eliminate the allergy. Patients must remain allergen-avoidant and remain on daily OIT to retain the built-up tolerance.

Biologicals in the treatment of IgE-mediated diseases

Therapies for other IgE-mediated diseases, similar in mechanisms of disease, have been developed in the biologicals class. Biologicals are products produced by living organisms and often have an immunomodulatory effect [10]. Due to the similarity in disease mechanism between IgE-mediated allergic diseases, these biologicals could be promising for use in the treatment of IMPA. One prime example of a biological that could be of interest in treating IMPA is omalizumab.

Omalizumab (brand name: Xolair; investigative ID: RG-3648) was approved for use in the EU in October 2005 [11]. It is currently indicated for use as add-on therapy in patients older than six years

with severe persistent allergic asthma. Additionally, it is used as an add-on treatment for chronic spontaneous urticaria and severe chronic rhinosinusitis with nasal polyps, in which antihistamines and corticosteroids, respectively, offer insufficient effects. Omalizumab is dosed using subcutaneous injections every two to four weeks, depending on the disease state [11].

Omalizumab is a humanised IgG1κ monoclonal antibody produced in a Chinese Hamster Ovary cell line. Omalizumab was constructed using DNA recombination and its antigen-binding fragment consists of human framework regions and murine complementary-determining regions. Omalizumab binds to an epitope in the Fc region of IgE and prevents binding of IgE to the high-affinity IgE-receptor FcεRI on basophils and mast cells. Additionally, omalizumab prevents binding of IgE to the low-affinity IgE-receptor FcεRII on the surface of B-cells. These mechanisms of action deplete free IgE and prevent or reduce the activation of the allergic cascade [11]. As a result, little to no effector cells are degranulated and mediators are not released into the circulation, preventing allergic symptoms upon allergen exposure. While the theory behind omalizumab efficacy is present, it remains to be seen what the effects would be in the clinic. Omalizumab could serve as monotherapy by depleting the IgE storage and thus prevent allergic reactions by taking away a key molecule in the cascade. Additionally, omalizumab could be used in tandem with OIT to reach much higher maintenance doses of OIT in a shorter time period. However, only a handful of phase I and II studies have thus far been performed for the use of omalizumab in peanut-allergic patients (Table 1).

Discussion

The use of omalizumab in the treatment of IMPA generally has insufficient reliable evidence to be regarded as sensible or not. High interstudy variability in methods and outcomes complicates the interpretation of the available evidence. Additionally, as omalizumab is a pharmaceutical product under investigation for possible new indications, some public trial reports appear intentionally vague or incomplete, further complicating the interpretation of available evidence. Although some studies show considerable potential for using omalizumab as monotherapy or add-on for peanut OIT, these drawbacks mean there is too little reliable evidence to form an informed recommendation.

Summary of available evidence

Omalizumab as monotherapy was examined in Trials I, II, and III (Table 1). Omalizumab monotherapy appears to significantly increase the threshold dose for a peanut-induced allergic reaction, showing this effect following only a few doses of omalizumab in adults aged 18-44 [12]. In adolescents aged 12-19, it was shown that individualising the doses of omalizumab based on the *in vitro* reactivity of basophils may enhance omalizumab monotherapy efficacy [14]. Omalizumab administration appears to be safe, with reported adverse events generally only concerning allergic symptoms upon peanut challenge. Due to a high risk of bias in these trials, the quality of evidence is very low. Trials I, II and III included a limited number of participants (14, 11, and 23). None of the trials used placebo arms. Additionally, the food challenge in Trial III was not blinded, while Trial II did not include any experimental peanut exposure [13, 14]. All three trials used different symptom-scoring systems. None of the trials corrected for multiple comparisons, resulting in a likely overestimation of significance. Furthermore, none of the trials appear to be powered for their primary outcome, meaning too few participants may have been included to properly detect effects in the primary outcome. Moreover, the trial application of Trial I suggests all nine measured outcomes are primary outcomes [12]. Due to the low number of participants, non-overlapping ages, dosages, and study setup, the available evidence is of insufficient quality to either recommend or not recommend omalizumab monotherapy as a treatment for IMPA.

Omalizumab as an add-on treatment for peanut OIT was examined in Trials IV, V, VI, and VII, and appears to be promising [Table 1]. Peanut OIT by itself has a desensitisation rate of 68% following 24-52 weeks of treatment, with 76% of treated subjects able to safely ingest (i.e., without an allergic reaction) 300 mg peanut protein (approximately one peanut kernel) and 56% of treated subjects able to safely ingest 1,000 mg peanut protein [8]. Adding omalizumab to OIT appears to reduce the time needed to reach the maintenance phase and allow for higher maintenance doses. However, the effect may decrease following omalizumab discontinuation [Table 1; 15, 18, 19]. The efficacy results are consistent across trials and are higher than the reported tolerated doses and time-to-effect of OIT monotherapy in the literature [8]. The long-term effects of omalizumab as an add-on therapy for OIT are unknown. One trial attempted to look at the long-term effects of omalizumab-initiated OIT, but due to high intra study heterogeneity in the method of OIT and the dosing regimen, the study was disregarded [20].

Adverse event rate varied from 1-3% per dose, which is higher than reported for OIT monotherapy in literature [8]. This increase in adverse event frequency is likely due to the much higher doses of OIT compared to OIT monotherapy.

The quality of the evidence from the included trials is low, mostly limited by risk of bias as a result of study designs and small sample sizes. Most trials only included a small number of participants receiving omalizumab. However, the population is fairly consistent between trials, with all trials reporting on omalizumab in children and adolescents. Three trials used a single-group, open-label treatment study design, while only one trial used a double-blinded, placebo-controlled study design. None of the trials appeared to correct for multiple comparisons, even though paired measurements at different time points were compared. While the body of evidence must certainly be expanded before omalizumab can find widespread use in the clinic as an add-on treatment for peanut OIT, it seems omalizumab can enhance the efficacy and shorten the time-to-effect of peanut OIT. As such, omalizumab as an add-on treatment for OIT cannot be wholeheartedly recommended at this moment, but as the body of evidence grows, it is expected that trust in this treatment will grow. Phase III and IV trials (NCT03881696; NCT04037176; NCT03881696) examining the use of omalizumab as an add-on for OIT are currently recruiting subjects.

Final remarks

Omalizumab may have a place in food allergy treatment, helping those with severe peanut allergies quickly build a small tolerance to their allergen as monotherapy or peanut OIT enhancer. This small tolerance can mean the difference between generalised anxiety stemming from the fear of even the smallest accidental exposure, to a normal diet with reasonable allergen avoidance. While omalizumab is not ready to be used in the treatment of peanut allergy as is, the supporting evidence forms a suitable base of knowledge to justify studying its potential in the treatment of peanut allergy in future, larger trials.

Trial NCT	Study phase	Study design	Number of subjects	Age range	Type of	Primary outcome(s)	Most important findings
NCT00949078 (Trial I) [12]	Phase II	OL, SG	14	18 - 44	Monotherapy	Kinetics of clinical response to omalizumab treatment; association between clinical improvement and allergic effector cell suppression	Strong, sustained increases in median threshold dose during open food challenges from 80 mg peanut protein (n = 14) before treatment to 6,500 mg after 8 weeks of treatment (n = 13, p = 0.002) and 5,080 mg after 6 months of treatment (n = 10, p = 0.005 compared to pre-treatment).
NCT00382148 (Trial II) (unpublished) [13]	Phase II	OL, SG	11	Unclear (inclusion criteria: 6 - 75)	Monotherapy	Serious adverse events over the course of 52 weeks of omalizumab treatment	No serious adverse events were associated with the use of omalizumab.
NCT02402231 (Trial III, IV-I, IV-II) [14-16]	Phase II	OL, SG	23	12 - 19	Monotherapy (III); add-on for OIT (IV-I, IV-II)	Trial III: Suppression of allergic reactions to peanuts following individualised dosing regimens of omalizumab Trial IV-I: Peanut OIT of daily 2,800 mg for 12 weeks after omalizumab discontinuation and passing a 2,800 mg open challenge Trial IV-II: Immunological effects of omalizumab treatment	Trial III: 15/23 subjects needed higher dosing of omalizumab to suppress a predictive basophil variable; median tolerated peanut protein dose increased 50-fold following omalizumab treatment (n = 14, p < 0.001). Trial IV-I: all subjects reached 2,800 mg maintenance dose in median 10 weeks of OIT + omalizumab treatment; 48% of subjects pass a 2,800 mg open challenge 12 weeks after omalizumab discontinuation. Trial IV-II: treatment skews cytokine profile towards a Th1 phenotype. No significant effect on Tregs was observed.
NCT00932282 (Trial V) (main results unpublished; partial publication) [17]	Phase I/II	OL, SG	13	12 - 19	Add-on for OIT	Response to a 10,000 mg peanut protein challenge 11 or 23 months after omalizumab discontinuation	Two cases of eosinophilic esophagitis, likely caused by OIT; 3/7 subjects in the 11-month group and 1/6 subjects in the 23-month group were able to safely ingest 10,000 mg peanut protein 2-4 weeks after stopping OIT.
NCT01290913 (Trial VI) [18]	Phase I/II	OL, SG	13	8 - 16	Add-on for OIT	Rush desensitisation to 250 mg peanut protein without symptoms	12/13 subjects reached a 2,000 mg maintenance dose after 8 weeks of omalizumab treatment; All of these subjects safely completed a 4,000 mg cumulative dose DBPCFC 12 weeks after omalizumab discontinuation.
NCT01781637 (Trial VII) [19]	Phase I/II	DBPC	36 (8 placebo)	7 - 19	Add-on for OIT	Tolerance to 2,000 mg peanut protein 6 weeks after omalizumab discontinuation	23/29 omalizumab-treated subjects passed the 2,000 mg open challenge 6 weeks after treatment cessation versus 1/8 in the placebo group (p < 0.01); 22/29 omalizumab-treated subjects vs 1/8 placebo-treated subjects passed a 4,000 mg open challenge 12 weeks after treatment cessation (p < 0.01).

Table 1: *Overview of publications and trials identified through the PubMed search and included in the analysis. One peanut kernel contains approximately 300 mg peanut protein. Abbreviations: OL – Open-label; SG – single group; OIT – oral immunotherapy; Tregs – Regulatory T-cells; DBPC – double-blinded, placebo-controlled; DBPCFC – double-blinded, placebo-controlled food challenge*

Acknowledgements

RAMS would like to thank Robbin Kramer, BSc, for feedback on the manuscript. Additionally, RAMS would like to thank Dr Nicolette W. de Jong, Associate Professor at the Department of Allergology and Clinical Immunology at the Erasmus MC, for close guidance and feedback during the preparation and writing of the literature thesis this article is based on.

References

1 Sicherer, S.H. & Sampson, H.A. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol 141, 41-58 (2018).
2. Warren, C.M., et al. Epidemiology and Burden of Food Allergy. Curr Allergy Asthma Rep 20, 6 (2020).
3. Stiemsma, L.T., et al. The hygiene hypothesis: current perspectives and future therapies. Immunotargets Ther 4, 143-157 (2015).
4. Anvari, S., et al. IgE-Mediated Food Allergy. Clin Rev Allergy Immunol 57, 244-260 (2019).
5. Dierick, B.J.H., et al. Burden and socioeconomics of asthma, allergic rhinitis, atopic dermatitis and food allergy. Expert Rev Pharmacoecon Outcomes Res 20, 437-453 (2020).
6. Van Splunter, M., et al. Mechanisms Underlying the Skin-Gut Cross Talk in the Development of IgE-Mediated Food Allergy. Nutrients 12(2020).
7. Fiocchi, A., et al. The use of biologics in food allergy. Clin Exp Allergy 51, 1006-1018 (2021).
8. De Silva, D., et al. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy 77, 1852-1862 (2022).
9. Reinwald, S., et al. Peanut oral immunotherapy: current trends in clinical trials. Immunother Adv 2, ltac004 (2022).
10. Patel, P.K., et al. Biologics and biosimilars. J Dermatolog Treat 26, 299-302 (2015).
11. Anonymous. Xolair/omalizumab: Summary of product characteristics. in, Vol. 2022 (ed.^(eds. (European Medicines Agency, 2009).
12. Savage, J.H., et al. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. J Allergy Clin Immunol 130, 1123-1129 e1122 (2012).
13. Anonymous. A Study of Xolair in Peanut-Allergic Subjects Previously Enrolled in Study Q2788g. in, Vol. (ed.^(eds. (Clinicaltrials.gov, 2006).
14. Brandstrom, J., et al. Individually dosed omalizumab: an effective treatment for severe peanut allergy. Clin Exp Allergy 47, 540-550 (2017).
15. Brandstrom, J., et al. Individually dosed omalizumab facilitates peanut oral immunotherapy in peanut allergic adolescents. Clin Exp Allergy 49, 1328-1341 (2019).
16. Van Der Heiden, M., et al. A pilot study towards the immunological effects of omalizumab treatment used to facilitate oral immunotherapy in peanut-allergic adolescents. Scand J Immunol 93, e13005 (2021).
Immunol Pract 7, 451-461 e457 (2019).
17. Burk, C.M., et al. Eosinophilic esophagitis during peanut oral immunotherapy with omalizumab. J Allergy Clin Immunol Pract 5, 498-501 (2017).
18. Schneider, L.C., et al. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol 132, 1368-1374 (2013).
19. Macginnitie, A.J., et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol 139, 873-881 e878 (2017).
20. Yee, C.S.K., et al. Long-Term Outcome of Peanut Oral Immunotherapy Facilitated Initially by Omalizumab. J Allergy Clin