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Joana Isabel de Matos Cunha Viana de Carvalho

Anti-IgE in treatment of food allergy – systematic review

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Dr. Luís Araújo

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
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"Para ser grande, sê inteiro: nada

Teu exagera ou exclui.

Sê todo em cada coisa. Põe quanto és

No mínimo que fazes."

Ricardo Reis, heterónimo Fernando Pessoa

Anti-IgE in treatment of food allergy – systematic review

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Abstract

Objective: Food allergy is an increasing health problem in Westernized societies. The avoidance of food allergens is the unique effective treatment. Due to strict diets, these patients have a nutritious handicap that can compromise their normal development. Our aim is to organize all scientific studies that have been performed in order to outline the role and efficacy of Omalizumab in treatment of food allergy. **Data Source:** We insert our query on four electronic databases: Isi Web of Knowledge, Pubmed, Scopus and Embase. **Study selection:** We performed a double blind selection of studies. Each reviewer applied the exclusion criteria on titles and abstracts, later they both applied the inclusion criteria on full text of potential eligible studies. Where the both of reviewers agreed, they either included or excluded the trial. Any disagreements were resolved by discussion between the reviewers. **Results:** A total of 1167 potential relevant papers were identified and 6 were included. All studies, unanimously, reported a general improvement of clinical status of food allergic patients. Almost all studies revealed a decrease of levels of total and specific IgE and also the wheal/erythema size in SPT. Increase of allergen threshold was demonstrated in the totality of included studies. Some studies concluded that the treatment with Omalizumab before OIT has an important impact on reduction of OIT duration. **Conclusion:** Omalizumab seems to be an important adjuvant drug for treatment of food allergy and it will potentially improve the quality of life of allergic food patients and of their families.

Keywords: Omalizumab; Anti-IgE; Food allergy; Food Hypersensitivity; allergen; IgE.

Introduction

Food allergy is an increasing health problem in Westernized societies, affecting almost 5% of young children and 3% to 4% of adults.[1] The most common implicated food allergens are cow's milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish, although considerable geographic variation occurs according to regional diet and cultural habits.[1, 2]

Food allergy is a food-related adverse effect mediated by an immune hypersensitivity that is reproducible after an exposure to a given food.[3] IgE-mediated food allergy is the most common and dangerous of the food hypersensitivity disorders and develops within seconds or minutes after exposure to a small quantity of food allergen. It may be manifested as acute urticaria / angioedema, atopic eczema dermatitis syndrome, oral allergy syndrome; gastrointestinal symptoms and anaphylaxis.[1] Some less common, food hypersensitivity disorders result from non-IgE, cell-mediated mechanisms like food protein-induced proctocolitis, food protein-induced enteropathy, food protein-induced enterocolitis syndrome and Heiner's syndrome.[1]

Food allergy evaluation requires a careful medical history, skin prick tests, laboratory studies and, in many cases, oral food challenges (OFC) to confirm the diagnosis.[2] Skin prick tests are the primary tool in the diagnosis of food allergy, with a negative predictive value greater than 95% (in IgE-mediated reactions) and positive predictive value ranging from 20–50%, depending on the history.[1] If the skin prick tests with commercial extracts are negative in a highly suggestive clinical history, prick-to-prick tests using fresh or native foods, especially with fruits and vegetables might be indicated, since they have proven to be more sensitive.[1] Laboratoty tests, mainly specific IgE (sIgE) measurements might also be usefull to identify causative allergens of suspected food allergen reactions. Although specific cut-off values levels have been published (defined as 95% predictive values of positive reactions after oral challenge with the same allergen) both for skin prick tests and sIgE,[1] none of this

methods is diagnostic of food allergy. [3] Actually, positive skin test or sIgE only prove allergic sensitization. Therefore, double-blind, placebo-controlled, oral food challenge is considered the gold standad test for diagnosis of food allergy.[4]

Avoidance of food allergens has been the standard care for food allergic patients. Beside avoidance, patients in high risk of anaphylactic reaction should carry an emergency kit (epinephrine, oral antihistamine and glucocorticosteroids).[1, 2] Patients, families and healthcare personal must be aware that intramuscular injection of adrenaline is the first line treatment of anaphylaxis and delayed administration of adrenaline is associated with fatal outcomes.[1, 2] Due to their diet avoidance of specific foods, these patients are at risk nutritional imbalance that may compromise their normal development. Hence, they may benefit a nutritionist support to compensate deficiency in certain nutrients. [1, 2]

Allergen specific IgE antibodies play a central role in the pathophysiology of immediate food allergic reactions, binding to high-affinity receptors on the surface of mast cells and basophils. [5] leading to the release of potent mediators, mainly histamine, and synthesize new mediators (prostaglandins, leukotrienes, and cytokines).[6]

Omalizumab is a recombinant humanized IgG1 monoclonal anti-IgE antibody that binds to the IgE molecule at the same epitope on the Fc region that binds to FcεRI.[7, 8] Omalizumab binds to circulating IgE, regardless of allergen specificity, forming small, biologically inert IgE–anti-IgE complexes with no activity on the complement cascade. [8-10] It also induces rapid reduction in free IgE levels by down regulation of the FceRI expression on inflammatory cells (basophils, monocytes and dendritic cells).[11-13] Omalizumab does not bind to the variable allergen specific region of IgE nor to cell-bound IgE, therefore it does not trigger degranulation of mast cells or basophils, decreasing the risk of an anaphylactic reaction. [10, 14, 15] Omalizumab was approved by FDA to treat allergic asthma in 2003. Since then, it has been shown that Omalizumab treatment reduces blood eosinophil levels in

patients with seasonal allergic rhinitis and asthma and sputum eosinophils in asthmatic patients. [4] Few studies have shown that the treatment with anti-IgE improves the symptomatology of food allergic patients. [16, 17]

The aim of this systematic review is to evaluate the role and efficacy of anti-IgE in the treatment of food allergy.

Methods

Search strategy

We used the following electronic databases: Isi Web of knowledge, Pubmed, Scopus and Embase. To reduce the risk of losing relevant studies, searches were not restricted by language, publication type or study design. Index and / or MESH terms were combined in the following query: (food OR milk OR casein OR lactoglobulin OR fish OR egg OR nut OR wheat OR apple OR bean OR orange OR peach OR lettuce OR peanut) AND (hypersensitivity* OR allerg*) AND (anti-IgE OR omalizumab).

Inclusion criteria

Studies were eligible for inclusion if they met all the following criteria:

1. Study design: Randomised controlled trials (RCTs), quasi-RCTs, controlled clinical trials or observational studies involving children or adults.
2. Diagnosis of food allergy supported by SPT (skin prick test), specific IgE (sIgE) and/or OFC (oral food challenge).
3. Treatment of food allergy with anti-IgE drugs.

Exclusion criteria

The following exclusion criteria were defined:

1. Article written in other language than English
2. Non-human studies

3. Review/ systematic review articles that do not present new original data about the subject.

Data collection and analysis

Two review authors independently checked and reviewed titles and abstracts of identified studies. Data extraction was independently performed by two reviewers with disagreements resolved through discussion. Quality assessment of RCTs was done according to CONSORT statement recommendations.[18]

Results

The last search was run on March 2013, and we obtained 1167 potential relevant papers. No additional studies were identified after screening all reference lists of the full-text papers reviewed. After all processes we obtained 6 studies that fulfilled the inclusion criteria: 2 double-blind placebo-controlled studies and 4 uncontrolled trials. This selection process is depicted on flow diagram according to PRISMA.[19]

Studies design

Only 2 RCTs [16, 17] designed to evaluate the efficacy and safety of anti-IgE in food allergy treatment were found. RCT are described in table 1 and their outcomes are resumed in table 2. Four additional non-RCTs were included, 3 published in full-text [20-22] and 1 reported only in resume.[23] Table 3 resumes non-RCTs data.

Diagnostic criteria of food allergy

Diagnosis of food allergy was supported by a double-blind, placebo-controlled OFC and SPT with commercial extracts with the exception of the study by Nadeau et al.[20] Specific IgE to peanut [23] and milk [20] were used in 2 studies. The main allergic symptoms described were: urticaria, angioedema, throat swelling, asthma, wheezing, and others symptoms.

Anti-IgE treatment

The biggest RCT including 59 active patients and 23 controls was published by Leung et al [17] in 2003, using an anti-IgE monoclonal antibody – TNX-901 – that has not been chosen for further development and was abandoned. Therefore the only RCT using a current available drug is the study by Samson et al[16]. This phase II trial was stopped early due to 2 anaphylactic reactions that occurred in OFC before omalizumab treatment and only 14 patients completed the study. A pre and post-omalizumab treatment comparison of food allergic patients was performed in 2 studies. Savage et al [22] evaluated 10 patients with peanut allergy treated with omalizumab for 6 months while Rafi et al [21] performed an observational study of the effect of omalizumab in patients with a moderate to severe asthma and concomitant food allergies. Two uncontrolled trials aimed to address the role of omalizumab before oral immunotherapy (OIT) with foods. Henson and coworkers [23] evaluated 6 patients with peanut allergy and Nadeau and coworkers [20] 11 patients with milk allergy.

Outcomes

Oral food challenge threshold was used as the main outcome in 5 of 6 studies. Although in both RCTs [16, 17] data seems to suggest an improvement in OFC tolerance, only the treatment with the highest dose (450 mg) of TNX-901 presented significant difference versus placebo.[17] Also in the uncontrolled study by Savage et al. [22] the dose of tolerated peanut protein on OFC increases significant after omalizumab treatment. In both uncontrolled studies evaluating omalizumab as an adjunctive treatment of OIT [20, 23] there seems to be a positive effect with most patients reaching the predefined maintenance dose.

A significant reduction in SPT mean flare is reported by Savage et al.[22] Total free IgE levels presents a significant post-treatment decrease in both RCTs. [16, 17]

Safety data is reports in all studies. Omalizumab was well tolerated in food allergic patients and no drug-related severe reactions were reported. Severe reactions reported, especially in

the study by Sampson et al. [16] that lead to premature interruption of the trial were related to food allergy reactions and not to anti-IgE treatment.

Quality assessment of RCTs reports is acceptable.

Discussion

In this systematic review we have evaluated the role of anti-IgE treatment in food allergy. Although there is still very limited data, all included studies support the concept that anti-IgE may have role as an additional treatment in food allergy and as a facilitator of oral immunotherapy with foods.

Despite that all studies addressed the same question – anti-IgE and its effectiveness in the treatment of food allergy – there was neither a systematic approaches to the outcomes nor an evaluation of the same allergen in the same conditions. Thereby, we performed a descriptive analysis where it was depicted and compared all outcomes of the included studies.

This study also presents some limitations that may hamper its conclusions. First, although we have tried to broaden our search in order to find all the publish evidence, there is always some chance that some relevant studies have not been included. Although we have searched the evidence in all languages to avoid indexing errors, we have then excluded all non-english papers and some relevant studies might be excluded. Second, and more important, our revision might be subject to publication bias.[24] It has been shown that systematic reviews performed when few studies are available, tend to overestimate effects, because ‘‘negative’’ studies are not published or face delayed publication. [24] It is possible that some studies, showing less extreme effects, remain unpublished and thus the observed benefit of anti-IgE may have been overestimated. The third limitation of our study results from the quality and amount of available evidence. The heterogeneity of the criteria used for the diagnosis of food

allergy, anti-IgE protocols used and outcomes reported limit the comparison of results and reinforces the need of more and better studies to elucidate this question.

Further studies are needed to clarify the effectiveness of anti-IgE in the treatment of food allergy. More DBPCS with study population pooled by age, food allergen and severity of allergic symptoms would be particularly relevant. Also a specific anti-IgE protocol for food allergic patients (currently most patients are treated with the same protocols used for asthma) should be evaluated, since most of this food allergic patients present higher total and sIgE levels than asthmatic patients. Currently, there are three registered ongoing studies on this subject. All these three studies are addressing peanut allergy. D. T. Umetsu et all [25], will perform a double blind, placebo controlled clinical trial multicenter study evaluating omalizumab as adjunctive treatment to OIT in patients with severe peanut allergy. W. Burks, [26], will perform a phase 2 randomized trial with Omalizumab in order to determine whether the addition of omalizumab will improve peanut OIT safety. . R.A. Wood and S. Saini, [27], are evaluating omalizumab efficacy in peanut allergy in a phase 2 non-randomized trial.

In conclusion, although currently published studies support the concept that anti-IgE treatment is safe and has a beneficial role in food allergy and oral immunotherapy with foods, further and better designed studies are needed to elucidate the effectiveness of food allergy treatment with anti-IgE.

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Table 1 Description of randomized-controlled trials (RCTs)

	Sampson 2011[16]	Leung 2003[17]
Study design	Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial	Randomized, double-blind, placebo-controlled, dose-ranging study.
n (active/control)	5/9	59/23
Sex (F/M)	6/8	37/45
Age	26.6 ± 22.5 placebo / 16.3 ± 11.1 active group	32.4 (13-59)
Inclusion criteria	Age: 6 – 75 years History of an immediate peanut allergy reaction after ingestion of food containing peanuts Positive double-blind, placebo-controlled OFC to peanut SPT positive to peanut extract and/or peanut sIgE > 0.35 kU_A/L Total IgE: 30-1330 IU/mL Body weight: 20-150 Kg Ability to perform reproducible spirometry	Age: 12- 60 years History of peanut allergy (urticarial, angioedema, bronchospasm or hypotension) Positive double-blind, placebo-controlled OFC to peanut SPT positive for peanut and negative for tuna oil Total IgE: 30-1000 IU/mL Body weight within 20% of ideal
Exclusion criteria	Tolerance to more than 250mg of peanut on OFC Reaction to any placebo on OFC Current treatment with specific immunotherapy Moderate persistent asthma and / or FEV1 < 80% predicted Treatment with daily inhaled corticosteroids > 600 mcg of fluticasone in adults or > 400mcg of in children Use of oral or injected steroids within 30 days of the initial OFC History of brittle asthma chronic medical condition Any of any significant medical condition	Pregnancy Uncontrolled asthma (FEV1<80%) Prior exposure to monoclonal antibodies Patients requiring medication with systemic corticosteroids, beta-blockers and acetylcholinesterases inhibitors during study period
Intervention	Omalizumab (0,016mg/Kg/IgE(IU/mL) monthly for 24 week. If dose required greater than 300mg, dose was divided and given every 2 weeks	TNX-901 (19 patients - 150mg; 19 - 300mg; 21 - 450mg), monthly during 4 months
Control	Placebo (0,016mg/Kg/IgE(IU/mL) monthly for 24 week. If dose required greater than 300mg, dose was divided and given every 2 weeks	Placebo, monthly during 4 months
Quality assessment*	20/37	21/37

FEV1 – Forced expiratory volume in 1 second; OFC – Oral Food Challenge; OIT – Oral Immunotherapy; SPT – Skin Prick Test; * - Quality assessment performed using CONSORT statement.

Table 2 - Outcomes of randomized-controlled trials (RCTs)

	Sampson 2011[16]	Leung 2003[17]
Oral Food Challenge Threshold	Limited data suggested an increase in tolerability to peanut flour in the omalizumab-treated versus placebo-treated subjects: 4 (44.4%) omalizumab-treated subjects vs 1 (20%) placebo-treated subject could tolerate >_1000 mg peanut flour during an OFC after 24 weeks of treatment with study drug (p=	The mean threshold of sensitivity to peanut at the final oral food challenge increased from base line in a dose-responsive manner, but only reached statistical significance for the 450-mg group (p<0.001).
	Large proportion of subjects did not achieve the pre-specified tolerability: 5 (55.6%) omalizumab-treated vs 4 (80%) placebo-treated subjects experienced reactions at <_1000 mg peanut flour. Change from baseline in maximum tolerable peanut dose after 24 weeks of treatment, there appears to be a greater shift in peanut tolerability in subjects treated with omalizumab for 24 weeks compared with placebo (p= 0.054).	group, but was statistical significant only in the 450-mg group (P=0.002). Although pairwise comparisons with placebo of the proportions of patients who tolerated a given dose were not significant, significant trends with increasing dose were noted for the 4-g and 8-g threshold (p=0.02 for both).
Skin prick tests	**Changes in SPT to peanut:** Not reported	**Changes in SPT to peanut:** Not reported
Total and specific IgE	**Changes in specific IgE to peanut:** Not reported **Changes of total free IgE from week 2 to OFC 3:** Omalizumab-treated group: ↓ 89 % (216.0 vs 4,24 IU/mL)	**Changes in specific IgE to peanut:** Not reported **Changes of total free IgE from baseline to week 4:** Placebo-group ↑ 4 % (199,5 vs 207.4) 150mg-group ↓ 88 %, (262.0 vs 30,4IU/mL) 300mg-group ↓ 89 %, (158.9 vs 17,0IU/mL) 450mg-group ↓ 93 %, (242.0 vs 16,6UI/mL).
Safety	Mild to moderate adverse events were reported in both groups during the treatment phase: placebo - 88.9%, and omalizumab - 76.5%. 2 mild adverse events were reported to omalizumab and none to placebo. Although the study intended to randomize 150 subjects, it was stopped early on the basis of the recommendation of the Data Safety Monitoring Committee because of the severity of 2 anaphylactic reactions during the qualifying oral food challenges (OFCs), before the administration of the study drug. Consequently, only 14 subjects reached the study's primary endpoint before the interruption of the trial.	The total number of systemic adverse events reported (45 to 50 per group) and the number of patients reporting adverse events (15 to 19 per group) were similar among the four groups.

FEV1 – Forced expiratory volume in 1 second; OFC – Oral Food Challenge; SPT – Skin Prick Test; 4W – 4 weeks; 8W – 8 weeks.

Table 3 - Description and outcomes non-randomized-controlled trials (non-RCTs.)

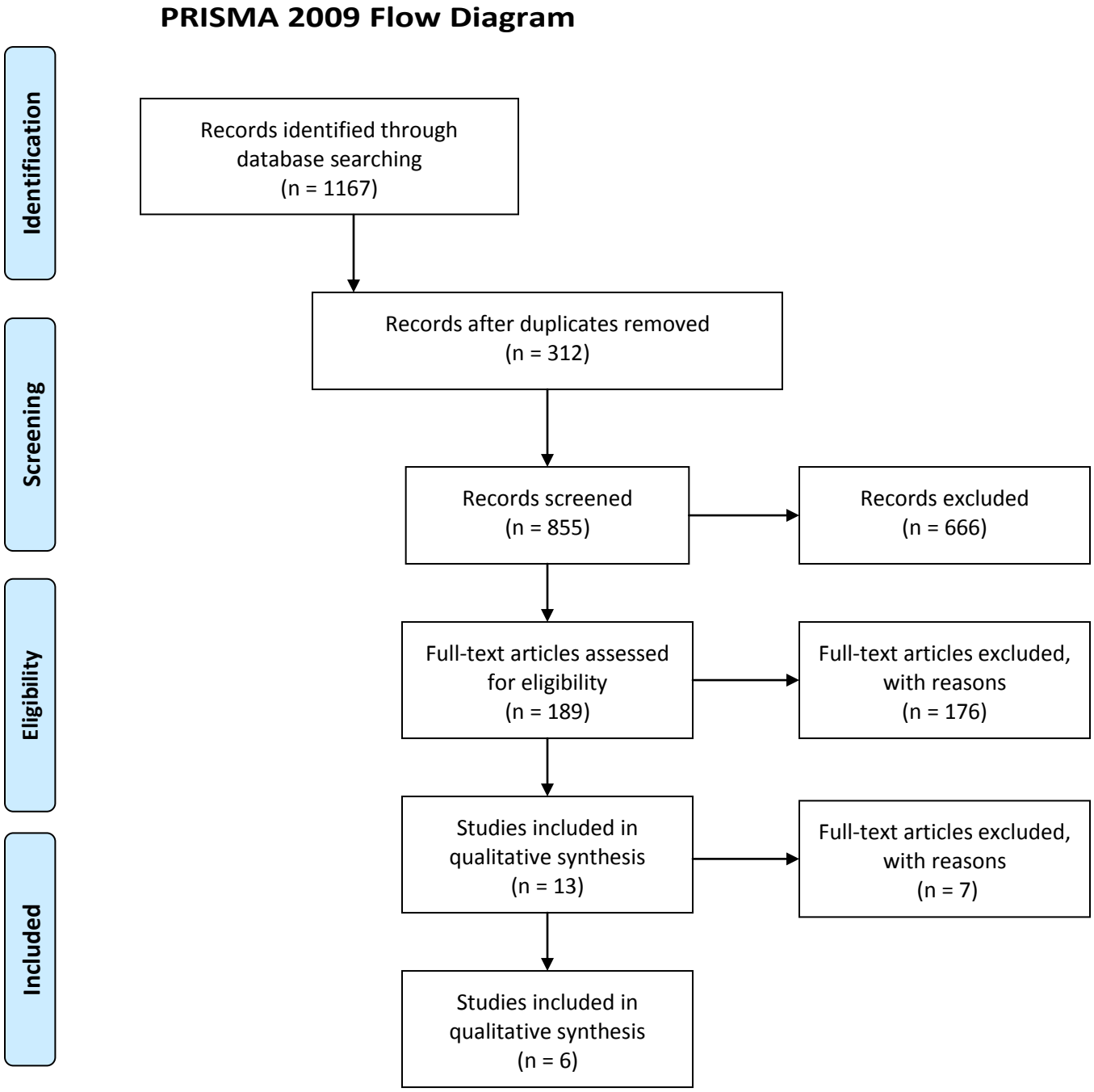
	Henson 2012[23]	Savage 2012[22]	Nadeau 2011[20]	Rafi 2010[21]
n	6	14	11	22
Sex (F/M)	Not reported	11/3	4/7	13/9
Age (range)	>12	23 (18-44)	8 (7-17)	38 (14-66)
Inclusion criteria	History of significant clinical symptoms occurring within 60minutes after ingesting peanuts Peanut sIgE >5KUA/L Positive SPT to peanut	Age: 18 - 50 years Clinical history of early-onset peanut allergy Total IgE: 30 – 700 IU/mL Peanut sIgE >0.35 KU_A/L Positive SPT to peanut Positive double-blind, placebo-controlled OFC to peanut Peanut allergen–induced basophil histamine release > 20% of total leukocyte content	History of IgE-mediated milk allergy Elevated milk-specific IgE	Patients treated with omalizumab for moderate to severe asthma with concomitant food allergies SPT positive to food before omalizumab treatment Unintended exposure to allergic food after initiation of omalizumab treatment
Exclusion criteria	History of severe anaphylaxis to peanut or omalizumab Currently participation in a study using an investigational n drug Participation in an interventional study for treatment of food allergy in the past 12 months Poor control of atopic dermatitis Moderate to severe persistent asthma Pregnancy	Severe persistent asthma, FEV1 <80% of predicted Oral corticosteroid use for asthma in last 6 months History of severe allergic reaction to peanut requiring intensive care unit admission Late-onset peanut allergy Eosinophilic enteropathy.	Not reported	Not reported
Intervention	Omalizumab 4 months before initiation of OIT and continued for one month after reaching maintenance dosing. +	Omalizumab (0,016mg/Kg/IgE(IU/mL), monthly or bimonthly, depending on dose during 6 months. OFC at screening (OFC1), week 5	Omalizumab (0,016mg/Kg/IgE(IU/mL), monthly or bimonthly, depending on dose during 16 weeks + OIT initiated 9 weeks after	Omalizumab(0,016mg/Kg/IgE(IU/mL), monthly or bimonthly, depending on dose for at least 1 year

	OIT (rush day(s), a build-up period, anda daily home maintenance phase with a final dose of 4000 mg of peanut protein.	(OFC2) and week 24 (OFC3)	omalizumab and continued until week 24 (2000 mg of milk protein is the target level at week 24). OIT in 2 phases: rush phase at day one in hospital; weekly dose escalation phase	
Control	Not applicable	Not applicable	Not applicable	
Clinical symptoms	All patients experienced symptoms on rush desensitization days: 20/21 reactions were mild (comparable to previously published safety data for rush desensitization without omalizumab) Median peanut starting dose after rush desensitization with omalizumab was 300 mg (range 100-400), higher than that seen without omalizumab pretreatment. On dose escalation days, 9.5% of doses (6 of 63) elicited symptoms in the omalizumab group, compared to 43.3% of doses (123 of 284) in previous studies [RR 0.22 (95%CI 0.10-0.48), p<0.0001]. .	Only 10 patients the treatment period and the 3 scheduled OFC (1 due to low FEv1 and 3 due to compliance issues)		All 22 patients reported a clinical improvement of food allergy, with a decrease or absence of clinical symptons after food ingestion: 13 reduction of food-induced asthma symptoms, 9 of sustemic symptoms, 8 of food-induced rhinosinusitis, 8 of food induced atopic dermatitis, 3 of food induced urticarial
Oral Food Challenge Threshold		Increase of dose of peanut protein tolerated from baseline OFC to subsequent OITs (6.010 vs 212 vs 212 mg; p<0.01)	9 of 10 patients reached a daily dose of 2000 mg and all tolerated the DBPCFC and an open challenge at week 24.	
Skin prick test (SPT)		Reduction of Mean flare size from baseline: ↓ 18% at OFC 2 (p>0.05) ↓ 52% at OFC 3 (p<0.01)	Changes not reported	
Total and sIgE		Changes not reported	Changes not reported	
Other		**Basophil histamine release:** ↓ 88% from baseline at OFC 2		

	(p<0.001) ↓ 75% from baseline at OFC 3 (p<0,001)	
Safety	1 patient was unable to complete OFC2 and OFC3 because of low FEV1	1 subject voluntarily discontinued the study due to abdominal migraines; eosinophilic esophagitis and other allergic disorders were ruled out. 21 reactions occurred during rush phase of OIT (14 mild, 5 moderate s and 2 severe) 12 reactions occurred during weekly dose escalation phase (10 mild, 1 moderate and 1 severe) The mean frequency for total reactions by week 24 was 1.6% (32 reactions of 2199 doses total for all 11 subjects). All patients experienced some adverse events, mostly mild (1%) needing no treatment. Moderate reactions occurred in 0.3% (requiring oral antihistamine) and severe reactions occurred in 0.1 % (only 1 patient required adrenaline injection). All subjects tolerated omalizumab treatment with no signs of allergic reactions.

FEV1 – Forced expiratory volume in 1 second; MD maintenance dose; OFC – Oral Food Challenge; OIT – Oral Immunotherapy; sIgE – Specific IgE to food allergen; SPT – Skin Prick Test;

Figure 1 - Study flowchart according to PRISMA.[19]



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

"tenho em mim todos os sonhos do mundo."

Fernando Pessoa

Na realidade tenho um universo de sonhos dentro de mim, cultivados um por um pelos meus pais, pela minha irmã e por todos aqueles que me rodeiam. São eles a terra fértil para a concretização dos meus sonhos, um por um.

De forma simples, humilde mas verdadeira,

ao Dr. Luís Araújo, ao Professor Doutor Luís Delgado e a todos os que intervieram de forma directa neste projecto permitindo a sua concretização,

à minha mãe que sempre me deu o empurrão para avançar,

ao meu pai que sempre me ensinou que o caminho a caminhar pode ser árduo mas recompensador no final,

à minha irmã que não se esquece nunca de me ensinar que a vida sem um sorriso e um miminho não é viver,

ao meu avô que sempre me incutiu o espirito de luta, sacrifício, lealdade para comigo própria,

à Professor Virgínia que sempre me ensinou a amar as coisas simples da vida e a viver numa incessante busca da felicidade,

aos amigos que cresceram comigo nesta viagem, àqueles que chegaram um pouco depois, àqueles que nunca deixaram de caminhar ao meu lado e que são um bocadinho de mim:

Um sentido

obrigada por embarcarem nesta viagem comigo!

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   2. Macy E, Bernstein JA, Castells MC, et al. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper. Ann Allergy Asthma Immunol. 2007;98:172-174.

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Example:

Learning Objectives: At the conclusion of this activity, participants should be able to:

- Describe the presentation of paradoxical vocal fold motion (PVFM).
- Discuss the diagnostic tests that are best used to evaluate a patient with suspected paradoxical vocal fold motion (PVFM).

Q1. Which of the following is true about paradoxical vocal fold motion (PVFM)?

A. Response to rescue bronchodilator use
B. Continuous symptoms
C. Obstructive ventilatory impairment on spirometry during acute episodes
D. Can be triggered by specific irritants
E. Hypoxia with acute episodes

Q1 ANS: D Can be triggered by specific irritants

Rationale:
Paradoxical vocal fold motion (PVFM) presents with symptoms that are often indistinguishable from asthma. Patients with PVFM without asthma typically have symptoms which occur on an intermittent basis, do not report response to asthma therapy including bronchodilator use, have spirometry evaluation without obstructive ventilatory impairment and are without hypoxia. Intrinsic irritants such as laryngopharyngeal reflux, postnasal drip or extrinsic irritants such as chemical exposure can trigger PVFM symptoms.

References:
1. Morris MJ, Christopher KL. Diagnostic criteria for the classification of vocal cord dysfunction. *Chest*. 2010;138:1213–1223.
2. Forrest LA, Husein T, Husein O. Paradoxical vocal cord motion: classification and treatment. *Laryngoscope*. 2012;122:844–853.

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