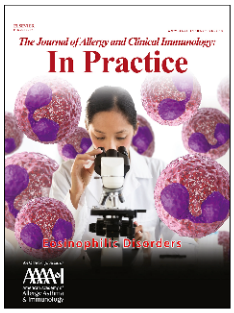
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Omalizumab in IgE-mediated food allergy: A systematic review and meta-analysis

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Omalizumab in IgE-mediated food allergy: A systematic review and meta-analysis

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Conflict of interests

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Abstract

Background: A growing number of studies have shown encouraging results with omalizumab (OMA) as monotherapy and as an adjunct to oral immunotherapy (OMA+OIT) in patients with single/multiple food allergies.

Objectives: To evaluate the efficacy and safety of OMA or OMA+OIT in patients with IgE-mediated food allergy.

Methods: An extensive literature search (inception–December 31, 2020) was performed to identify randomized, controlled, and observational studies that assessed OMA as monotherapy or OMA+OIT in patients with IgE-mediated food allergy. Outcomes: increase in tolerated dose of foods, successful desensitization, sustained unresponsiveness, immunological biomarkers, severity of allergic reactions to food, quality of life (QoL), and safety. A $P < 0.05$ was considered significant.

Results: In total, 36 studies were included. OMA monotherapy (vs pre-OMA) significantly increased the tolerated dose of multiple foods, increased the threshold of tolerated dose for milk, egg, wheat, and baked milk, improved QoL, and reduced food-induced allergic reactions (all $P < 0.01$). OMA+OIT significantly increased the tolerated dose of multiple foods (vs placebo and pre-OMA), desensitization (vs placebo+OIT and pre-OMA) (all $P \leq 0.01$), and improved QoL (vs pre-OMA) and IgG4 levels (both $P < 0.01$). No major safety concerns were identified.

Conclusions: In IgE-mediated food allergy, OMA can help patients for consumption of multiple foods and allow for food dose escalation. As an adjunct to OIT, OMA can also support high-dose

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desensitization and higher maintenance doses. Further studies are warranted to empirically evaluate the effect of OMA and confirm these findings.

Highlights box

What is already known about this topic?

Immediate-type food allergy is mediated by IgE. Omalizumab, an anti-IgE, has potential in the treatment of this condition; however, there is a lack of clarity in the available evidence supporting its potential clinical application.

What does this article add to our knowledge?

To our knowledge, this is the first meta-analysis summarizing the available data for omalizumab as monotherapy or as an adjunct to oral immunotherapy in patients with IgE-mediated food allergy. No new safety signals were identified.

How does this study impact current management guidelines?

Omalizumab was beneficial as a monotherapy and as an adjunct to oral immunotherapy in patients with IgE-mediated food allergy. It represents a potential treatment modality which will be further evaluated in the phase III OUtMATCH study.

Keywords: IgE-mediated food allergy, omalizumab, oral immunotherapy, food (allergen) tolerance, desensitization, sustained unresponsiveness, meta-analysis

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Abbreviations:

AE, adverse event

BHR, basophil histamine release

CM, cow's milk allergy

FA, food allergy

FAIM, Food Allergy Independent Measure

FAQLQ-CF, Food allergy quality of life questionnaire-child form

FAQLQ-TF, Food allergy quality of life questionnaire-teenager form

FAQL-PB, Food allergy quality of life-parental burden questionnaire

FcεRI, high-affinity IgE receptor

IFN-ɣ, interferon gamma

IgE, immunoglobulin E

IgG4, immunoglobulin G4

IL, interleukin

mAB, monoclonal antibody

MD, mean difference

MH, Mantel-Haenszel

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OFC, oral food challenge

OIT, oral immunotherapy

OMA, omalizumab

PedsQL, Pediatric Quality of Life

QoL, quality of life

RoB, risk of bias

RR, rate ratio

SD, standard deviation

SPT, skin prick test

SU, sustained unresponsiveness

TH1, T-helper 2 cell

TH2, T-helper 2 cell

Treg, T regulatory cell

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Introduction

Food allergy (FA) is a chronic disease characterized by an adverse immune-mediated response to a dietary protein, typically occurring in the first few minutes to 2 hours after consumption.[1] It is on the rise globally with prevalence estimates ranging from 0.2% to >10%.[2] FA has a negative impact on the quality of life (QoL) of patients and caregivers, especially in those allergic to multiple and staple foods including eggs, milk, nuts, and seafood.[2]

Immunoglobulin E (IgE)-mediated FA is triggered by the accidental ingestion of allergens and involves the activation of the allergic cascade via high-affinity IgE receptor FcεRI expressed on the cell surface of basophils and mast cells.[3] This leads to the release of inflammatory mediators that affect the ocular, cutaneous, respiratory, gastrointestinal, cardiovascular, and neurological systems.[3] IgE-mediated FA is a leading cause of severe to fatal anaphylaxis,[3,4] affecting individuals across different age groups.[1,5]

The management of persistent FAs involves strict allergen avoidance and immediate treatment in the event of an allergic reaction, including adrenaline auto-injection in the most severe cases.[1] Food allergen–specific immunotherapy, an immunomodulatory treatment, was shown to increase the dose of tolerated food and reduce the risk of accidental reactions.[6] However, it is associated with a risk of allergic reactions, requires prolonged treatment, and should be performed in a specialized setting during the initial dose escalation and the first dose of each updosing level. Palforzia® is a recently approved oral immunotherapy (OIT) used in patients (aged 4–17 years) who are allergic to peanuts.[7]

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To address the need for a treatment beyond allergen avoidance, the anti-IgE monoclonal antibody omalizumab (OMA) as monotherapy and as an adjunct to OIT (OMA+OIT) has been evaluated in patients with IgE-mediated FA.[8,9] OMA binds with IgE antibodies and prevents their interaction with FcεRI receptors on mast cells and basophils, thereby inhibiting degranulation and release of mediators of the allergic response.[8,10] OMA has been approved for use in a variety of indications including moderate-to-severe allergic asthma, nasal polyposis, and chronic spontaneous urticaria.[11] Given its mechanism, OMA may have a potential clinical application in the treatment of IgE-mediated FA (Figure 1).[8,12] Studies have indicated that OMA increases the threshold of reactivity to foods and improves the tolerated dose of foods when given as monotherapy[9,13,14] or as an adjunct to OIT.[15–17] OMA may also prevent systemic reactions to OIT and anaphylaxis when given as an adjunct to OIT.[18,19]

While a substantial number of studies have investigated OMA in IgE-mediated FA[13,14–17], there is a relative lack of understanding on its potential clinical applications. The current meta-analysis evaluated the efficacy and safety of OMA monotherapy and OMA+OIT in patients with IgE-mediated FA.

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Materials and methods

Literature search

A systematic literature search was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[20] to identify randomized controlled trials (RCTs), controlled clinical trials (CCTs), and observational studies in patients with FA (inception–December 2020). The databases searched were PubMed/MEDLINE, EMBASE, ISI Web of Science, TRIP, Cochrane Central, clinical trial registry (https://clinicaltrials.gov/), and Novartis clinical trials database (www.novartisclinicaltrials.com). The MeSH and search terms used were "food hypersensitivity" OR "food allergy" AND "omalizumab" OR "Xolair"; studies were filtered by clinical trial, publication type, and language (English). This protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; number: CRD42021245895).

Eligibility criteria

RCTs, CCTs, and observational studies in children and adults (of any age) with a clinician-diagnosed IgE-mediated FA (single and multiple food allergies),[21] documented skin prick test (SPT), allergen-specific IgE, and/or oral food challenge (OFC) were included. The included studies investigated OMA monotherapy/OMA+OIT. Preclinical and retrospective studies, case reports, commentaries, and consensus reports were excluded.

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220 **Outcomes**

221 The outcomes included in this meta-analysis were increase in tolerated dose, successful
222 desensitization, sustained unresponsiveness (SU), as diagnosed by the OFC test, measurement of
223 antigen-specific IgE (sIgE) levels, antigen-specific IgG4 (sIgG4) levels, total IgE levels, antigen-
224 specific IgE/IgG4 levels; reduction in wheal size (via SPT); decrease in the severity of food
225 allergic reactions (Ewan scale) including urticaria, atopic dermatitis, rhinosinusitis, asthma, and
226 anaphylaxis[22–24]; and changes in QoL using validated questionnaires (FA Quality of Life
227 Questionnaire-Child Form [FAQLQ-CF], FA Quality of Life-Questionnaire-Teenager Form
228 [FAQLQ-TF], FA Quality of Life-Parental Burden Questionnaire [FAQL-PB]), and Pediatric
229 Quality of Life [PedsQL]).[25,26] Safety assessments included the evaluation of any adverse events
230 (AEs), serious AEs[27] (IgE-mediated/non-IgE-mediated/mixed IgE/local/systemic adverse
231 reactions), and patients' perceived FA-related risk.[28] The changes in treatment outcomes were
232 compared with prior treatment (pre-OMA)/placebo (Table 1).

233 **Data extraction and normalization**

234 Two reviewers independently assessed the identified studies; any disagreements were resolved by
235 discussion with all authors to obtain consensus. Data extraction was performed for patient
236 demographics and baseline clinical characteristics, efficacy, and safety endpoints. Numerical
237 values were extracted from studies that reported results in graphical format only. For analysis, data
238 reported in any format were normalized in the form of continuous (mean, standard deviation [SD],
239 and total) or binary data (events, total).

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Risk of bias

The risk of bias (RoB) was assessed using Cochrane RoB tool (RCTs using authors' judgements) and ROBINS-I scale (CCTs and observational studies).[29]

Data analysis

Meta-analysis was performed using Review Manager (version 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and R statistical software (version 3.4.1, Meta package). Outcomes were pooled as forest plots using mean differences (MDs) (inverse variance [IV] or generic IV method), Mantel-Haenszel risk ratios (RRs), or risk differences (RDs). Standard deviation was converted to standard error (SE). The effect measures were analyzed using a random-effects model for all outcomes, to address the clinical variation across studies. Data from single studies with measurements taken at different time points were pooled to estimate the effect of intervention over a period of time. If a study showed no events in one or both treatment arms, the meta-analytical method in R package meta applied continuity correction of 0.5 in studies with zero cell frequencies to avoid computational errors in ratio measures. The precision of estimates was quantified using 95% confidence intervals (CIs) derived from SE of the pooled effect measure. Studies were weighted using the DerSimonian and Laird random-effects model. *P* values were evaluated using a two-tailed test with $P < 0.05$ considered as statistically significant. Results were grouped based on the outcomes and treatments.

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Results

A total of 976 studies were screened. After removal of duplicates, 751 studies were excluded based on disease condition, intervention, outcomes, study design, or relevance. A total of 36 studies (9 RCTs, 19 CCTs, and 8 observational studies)[13–19,30–51,53–59] with varying study durations met the eligibility criteria (Figure 2). Details of the included patient populations (n = 953) and the study characteristics are presented in Table E1. OMA was administered as a monotherapy in 12 studies and as an adjunct to OIT in the remainder. The comparators were either placebo or food flour allergen (OIT) or baseline prior to treatment. Here, we present the results of increase in tolerated dose, increase in threshold of allergens, successful desensitization, SU, QoL, food allergic reactions, immunological outcomes, and safety. Please see Online Repository Text for additional findings on SU (Figure E1), desensitization (Figure E2), and food allergic reactions (Figure E3) along with the results of consumption of allergenic foods (Figure E4), OMA dosages (Figure E5), risk score of severe adverse reactions (Figure E6), and RoB (Figure E7, Table E4A and Table E4B).

Increase of tolerated dose to multiple foods in patients receiving OMA vs pre-OMA

A meta-analysis of 4 studies[50,56,57,59] (n = 210) showed that OMA (duration: 9–22 weeks) significantly increased the tolerated dose of multiple foods vs pre-OMA over a period of 17–22 weeks (RR: 24.88; $P < 0.001$, Figure 3A). In patients with severe and persistent allergy (n = 7, one study[37]), OMA monotherapy did not significantly increase the tolerated dose of cow's milk (CM) and eggs compared to pre-OMA at Week 16 as assessed in a single-blind food challenge test (RR: 10.38, $P = 0.09$, Figure 3B).

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Threshold of tolerated dose to multiple foods in patients receiving OMA vs pre-OMA

A significant increase in the threshold of tolerated dose for multiple foods (milk, egg, wheat, and baked milk) was observed with OMA at 17 weeks vs pre-OMA in a single study[57] (n = 15) (MD: 2794.89, $P < 0.001$, Figure 3C).

Increase of tolerated dose to multiple foods in patients receiving OMA+OIT vs placebo

Analysis of data from two studies[30,31] showed that patients (n = 108) receiving OMA+OIT (OMA duration: 16 weeks) were able to significantly tolerate 2 g (RR: 1.72; $P = 0.007$, Figure 4A) and 4 g (RR: 1.79; $P = 0.01$, Figure 4B) of ≥ 2 foods during OFC at 36 weeks compared with placebo.

Increase of tolerated dose to different foods in patients receiving OMA+OIT vs pre-OMA

Analysis from Salguero and Chason, 2017[43] showed a significant increase in the tolerated dose of different foods in patients (n = 70) who passed OFC to CM and eggs after 13 weeks' treatment with OMA+OIT vs pre-OMA (RR: 16.40; $P = 0.004$, Figure 4C). In patients with severe FA (n = 23, one study[18]), OMA+OIT significantly increased the tolerated dose of peanut at 32 weeks (RR: 31.00; $P = 0.01$, Figure 4D) vs pre-OMA (OMA duration: 24 weeks).

Successful desensitization with OMA+OIT vs placebo+OIT

Analysis from one study[19] demonstrated a significantly increased desensitization in patients with allergy to peanuts (n = 37, single study) with OMA+OIT (OMA duration: 19 weeks) vs placebo+OIT, as assessed at timepoints of 25 and 41 weeks (RR: 6.08, $P = 0.007$, Figure 5A).

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298 Patients were challenged to peanut to assess desensitization after 6 and 12 weeks of OMA
299 withdrawal.

300 **Increase of tolerated dose of food allergens and successful desensitization with OMA+OIT**
301 **vs pre-OMA**

302 In patients with allergy to CM, analysis of 6 studies[38,42,44,46,55,58] showed a significant increase in
303 the tolerated dose and desensitization with OMA+OIT (OMA duration: 10–20 weeks) over 9–17
304 weeks (RR: 9.23, $P < 0.001$; Figure 5B) and at 24 weeks (RR: 19.97, $P = 0.002$; Figure 5C).
305 Analysis from one study[35] showed a significant increase in tolerated dose and desensitization
306 with OMA+OIT in patients with allergy to peanut flour (RR: 25.00; $P = 0.001$, Figure 5D) vs
307 pre-OMA.

308 **Quality of life in patients receiving OMA+OIT or OMA vs pre-OMA**

309 Assessment of changes in QoL in patients (n = 27) receiving OMA+OIT or OMA and their
310 parents were evaluated using FAQLQ-CF, FAQLQ-TF, FAQL-PB and PedsQL.[17,57] In patients
311 with peanut allergy receiving OMA+OIT (OMA duration: 22 weeks), significant improvements
312 in the parental and patients' QoL (parental QoL; MD: −0.76, $P = 0.02$, patients' QoL; MD: –
313 2.00, $P < 0.001$ Figure 6A) from baseline (pre-OMA) were observed at various time points (52–
314 261 weeks).[17] In addition, OMA monotherapy for 17 weeks significantly improved QoL using
315 generic core scales of cognitive, social, emotional, and physical functioning domains, and total
316 scores from both the parents' (MD: 26.91, $P < 0.001$, Figure 6B) and patients' (MD: 26.15, $P <$
317 0.001, Figure 6B) perspective compared with pre-OMA.[57]

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Food allergic reactions in patients receiving OMA vs pre-OMA

Analysis from one study[49] demonstrated that OMA significantly reduced accidental or intentional food-induced allergic reactions (urticaria, atopic dermatitis, rhinosinusitis, asthma, and anaphylaxis; RR: 16.21; $P < 0.001$, Figure 7A) at 52 weeks in patients with multiple FA (n = 22) vs pre-OMA. Also, a reduction in allergic reactions (MD: 5.21; $P < 0.001$, Figure 7B) was noted at 18 weeks in patients with an allergy to peanuts (n = 14) receiving OMA compared to pre-OMA.[14]

Immunological assessments

The efficacy of OMA and OMA+OIT across various immunological parameters was evaluated in seven studies[14–17,32,34,38] (n = 196 patients, Table E2). No significant reductions in sIgE levels were observed with OMA+OIT vs placebo/placebo+OIT in patients with allergy to CM, casein, α-lactalbumin, and β-lactoglobulin allergens (MD: 20.13; $P = 0.35$).[16,32] Similar findings were observed in patients with peanut allergy treated with OMA or OMA+OIT compared with pre-OMA (MD: −39.48; $P = 0.28$).[14,15,17] OMA+OIT significantly increased antigen-specific IgG4 levels to CM, casein, α-lactalbumin, and β-lactalbumin allergens compared with placebo/placebo+OIT (MD: 20.29; $P = 0.005$)[16,32] but did not significantly increase IgG4 levels when compared with pre-OMA in subjects with peanut allergy (MD: 24.50; $P = 0.25$).[15,17] A significant improvement in the IgE:IgG4 ratio was observed compared with pre-OMA in subjects with peanut allergy (MD: −0.28; $P = 0.04$).[17]

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No significant reductions in the total IgE levels were observed with OMA+OIT in subjects with CM allergy vs those receiving placebo (MD: 296.25; $P = 0.51$).[32] Similar findings were reported in patients with peanut allergy when receiving OMA as monotherapy or as an adjunct to OIT vs pre-OMA (MD: -89.39; $P = 0.36$).[14,17] Also, OMA as an adjunct to multiple food allergen OIT did not reduce total IgE levels following dose escalation (1200 mg) (MD: -160.00; $P = 0.65$).[34] A significant reduction in SPT was reported with cow's milk, cashew, and ovalbumin compared with pre-OMA at 52 weeks (RR: 13.22; $P = 0.009$).[38] While there was no significant reduction in the wheal size to standard CM extract, fresh CM, and microwave-heated CM with OMA+OIT compared with placebo (MD: -1.43; $P = 0.34$),[32] a significant decrease was noted in patients with peanut allergy vs pre-OMA (MD: -4.32; $P < 0.001$).[14,15,17]

Safety

In total, ten studies evaluated the safety of OMA and OMA+OIT (n = 321).[16,17,19,31,33,35,36,39,43,44] No major safety concerns were identified with either OMA or OMA+OIT. Cases of anaphylaxis were reported in a few studies[16,44] in patients receiving OMA+OIT vs placebo+OIT; however, the results were not significant. An increase in the rate of anaphylaxis was reported in a single study in patients allergic to peanuts receiving OMA+OIT vs placebo+OIT.[19] Notable AEs included gastrointestinal, general, respiratory, thoracic, and mediastinal disorders. Other notable AEs included a mild allergic reaction and flushing in patients allergic to peanuts (OMA+OIT vs pre-OMA[35]) and CM (OMA+OIT vs placebo+OIT[16]). No increases in other AEs were found (Table E3).

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Discussion

The current meta-analysis of 36 studies (~1000 subjects) was conducted to comprehensively understand the overall efficacy of OMA and OMA+OIT in patients with IgE-mediated FA. An array of outcome measures, including an increase in tolerated dose to food allergen(s), desensitization, SU, immunological assessments (sIgE, sIgG4, total IgE levels, antigen-specific IgE/IgG4 antibodies and SPT), QoL, and safety, were assessed.

Overall, OMA monotherapy or OMA+OIT significantly improved the tolerated dose of foods and enabled the consumption of multiple foods at increased reactivity thresholds. Additionally, in patients with severe and persistent FA, OMA facilitated successful desensitization, although it did not significantly change the cumulative tolerated dose. In patients with CM allergy, desensitization with OMA was observed after discontinuation of OIT at Week 8 until rechallenge at Month 32, although the result did not reach statistical significance.[32]

The immunological assessments showed significant improvements in IgG4 levels following OMA treatment, although no reductions in antigen-specific and total IgE levels were observed. The increase in IgG4 levels together with an improvement in the IgE:IgG4 ratio may potentially indicate an immunomodulatory effect of OMA with or without OIT. Similar findings were observed in the additional analysis of data from the PRROTECT trial[60] where IgE blockade by OMA facilitated more rapid escalation of peanut doses in the build-up phase, had fewer reactions, and exhibited a lasting impact on the reduction in peanut specific IgE levels, an increase in inhibitory IgG and IgG4:IgE ratio, indicating an additional immunomodulatory effect. The clinical outcomes of OMA+OIT may not always correlate with the response to

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treatment, the induction of allergen tolerance, or the reduction in IgE levels, highlighting other immunomodulatory effects of OMA[12,61]; however, it is difficult to differentiate the effect of OMA from OIT when they are used in combination.

The improvements across the range of outcomes assessed could be largely due to the specific mechanisms of action of OMA combined with OIT. It should be emphasized that IgE-mediated FA typically involves the production of high levels of allergen-specific free IgE molecules that bind to FcεRI receptors on basophils and mast cells. Allergic symptoms typically occur upon re-exposure following degranulation of these cells in response to IgE recognition of cognate epitopes.[12] Similarly, OIT is known to induce T regulatory (Treg) cells that suppress immune responses. The inhibition of IgE cross-linking in vitro by OMA can also activate Treg cells[62] that are thought to modulate immune responses in addition to interfering with IgE production and inducing the production of IgG4.[63] Allergen-specific immunotherapy can also induce desensitization of FcεRI receptors on mast cells and basophils and help generate Treg cells, which together enable early desensitization.[64] Furthermore, a recent study showed a decrease in frequency of the OX40 ligand on TH2 cells and reduced expression of CD86 on antigen-presenting cells (APCs). This was evident only after OMA+OIT treatment, suggesting that the combination approach influences T-cell–APC crosstalk favoring desensitization.[61]

From this, it can be deduced that while OMA effectively suppresses free IgE molecules, the use of OMA+OIT not only helps in the formation of biologically inert anti-IgE–antibody complexes but also downregulates FCεRI expression and results in immune repolarization toward TH1.[16] Therefore, the combination of OMA+OIT can lead to allergen desensitization through

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399 downregulation of FcεRI expression in basophils, reduction in allergen-specific IgE levels, and
400 an increase in IgG4 levels.[12]
401 Another positive finding from this meta-analysis is the significant improvement in patients' and
402 parental QoL. These improvements may be attributed to the reductions in dietary restrictions,
403 reduced allergic reactions to accidental food exposure, and a decreased risk of anaphylaxis,
404 together with improvements in various domains of QoL.[51,57]

405 In line with previous clinical experience, OMA showed no major safety concerns in patients with
406 IgE-mediated FA. In OIT protocols, safety is a major concern[66–67]; however, reductions in
407 adverse reactions were noted in subjects receiving OMA during OIT dose escalation, dose-
408 related reactions necessitating treatment, and doses needed to achieve maintenance.[16] Studies
409 have indicated that OMA can decrease episodes of anaphylaxis in patients with recurrent and/or
410 unprovoked anaphylactic reactions,[47] reiterating a potential benefit, especially in patients at a
411 high risk of FA-related severe anaphylaxis.[49] The safety of OMA is well established and has
412 reached >1.86 million patient-years of exposure as of March 28, 2022 (Unpublished data, Xolair
413 (omalizumab). Data on file. Safety update. Period covered: 29 Jan 2018 - 28 March 2022. Issued:
414 19 May 2022).

415 The current meta-analysis provided evidence of the efficacy of OMA in patients with IgE-
416 mediated FA and corroborates the findings from individual studies that OMA can enable
417 successful consumption of multiple allergenic foods while on therapy. Furthermore, the addition
418 of OMA to OIT may allow more rapid dose escalation, high-dose desensitization, and higher
419 maintenance doses of immunotherapy. These findings also highlight the positive impact of OMA

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and OMA+OIT on the QoL of patients and caregivers, while also offering the potential for an alternative treatment option. The ongoing phase III OUtMATCH (NCT03881696) trial will investigate if OMA helps patients with multiple food allergies to consume foods without dose-limiting symptoms.

To the best of our knowledge, the current meta-analysis provides the first comprehensive assessment of the overall efficacy and safety of OMA and OMA+OIT in subjects with single or multiple IgE-mediated FAs. Patients showed an improvement in tolerance to food allergen(s) and increases in allergen reactivity thresholds and QoL.

However, the current meta-analysis did not indicate the development of SU, probably owing to the small number of studies, variations in sample sizes, treatment durations of OMA and OIT and the differences in the strength of the maintenance dose, calling for the need for further studies. While significant improvements in QoL were also noted with OMA and OMA+OIT, owing to the small number of studies that evaluated this objective, the results should be interpreted cautiously. Moreover, the substantial heterogeneity observed in some studies, as well as variations in OMA treatment schedules (dosage, duration), OIT protocols (escalations, maintenance), limited number of studies for certain assessments, ambiguity in patient selection and a high RoB in some studies (in addition to the authors' judgements on the RoB in the RCTs) could have affected the outcomes. Also, the predefined eligibility criteria, the clinical and demographic features of the study population, baseline IgE levels, and SPT reactivity along with pooling of data from single studies for certain outcomes could have also contributed to some

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inconsistency in the results. It is important to note that the doses of OMA used in these studies were based on weight and serum total IgE.

Considering that OMA has shown encouraging results in our analyses, it should be explored further either as a monotherapy or as an adjunct for improving the OIT efficacy and benefit/risk ratio, especially when used as a first intervention or in patients who have failed a previous OIT. It is crucial to recognize the role of OMA and OMA+OIT in patients with severe FA (who experience repeated anaphylactic reactions even at low allergen thresholds and/or for staple foods) or difficult FA (multi-food allergies, presence of comorbidities) in order to implement personalized treatment. In addition, studies are required to understand the efficacy of OMA monotherapy in preventing reactions to real-world exposures to allergens. Clarity is needed on the duration of treatment and the best tool(s) to measure efficacy (considering age, patients' needs and expectations, impact on QoL, and anxiety). Biomarkers for the prediction of treatment response and for evaluation of the response, along with the impact on the immune system (including microbiota), can help in understanding the mechanisms for the success or failure of treatment. The cost-effectiveness of using OMA or OMA+OIT as a treatment approach needs to be established. In addition, there is a need to determine if OMA can potentially act as a disease-modifying treatment, especially when administered in very young patients.

The current systematic review and meta-analysis showed that OMA was beneficial in patients with IgE-mediated FA (single/multiple foods) and that this represents a potential treatment modality. However, studies with an adequate design to objectively evaluate the effect of OMA are limited, and further data are warranted to confirm these findings. Combined treatment with

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anti-IgE monoclonal antibody (mAb) and specific food-allergen OIT is an attractive option, not only because of the potential ability of anti-IgE mAb to decrease immediate side effects from OIT, but also the possibility to enhance the immunomodulatory effect of OIT. Owing to the key role of the IgE–FcεRI axis in the pathogenesis of this disease, using OMA may be a logical approach in treating IgE-mediated FA. Results from the ongoing phase III OUtMATCH study will further confirm the role of OMA in patients with IgE-mediated FA.

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Author's contributions

All authors have contributed equally to the conceptualization of work, literature search, analysis, and interpretation of data, intellectual content of the manuscript and approved the final version for publication.

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Figure Legends

Figure 1. Modulation of immune responses using a combination of anti-IgE treatment(s) and OIT in IgE-mediated FA: Mechanism of allergy and post-treatment desensitization.

FcεRI, high-affinity IgE receptor; IFN-γ, Interferon gamma; IgE, immunoglobulin E; IgG4, immunoglobulin G4; IL, interleukin; OIT, oral immunotherapy; TH2, T-helper 2 cell; TH1, T-helper 1 cell; Treg, T regulatory cell

**Allergen may enter the cell via the gastrointestinal tract, the respiratory tract or the skin.*

OMA results in the formation of IgE–anti-IgE antibody complexes, downregulation of FCεRI expression, and altered antigen presentation, resulting in the depletion of TH2 cells. OIT induces Treg suppression of immune responses and repolarization toward TH1. The treatment with anti-IgE/OIT combination can cause allergen desensitization through downregulation of FcεRI expression in basophils, reduction in allergen-specific IgE levels, and an increase in IgG4 levels.[3,12]

Figure 2. PRISMA flowchart

Figure 3. Increase of tolerated dose to (A) multiple foods and (B) cow's milk and eggs, (C) Threshold of tolerated dose to multiple foods in patients receiving OMA vs pre-OMA

CM, cow's milk allergy; MH, Mantel-Haenszel; MD, mean difference; OMA, omalizumab

Lefevre et al.: included patients allergic to different foods; Azzano et al. and Fiocchi et al.: included patients with multiple food allergies. Alba Jorda et al.: not clear.

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Figure 4. Increase of tolerated dose to multiple foods (A) 2 g of ≥2 allergens (B) 4 g of ≥2 allergens in patients receiving OMA+OIT vs placebo and increase of tolerated dose to cow's milk and eggs (C) and peanut (D) in patients receiving OMA+OIT vs pre-OMA

CM, cow's milk allergy; MH, Mantel-Haenszel; OMA, omalizumab; OIT, oral immunotherapy.

Figure 5. Increase of tolerated dose and desensitization in patients with allergy to (A) peanuts receiving OMA+OIT vs placebo+OIT and cow's milk (B and C) and peanut flour (D) receiving OMA+OIT vs pre-OMA

CM, cow's milk allergy; MH, Mantel-Haenszel; OMA, omalizumab; OIT, oral immunotherapy
In Sousa et al., all patients tolerated 150 mL of raw milk without IgE-mediated reaction. In Hernandez et al., all patients achieved a 250-mL daily dose. In Schneider et al., 12 out of 13 children (92%) were able to tolerate 4000-mg dose of peanuts following 20 weeks.

Figure 6. Quality of life in patients with allergy to (A) peanuts receiving OMA+OIT vs pre-OMA and (B) multiple foods receiving OMA vs pre-OMA

MD, mean difference; OMA, omalizumab; OIT, oral immunotherapy; PedsQL, pediatric quality of life; QoL, quality of life.

Figure 7. Food allergic reactions in patients with allergy to multi-foods (A) and peanuts (B) receiving OMA vs pre-OMA

BHR, basophil histamine release; MD, mean difference; MH, Mantel-Haenszel; OMA, omalizumab.

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Table

Table 1. Definitions/criteria/assessments used in the meta-analysis

We included all studies that used an OFC test either open or blinded (single or double)

Increase in the tolerated dose (or threshold of reactivity):

- an increase in the amount of allergen (increase in threshold) that is tolerated in an OFC after the intervention

Successful desensitization:

- a temporary state of clinical nonreactivity dependent upon persistent allergen exposure

Sustained unresponsiveness:

- food can be consumed safely (on negative OFC) without any treatment, even after a period with food eviction

Immunological assessments: total IgE, specific IgE, IgG4, IgE/IgG4 ratios, skin-prick testing

Classification of severity of allergic reactions: allergic reactions by Ewan scale

Risk score of severe adverse reactions: risk scores range from 0 to 6, with higher scores indicating a greater negative impact on QoL/greater perceived risk

QoL assessments: FAQLQ: two forms, Food Allergy Quality of Life Questionnaire-Child Form (for patients aged 7–12 years) and Food Allergy Quality of Life Questionnaire-Teenager Form (for patients aged 13–17 years). Questions are common for both age versions with items that address the impact of allergen avoidance, dietary restriction, risk of accidental

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exposure, and emotional burden on quality of life. Items were rated on a 7-point Likert scale (0 = not troubled to 6 = extremely troubled) and averaged for a total score.

PedsQL: systematically assesses patients' and parents' perceptions of HRQoL in pediatric patients. It consists of 23 items comprising physical, emotional, social, and school functioning domains. Items on the PedsQL scale are reverse scored and transformed to a 0–100 scale. Higher scores (>80) indicate better health-related QoL.

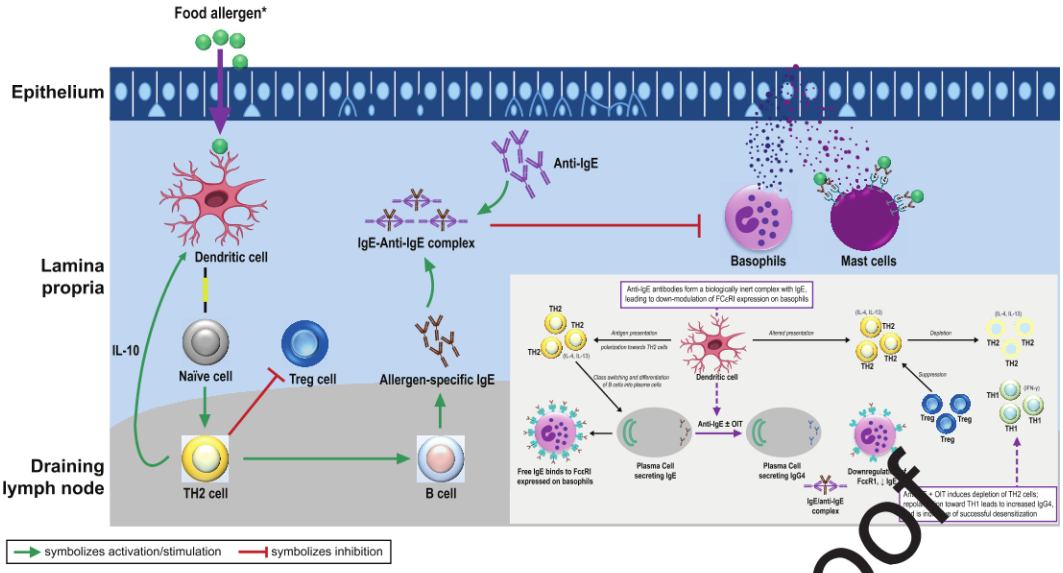
For all efficacy outcomes, the response rates were evaluated from the start to the response evaluated intervals/the end of the trial/post-omalizumab (summary measure; MD, 95% CI or RR, 95% CI)

Safety endpoints: Any AEs, serious AEs, IgE-mediated, non-IgE–mediated, mixed IgE, local, and systemic adverse reactions along with assessment of patient perceived risk. Patients completed questions from the validated FAIM, a self-report instrument that reflects the patient's perceived food allergy related risk. Questions completed for this study included the perceived expectation of a severe reaction or death following an accidental exposure. Perceived risk was rated on a 7-point Likert scale (0 = 0% chance to 6 = 100% chance).

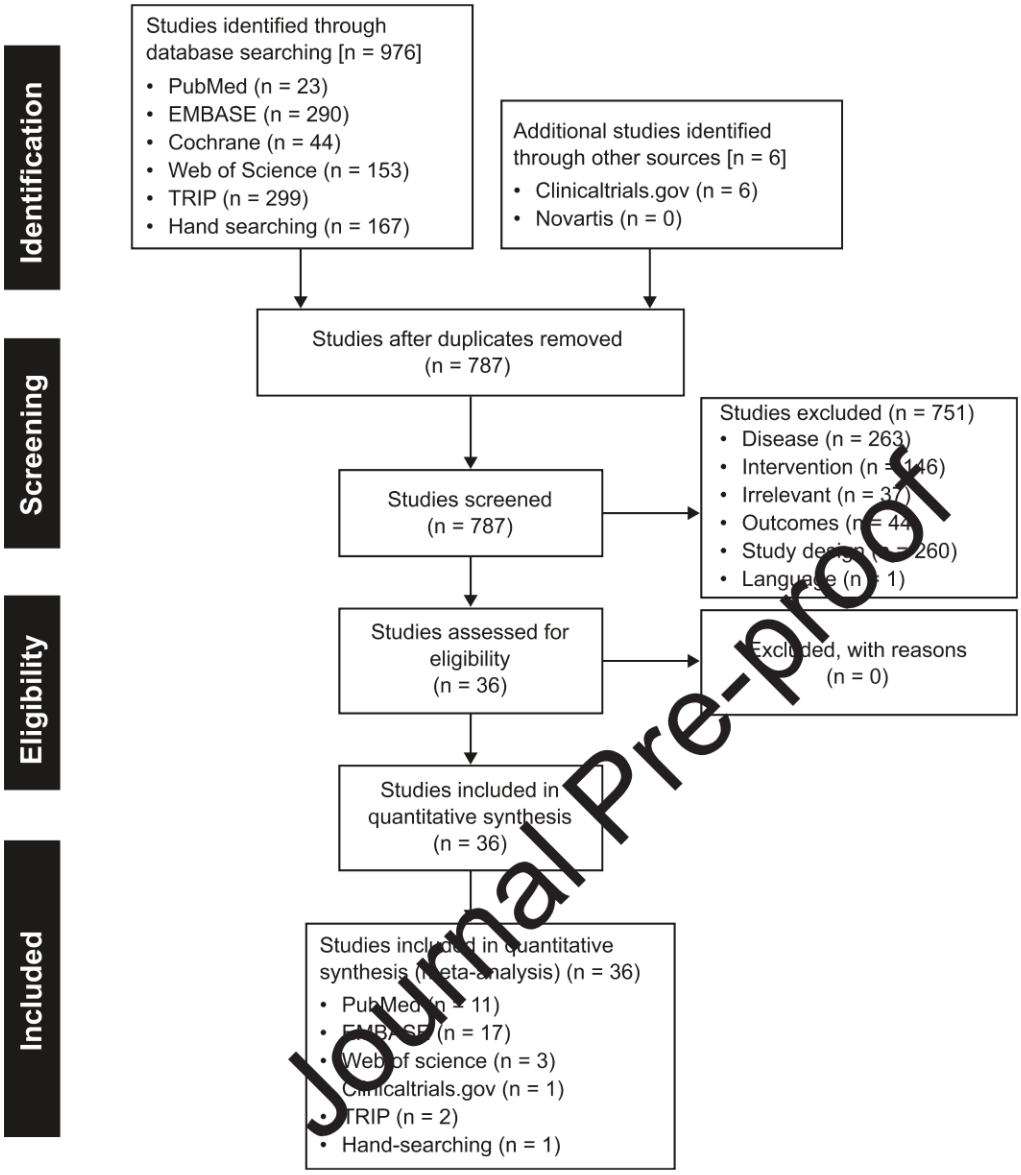
Percentage of patients who had any AE/SAEs were evaluated from baseline to the response evaluated intervals/the end of the trial/post-omalizumab (summary measure; MD, 95% CI or RR, 95% CI)

AE, adverse event; FAIM, Food Allergy Independent Measure; FAQLQ, Food Allergy Quality of Life Questionnaire; HRQoL, health-related quality of life; IgE, immunoglobulin E; IgG, immunoglobulin G; MD, mean difference; OFC, oral food challenge; PedsQL, pediatric quality of life; QoL, quality of life; RR, rate ratio; SAE, severe AE.

Journal Pre-proof



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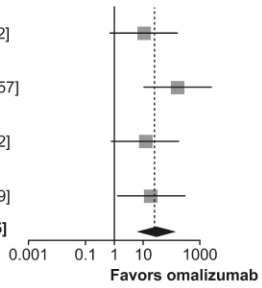


Journal Pre-proof

(A)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Successfully consumed multiple allergic foods								
Lefevre 2016[50]	Food allergy	22 weeks	5	8	0	8	24.9%	11.00 [0.71; 169.42]
Highest tolerated dose, ≥1200 mg								
Azzano 2021[59]	Food allergy		76	181	0	181	24.2%	153.00 [9.56; 2449.57]
Restriction free diet								
Alba Jordá 2019[56]	Food allergy		6	6	0	6	26.3%	13.00 [0.91; 186.42]
Achieved tolerance to all foods								
Fiocchi 2019[57]	Food allergy	17 weeks	9	15	0	15	24.6%	19.00 [1.21; 298.79]
Total (95% CI)							**100.0%**	**24.88 [6.35; 97.45]**

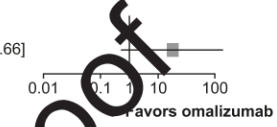
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.26$, df = 3 ($P = 0.52$); $I^2 = 0\%$
Test for overall effect: Z = 4.61 ($P < 0.001$)



(B)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Tolerated single-blind food challenge								
Peloche 2011[37]	CM and egg allergy	16 weeks	4	6	0	7	100.0%	10.38 [0.68; 158.66]

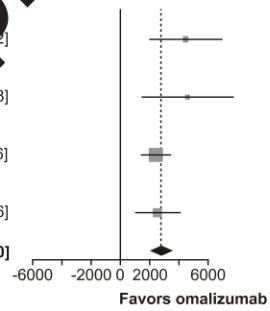
Test for overall effect: Z = 1.68 ($P = 0.09$)



(C)

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Food tolerance threshold of Egg						
Fiocchi 2019[57]	Food allergy	17 weeks	4470.59	1246.26	10.4%	4470.59 [2027.96; 6913.22]
Food tolerance threshold of wheat						
Fiocchi 2019[57]	Food allergy	17 weeks	4588.23	1602.45	6.3%	4588.23 [1447.48; 7728.98]
Food tolerance threshold of milk						
Fiocchi 2019[57]	Food allergy	17 weeks	2409.09	511.32	57.4%	2409.09 [1406.92; 3411.26]
Food tolerance threshold of Baked milk						
Fiocchi 2019[57]	Food allergy	17 weeks	2541.66	778.84	26.0%	2541.66 [1015.16; 4068.16]
Total (95% CI)					**100.0%**	**2794.89 [2002.19; 3587.60]**

Heterogeneity: $Tau^2 = 23716.65$; $Chi^2 = 3.73$, df = 3 ($P = 0.29$); $I^2 = 20\%$
Test for overall effect: Z = 6.91 ($P < 0.001$)

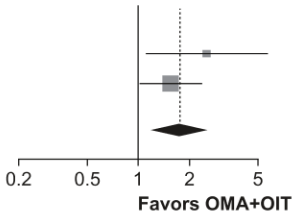


Journal Pre-proof

(A)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Tolerated 2 g of ≥2 allergens								
Andorf 2018[30]	Multifood allergy	36 weeks	30	36	4	12	22.6%	2.50 [1.11; 5.64]
Andorf 2019[31]	Multifood allergy	36 weeks	34	40	11	20	77.4%	1.55 [1.02; 2.35]
Total (95% CI)							**100.0%**	**1.72 [1.16; 2.55]**

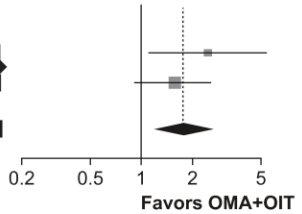
Heterogeneity: $Tau^2 = 0.0069$; $Chi^2 = 1.06$, df = 1 ($P = 0.30$); $I^2 = 6\%$
Test for overall effect: Z = 2.70 ($P = 0.007$)



(B)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Tolerated 4 g of ≥2 allergens								
Andorf 2018[30]	Multifood allergy	36 weeks	30	36	4	12	29.4%	2.50 [1.11; 5.64]
Andorf 2019[31]	Multifood allergy	36 weeks	28	40	9	20	70.6%	1.56 [0.92; 2.63]
Total (95% CI)							**100.0%**	**1.79 [1.15; 2.78]**

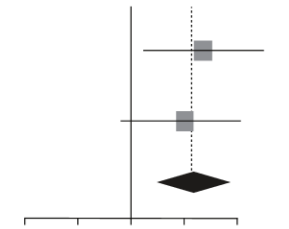
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.92$, df = 1 ($P = 0.34$); $I^2 = 0\%$
Test for overall effect: Z = 2.58 ($P = 0.01$)



(C)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Tolerated 250 mL of CM (13 weeks)						
Salguero 2017[43]	12	12	0	12	48.6%	25.00 [1.65; 377.92]
Tolerated 3 eggs in a week (13 weeks)						
Salguero 2017[43]	5	5	0	5	51.4%	11.00 [0.78; 154.58]
Total (95% CI)					**100%**	**16.40 [2.47; 108.99]**

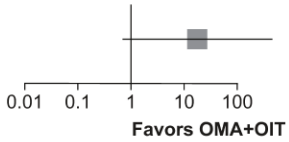
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.18$; df = 1 ($P = 0.67$); $I^2 = 0\%$
Test foor overall effect: Z = 2.89 ($P = 0.004$)



(D)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Tolerated 2.8 g of Peanut Protein (32 weeks)						
Brandstrom 2017[18]	15	23	0	23	100.0%	31.00 [1.97; 488.57]

Test for overall effect: Z = 2.44 ($P = 0.01$)

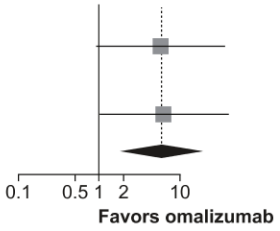


Journal Pre-proof

(A)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Passed the 4 g peanut protein OFC test								
MacGinnitie 2017[19]	Food allergy	41 weeks	16	22	1	8	49.8%	5.82 [0.91; 37.05]
Tolerated 2 g peanut protein								
MacGinnitie 2017[19]	Food allergy	25 weeks	23	29	1	8	50.2%	6.34 [1.00; 40.06]
Total (95% CI)							**100.0%**	**6.08 [1.65; 22.43]**

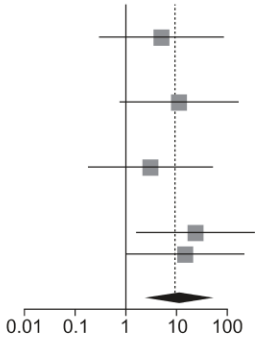
Heterogeneity: Tau² = 0; Chi² = 0.00, df = 1 (*P* = 0.95); I² = 0%
Test for overall effect: Z = 2.71 (*P* = 0.007)



(B)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Tolerated 200 mL of CM								
Arasi 2017[44]	CM allergy	17 weeks	2	6	0	6	18.8%	5.00 [0.2[illegible]85.16]
Tolerated 6.5 g of CM Protein at maintenance phase								
Demir 2018[46]	CM allergy		5	7	0	7	20.6%	11.00 [0.73; 165.72]
Tolerated 2.5 g of CM								
Pajno 2015[42]	CM allergy	9 weeks	1	3	0	3	18.8%	[illegible].00 [0.18; 51.20]
Desensitization								
Sousa 2020[55]	CM allergy		11	11	0	11	20.[illegible]%	23.00 [1.53; 345.98]
Hernández 2020[58]	CM allergy	12-16 weeks	7	7	0	7	21.1%	15.00 [1.03; 218.30]
Total (95% CI)			**34**			**4**	**100.0%**	**9.23 [2.70; 31.60]**

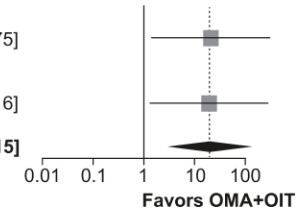
Heterogeneity: Tau² = 0; Chi² = 1.36, df = 4 (*P* = 0.85); I² = 0%
Test for overall effect: Z = 3.54 (*P* < 0.001)



(C)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Tolerated 1.992 g of CM (9 weeks)								
Bedoret 2012[38]	CM allergy	9 weeks	10	11	0	11	49.9%	21.00 [1.39; 317.75]
Passed DBPCFC Test for 7.25 g desensitization of CM (24 weeks)								
Bedoret 2012[38]	CM allergy	24 weeks	9	10	0	10	50.1%	19.00 [1.26; 286.16]
Total (95% CI)							**100.0%**	**19.97 [2.93; 136.15]**

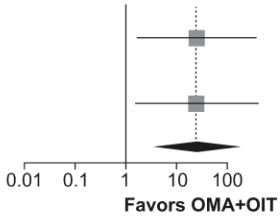
Heterogeneity: Tau² = 0; Chi² = 0.00, df = 1 (*P* = 0.96); I² = 0%
Test for overall effect: Z = 3.06 (*P* = 0.002)



(D)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Tolerated 4 g of peanut flour								
Schneider 2013[35]	Peanut allergy	20 weeks	12	13	0	13	50.0%	25.00 [1.64; 381.1]
Tolerated 8 g of Peanut Flour (32 weeks)								
Schneider 2013[35]	Peanut allergy	32 weeks	12	13	0	13	50.0%	25.00 [1.64; 381.1]
Total (95% CI)							**100.0%**	**25.00 [3.64; 171.6]**

Heterogeneity: Tau² = 0; Chi² = 0.00, df = 1 (*P* = 1.00); I² = 0%
Test for overall effect: Z = 3.28 (*P* = 0.001)



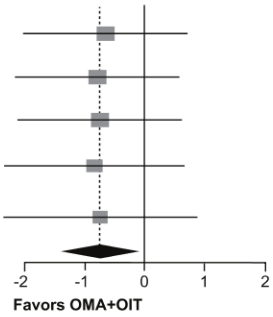
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(A)

Parental QoL

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Parent QoL (52 weeks)						
Yee 2019[17]	Peanut allergy	52 weeks	-0.65	0.70	21.9%	-0.65 [-2.02; 0.72]
Parent QoL (104 weeks)						
Yee 2019[17]	Peanut allergy	104 weeks	-0.80	0.70	21.8%	-0.80 [-2.17; 0.57]
Parent QoL (156 weeks)						
Yee 2019[17]	Peanut allergy	156 weeks	-0.75	0.70	21.8%	-0.75 [-2.12; 0.62]
Parent QoL (209 weeks)						
Yee 2019[17]	Peanut allergy	209 weeks	-0.85	0.77	18.1%	-0.85 [-2.35; 0.65]
Parent QoL (261 weeks)						
Yee 2019[17]	Peanut allergy	261 weeks	-0.75	0.81	16.4%	-0.75 [-2.33; 0.83]
Total (95% CI)					**100.0%**	**-0.76 [-1.40; -0.12]**

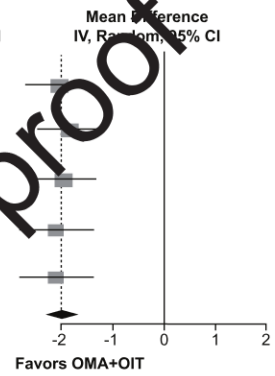
Heterogeneity: Tau² = 0; Chi² = 0.04, df = 4 (*P* = 1.00); I² = 0%
Test for overall effect: Z = -2.32 (*P* = 0.02)



Patients' QoL

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Patient QoL (52 weeks)						
Yee 2019[17]	Peanut allergy	52 weeks	-2.05	0.33	21.1%	-2.05 [-2.70; -1.40]
Patient QoL (104 weeks)						
Yee 2019[17]	Peanut allergy	104 weeks	-1.85	0.32	22.8%	-1.85 [-2.47; -1.23]
Patient QoL (156 weeks)						
Yee 2019[17]	Peanut allergy	156 weeks	-1.95	0.32	21.9%	-1.95 [-2.59; -1.31]
Patient QoL (209 weeks)						
Yee 2019[17]	Peanut allergy	209 weeks	-2.11	0.37	17.2%	-2.11 [-2.84; -1.39]
Patient QoL (261 weeks)						
Yee 2019[17]	Peanut allergy	261 weeks	-2.11	0.37	17.2%	-2.11 [-2.84; -1.39]
Total (95% CI)					**100.0%**	**-2.00 [-2.30; -1.71]**

Heterogeneity: Tau² = 0; Chi² = 0.45, df = 4 (*P* = 0.98); I² = 0%
Test for overall effect: Z = -13.19 (*P* < 0.001)

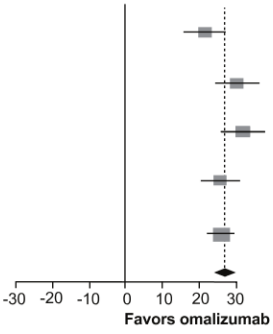


(B)

Parental judgement of QoL

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Cognitive functioning PedSQL, parental judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	21.50	2.91	17.6%	21.50 [15.79; 27.21]
Emotional functional PedsQL, parental judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	30.25	2.89	17.8%	30.25 [24.58; 35.92]
Physical functoning PedsQL, parental judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	31.90	3.01	16.9%	31.90 [25.99; 37.81]
Social functioning PedSQL, parental judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	25.75	2.65	19.5%	25.75 [20.56; 30.94]
Total score PedsQL, parental judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	26.00	1.69	28.2%	26.00 [22.68; 29.32]
Total (95% CI)					**100.0%**	**26.91 [23.72; 30.10]**

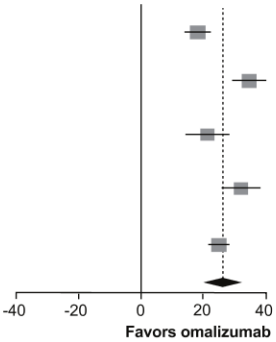
Heterogeneity: Tau² = 6.52; Chi² = 7.97, df = 4 (*P* = 0.09); I² = 50%
Test for overall effect: Z = 16.55 (*P* < 0.001)



Patient's judgement of QoL

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Cognitive functioning PedSQL, patient's judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	18.25	2.06	21.2%	18.25 [14.20; 22.30]
Emotional functional PedsQL, patient's judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	34.75	2.70	19.9%	34.75 [29.45; 40.05]
Physical functoning PedsQL, patient's judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	21.25	3.52	18.0%	21.25 [14.36; 28.14]
Social functioning PedSQL, patient's judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	32.00	3.16	18.9%	32.00 [25.81; 38.19]
Total score PedsQL, patient's judgement						
Fiocchi 2019[57]	Food allergy	17 weeks	25.00	1.67	21.9%	25.00 [21.73; 28.27]
Total (95% CI)					**100.0%**	**26.15 [20.03; 32.28]**

Heterogeneity: Tau² = 41.78; Chi² = 29.71, df = 4 (*P* < 0.01); I² = 87%
Test for overall effect: Z = 8.37 (*P* < 0.001)



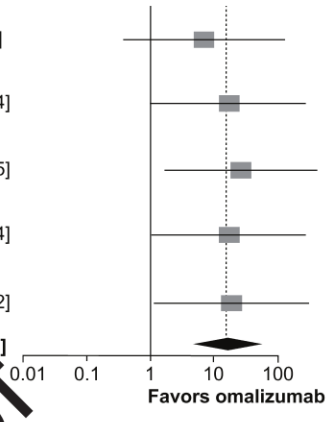
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(A)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Reduction in food induced urticaria								
Rafi 2010[49]	Food allergy	52 weeks	3	22	0	22	18.7%	7.00 [0.38; 127.86]
Reduction in food induced atopic dermatitis								
Rafi 2010[49]	Food allergy	52 weeks	8	22	0	22	20.2%	17.00 [1.04; 277.24]
Reduction in food induced asthma symptoms								
Rafi 2010[49]	Food allergy	52 weeks	13	22	0	22	20.6%	27.00 [1.71; 427.25]
Reduction in food induced rhinosinusitis symptoms								
Rafi 2010[49]	Food allergy	52 weeks	8	22	0	22	20.2%	17.00 [1.04; 277.24]
Reduction in food induced anaphylaxis								
Rafi 2010[49]	Food allergy	52 weeks	9	22	0	22	20.3%	19.00 [1.18; 307.22]
Total (95% CI)							**100.0%**	**16.21 [4.62; 56.95]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.47$, df = 4 ($P = 0.98$); $I^2 = 0\%$

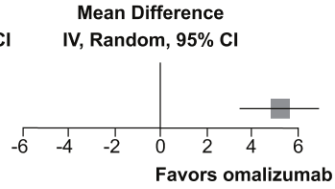
Test for overall effect: Z = 4.35 ($P < 0.001$)



(B)

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Dose of peanut protein inducing allergic symptoms (BHR, 18 weeks)						
Savage 2012[14]	Peanut allergy	18 weeks	5.21	0.87	100.0%	5.21 [3.5; 6.92]

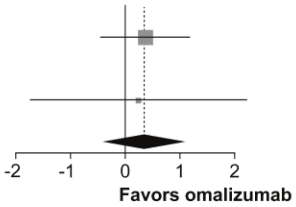
Test for overall effect: Z = 5.96 ($P < 0.001$)



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Study or Subgroup	Population	Timepoint	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Risk Ratio IV, Random, 95% CI
Desensitization: Sucessfully consumed dose(10g) of CM (122 Weeks)										
Wood 2016[1]	CM allergy	122 weeks	9.58	1.22	26	9.22	1.66	24	85.5%	0.36 [-0.45; 1.17]
Tolerance: Sucessfully consumed dose(10g) of CM (139 Weeks)										
Wood 2016[1]	CM allergy	139 weeks	7.47	3.47	24	7.23	3.21	20	14.5%	0.24 [-1.74; 2.22]
Total (95% CI)									**100.0%**	**0.34 [-0.41; 1.09]**

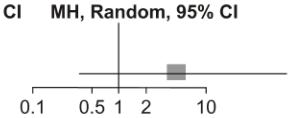
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.01$, df = 1 ($P = 0.91$); $I^2 = 0\%$
Test for overall effect: Z = 0.89 ($P = 0.37$)



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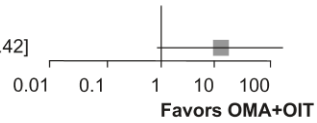
(A)

Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Desensitization								
Crisafulli 2019[2]	Food allergy	16 weeks	2	5	0	5	100.0%	5.00 [0.3; 81.97]
Test for overall effect: Z = 1.13 (*P* = 0.26)								



(B)

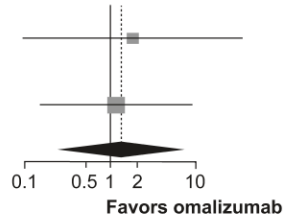
Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Desensitization								
Takahashi 2017[3]	CM allergy	32 weeks	10	10	0	6	100.0%	13.00 [0.91; 186.42]
Test for overall effect: Z = 1.89 (*P* = 0.06)								



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Study or Subgroup	Population	Timepoint	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, Random, 95% CI
Grade 1 food allergic reactions assessed by Ewan scale (52 weeks)								
NCT00382148[4]	Peanut allergy	52 weeks	1	7	0	4	32.4%	1.80 [0.09; 35.42]
Grade 3 food allergic reactions assessed by Ewan scale (52 weeks)								
NCT00382148[4]	Peanut allergy	52 weeks	2	7	1	4	67.6%	1.14 [0.15; 8.99]
Total (95% CI)							**100.0%**	**1.32 [0.24; 7.22]**

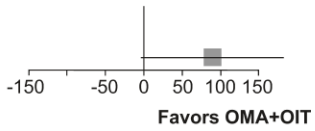
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.06$, df = 1 ($P = 0.81$); $I^2 = 0\%$
Test for overall effect: Z = 0.32 ($P = 0.75$)



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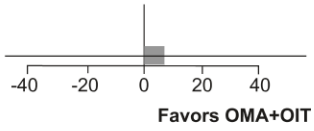
(A)

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Rate of continued consumption of allergens						
Azzano 2021[5]	Food allergy	104 weeks	90.30	47.36	100.0%	90.30 [-2.52; 183.12]
Test for overall effect: Z = 1.91 (*P* = 0.06)						



(B)

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Food dose progression per week						
Azzano 2021[5]	Food allergy		3.80	26.77	100.0%	3.80 [-48.67; 56.27]
Test for overall effect: Z = 0.14 (*P* = 0.89)						

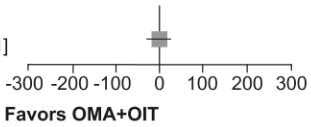


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(A)

Study or Subgroup	Population	Timepoint	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Omalizumab monthly dosage (mg/kg/IgE [IU/mL]), adjusted for weight and total IgE						
Azzano 2021[5]	Food allergy		-0.80	13.73	100.0%	-0.80 [-27.71; 26.11]

Test for overall effect: Z = -0.06 (*P* = 0.95)

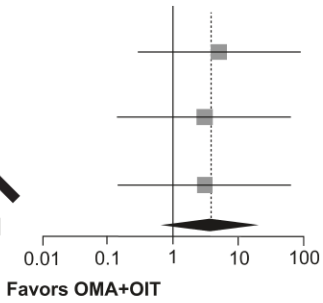


(B)

Study or Subgroup	Population	TimePoint	Experimental Event	Experimental Total	Control Event	Control Total	Weight	Risk Ratio MH, Random, 95% CI
Omalizumab every 8 weeks								
Hernández 2020[6]	CM allergy	20 months	2	7	0	7	36.0%	5.00 [0.29; 87.54]
Omalizumab every 7 weeks								
Hernández 2020[6]	CM allergy	20 months	1	7	0	7	32.0%	3.00 [0.14; 62.49]
Omalizumab every 5 weeks								
Hernández 2020[6]	CM allergy	20 months	1	7	0	7	32.0%	3.00 [0.14; 62.49]
Total (95% CI)							**100.0%**	**3.61 [0.65; 20.06]**

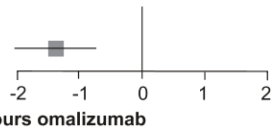
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.08$, df = 2 (*P* = 0.96); $I^2 = 0\%$

Test for overall effect: Z = 1.46 (*P* = 0.14)

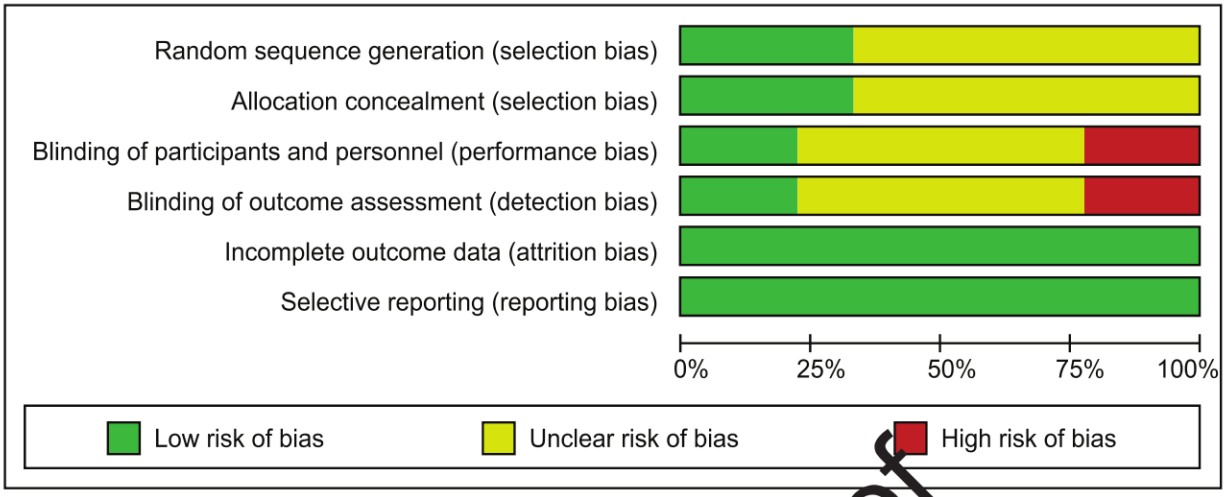


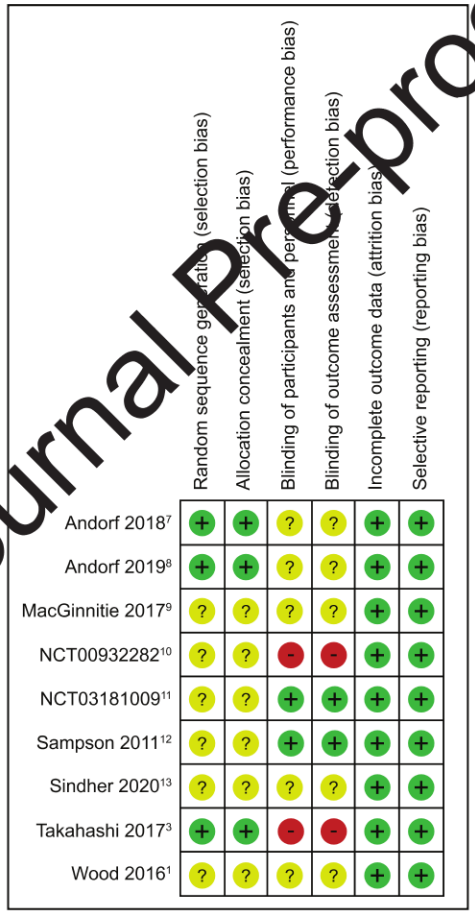
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Study or Subgroup	Population	Timepoint	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Risk score for patients (52-61 weeks)										
Yee 2019[14]	Peanut allergy	52-261 weeks	0.45	0.28	10	1.82	1.07	11	100.0%	-1.37 [-2.03; -0.71]
Test for overall effect: Z = -4.10 (P < 0.001)										



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Results

Sustained unresponsiveness

Patients with allergy to cow's milk (one study[1], n = 57) received OMA monotherapy for 17 weeks followed by OMA+OIT for 122 weeks and only OIT for the next 8 weeks. Assessment of data in a meta-analysis at 122 weeks and 139 weeks did not show significant changes in tolerance or successful desensitization (defined as a persistence of desensitization after discontinuation of treatment) with OMA+OIT vs placebo+OIT (RR: 0.34; *P* = 0.37, Figure E1).

Desensitization

A meta-analysis of data from one study[2] that assessed desensitization as a specified outcome showed that OMA+OIT did not aid in allergen desensitization in patients (n = 8) with severe allergic diseases vs pre-OMA at 16 weeks (RR: 5.00, *P* = 0.26, Figure E2A). However, meta-analysis of data from another RCT[3] at 32 weeks showed that OMA+OIT favored desensitization in patients with allergy to cow's milk (n = 16) vs placebo (RR: 13.00, *P* = 0.06, Figure E2B).

Food allergic reactions

In an analysis from one study,[4] OMA did not reduce the severity of grade 1 and grade 3 allergic reactions as measured using the Ewan scale at 52 weeks in patients with peanut allergy (n = 11) (RR: 1.32; *P* = 0.75, Figure E3) vs placebo.

Consumption of allergenic foods

A meta-analysis of data from a study[5] conducted in patients with multi-food allergy (n = 181) showed that OMA+OIT favored an increase in the rate of continued consumption of allergenic

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22 foods vs pre-OMA (MD: 90.30, $P = 0.06$, Figure E4A) at 104 weeks. Data from the same study
23 did not show a significant increase in food dose progression per week (MD: 3.80, $P = 0.89$,
24 Figure E4B).

25 **OMA dosages**

26 A meta-analysis of data from a study[5] conducted in patients with multi-food allergy (n = 181)
27 receiving OMA+OIT did not find a change in monthly OMA dosage (MD: −0.80, $P = 0.95$,
28 Figure E5A) vs pre-OMA. Another study[6] (n = 7) reported no significant increases in the interval
29 between OMA doses assessed over 20 months for patients with severe persistent cow's milk
30 allergy receiving OMA+OIT compared to pre-OMA (RR: 3.61, $P = 0.14$, Figure E5B).

31 **Risk score of severe adverse reactions**

32 The risk score of severe adverse reactions significantly decreased in patients (n = 13) with peanut
33 allergy receiving OMA vs pre-OMA over 52–261 weeks (MD: −1.37, $P < 0.001$, Figure E6).

34 **Risk of bias**

35 Of the 36 studies included, the risk of bias was identified in nine studies[1,3,7-13] based on the
36 assessment of random sequence generation, allocation concealment, blinding, incomplete
37 outcome reporting, and selective reporting (Figure E7). Bias was observed in selection,
38 performance, detection, attrition, and reporting of data. The risk of bias in RCTs (authors'
39 judgements), CCTs, and observational studies (using ROBINS-I scale) is presented in Tables
40 E4A and E4B, respectively.

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Figure Legends

Figure E1. Sustained unresponsiveness in patients with cow's milk receiving OMA+OIT vs placebo+OIT

CM, cow's milk allergy; OMA, omalizumab; OIT, oral immunotherapy

Figure E2. Desensitization with OMA+OIT in patients with (A) severe allergic disease vs. pre-OMA (B) allergy to cow's milk vs placebo

MH, Mantel–Haenszel; OMA, omalizumab; OIT, oral immunotherapy

Figure E3. Food allergic reactions in patients with peanut allergy receiving OMA vs placebo

MH, Mantel–Haenszel; OMA, omalizumab

Figure E4. Consumption of allergenic foods (A) and food dose progression per week (B) in patients with multi-food allergy receiving OMA+OIT vs pre-OMA

MD, mean difference; OMA, omalizumab; OIT, oral immunotherapy

Figure E5. Changes in monthly OMA dosage in patients with multi-food allergy (A) OMA dose intervals for patients with severe persistent cow's milk allergy (B) receiving OMA+OIT vs pre-OMA

CM, cow's milk; MD, mean difference; MH, MH, Mantel–Haenszel; OMA, omalizumab; OIT, oral immunotherapy

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Figure E6. Risk score of severe adverse reactions in patients with peanut allergy receiving OMA vs pre-OMA

Figure E7. Risk of bias identified in these meta-analysis

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Tables

Table E1. Details of studies included in the current meta-analysis categorized by the type of trial/study

Study (First author, year, country)	Type of allergy	Sample size (Male/ Female)	Mean age, years (SD)	Patients ≤18 years, n	Intervention	Comparator	Treatment duration	Study duration, weeks	Outcome measures
Randomized clinical trials									
Wood 2016, USA[1]	CM allergy	57 (40/17)	OMA, 11.7 (9.5–15.0); Placebo 9.5 (8.0–13.2)†	57	OMA + OIT	Placebo + OIT	122W (1–17W OMA [m] +17–122W OMA+OIT); 8W OIT (122–130W)	139W	Primary outcome: OFC; secondary outcomes: antigen-specific IgE, serum antigen-specific IgG4, ADRs
Takahashi 2017, Japan[3]	CM allergy	16 (11/5)	OMA, 9.5 (8.3–10); Placebo, 9.5 (7.5–10.8)‡	16	OMA + OIT	Placebo	24W (1–8W OMA [m] +8–24W OMA+OIT) 8W (OIT 24–32W)	32W	Primary outcome: OFC; secondary outcomes: total serum IgE levels, antigen-specific IgE, antigen-specific IgG4, SPT

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Andorf, 2018, USA[7]	Multiple FA	48 (24/24)	OMA, 8 (7–1.3); Placebo, 7 (6.0–8.0)†	48	OMA + OIT	Placebo	16W (1–8W OMA [m]); 8–16W (OMA+OIT)	36W	Primary outcome: OFC; Secondary outcomes: ADEs
Andorf 2019, USA[8]	Multiple FA	60 (37/23)	1 g group, 9.1 (2.4); 300 mg group 10.0 (4.0); Placebo group, 10.3 (3.6)	NR	OMA + OIT	Placebo	16W (1–8W OMA[m]; 8–16W OMA+OIT) 17–30W (OIT)	36W	Primary outcome: OFC; secondary outcomes: ADEs
MacGinnitie 2017, USA[9]	Peanut allergy	37 (22/15)	OMA, 10 (7–19); Placebo 10 (6–17)†	NR	OMA + OIT	Placebo + OIT	19W (1–12W OMA [m] + 12–19W OMA+OIT)	139W	Outcomes: OFC, serious and non-serious ADEs
NCT00932282, USA[10]	Peanut allergy	13 (7/6)	52W OIT, 14.4 (12.6–19.9); 104W OIT 14.1	12	OMA + 52W OIT	OMA + 104W OIT	43W (17W OMA [m] + 52W/104W OIT)	156W	Primary outcome: OFC; Secondary outcomes: serious and non-serious ADEs

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			(12.6–16.1)]‡						
NCT03181009, USA[11]	Multiple FA	60 (NR)	300 mg group, 10 (4–20); 1200 mg group, 10 (4–17)‡	NR	OMA + Food flour (300 mg)	OMA + Food flour (1200 mg)	8W OMA (m) +18W OIT	26W	Outcomes: total serum IgE levels, serious and non-serious ADEs
Sampson 2011, USA[12]	Peanut allergy	14 (8/6)	OMA, 26.6 (22.5); Placebo, 16.3 (11.1)	7	OMA	Placebo	22W OMA (m)	24W	Outcomes: OFC, ADEs
Sindher 2020, USA[13]	Multiple FA	NR	NR	NR	OMA + mOIT (300 mg)	OMA + mOIT (1200 mg)	31W (13W OMA + 18W mOIT)	18W	Outcomes: Peanut sIgG4/sIgE ratio and AEs
CCTs: Controlled clinical trials									
NCT00382148, USA[4]	Peanut allergy	11 (7/4)	OMA, 17.3 (8.9); Placebo, 32.0 (23.5)	10	OMA (OMA in Q2788 g)	OMA (Placebo in Q2788 g)	52W OMA (m)	52W	Primary outcome: serious ADEs; secondary outcomes: non-serious ADEs, allergic reactions, Ewan scale

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Yee 2019, USA[14]	Peanut allergy	13 (8/5)	8–15*	13	OMA + OIT	Pre-OMA	22 W (1–12W OMA [m]; 13-22W OMA+OIT) 21–317W OIT	317W	Outcomes: OFC, total serum IgE levels, SPT, antigen-specific IgE, antigen-specific IgG4 levels, patients' QoL
Peloche 2011, Spain[15]	CM & egg allergy	7 (NR)	≥ 6*	7	OMA	Pre-OMA	16W OMA (m)	16W	Outcomes: OFC, ADEs
Bedoret 2012, USA[16]	CM allergy	11 (7/4)	8 (7–17)‡	10	OMA + OIT	Pre-OMA	16W (1–9W OMA [m] +9–16W OMA+OIT); 17–52	52W	Outcomes: OFC, SPT
Mehrotra 2012, USA[17]	Multiple FA	41 (NR)	5–25*	7	OMA + OIT	OIT	15W (1–9W OMA [m] +9–15W OMA+OIT)	28W	Outcome: serious ADEs
Savage 2012, USA[18]	Peanut allergy	14 (3/11)	23 (18–44) ‡	NR	OMA	Pre-OMA	26W OMA(m)	26W	Outcomes: OFC, total serum IgE levels, antigen-specific IgE levels, SPT

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Dominguez 2013, USA[19]	Multiple FA	27 (NR)	8 (4–17)‡	27	OMA + OIT	Pre-OMA	9W OMA (m) +12W OIT	23W	Outcome: OFC
Schneider 2013, USA[20]	Peanut allergy	13 (8/5)	16 (7–15)‡	13	OMA + OIT	Pre-OMA	20W (1–12W OMA [m] +12–20W OMA+OIT)	32W	Outcome: OFC
Bégin 2014, USA[21]	Multiple FA	25 (19/6)	7.4 (4.5–15.4)‡	NR	OMA + OIT	Pre-OMA	16W (1–8W OMA [m] +9–16W OMA+OIT)	16W	Outcomes: antigen-specific IgE levels, antigen-specific IgG4 levels, SPT
Loizou 2015, USA[22]	FA with eosinophilic esophagitis	15 (11/4)	12–71*	15	OMA	Pre-OMA	12W OMA (m)	12W	Outcome: antigen-specific IgE levels
Pajno 2015, Italy[23]	CM allergy	3 (NR)	9, 11, 12 years	51	OMA + OIT	Pre-OMA	10W (1–10W OMA [m] +OIT NR)	NR	Outcome: OFC
Salguero 2016, Spain[24]	CM & egg allergy	70 (NR)	NR	70	OMA + OIT	Pre-OMA	NR	NR	Outcome: OFC, ADEs

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Arasi 2017, Italy[25]	CM allergy with asthma	6 (4/2)	9.8 (2.31)	6	OMA + OIT	Pre-OMA	16W (1–8W OMA [m] +8–16W OMA+OIT)	16W	Outcomes: OFC, serious and non-serious ADEs
Brandstrom 2017, Sweden[26]	Peanut allergy	23 (7/15)	12–19*	NR	OMA + OIT	Pre-OMA	32W (8–24W OMA [m]; 8–32W OMA+OIT)	32W	Outcome: OFC
Mennini 2017, Italy[27]	Multiple FA with Asthma	6 (5/1)	6.98 (1.78 –17.12)‡	6	OMA	Pre-OMA	8W OMA (m)	8–16 W	Outcome: OFC
Demir 2018, Turkey[28]	CM allergy with asthma	7 (NR)	4–19*	NR	OMA + OIT	Pre-OMA	NR	NR	Outcomes: OFC
Ruano 2019, Spain[29]	CM allergy with asthma	5 (NR)	8 (6–9)§	5	OMA + OIT	OIT	16W OMA (m) + OIT (NR)	NR	Outcome: ADEs
Sindher 2019, USA[30]	Multiple FA	41 (NR)	7–18*	41	OMA + OIT	Low dose group (< 0.016 mg/kg/ IU/mL)	16W +NR	NR	Outcome: ADEs

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Gernez 2011, USA[31]	Nut allergy	16 (8/8)	NR	13	OMA	Pre-OMA	8W OMA (m)	8W	Outcome: Decrease in free IgE (kU/L)
Observational studies									
Crisafulli 2019, Italy[2]	CM allergy with severe allergic diseases	8 (NR)	7–15*	8	OMA + OIT	Pre-OMA	16–104W (OMA+OIT)	NR	Outcomes: OFC
Azzano 2021, Canada[5]	FA	181 (120/61)	9.4 (5.2–13.9)†	61	OMA + OIT	Pre-OMA	9W OMA +NR	104W	Outcome: Rate of continued consumption of allergens, food dose progression per week, tolerated dose, AEs
Hernández 2020, Spain[6]	Severe persistent CM allergy	7 (2/5)	16 (15–19)‡	NR	OMA + OIT	Pre-OMA	17W OMA +NR	87W	Outcome: Desensitization, OMA dosage
Rafi 2010, USA[32]	Multiple FA with asthma	22 (9/13)	38 (4–66)§	5	OMA	Pre-OMA	52W OMA (m)	52W	Outcome: free from symptoms
Lefèvre 2016, France[33]	Multiple FA	8 (NR)	11.6 (3.3)	8	OMA	Pre-OMA	13–22W OMA (m)	13–22W	Outcome: OFC

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Sousa 2020, Brazil[34]	Severe CM allergy	NR	5.9**	11	OMA + OIT	Pre-OMA	NR	NR	Outcomes: Desensitization and adverse reactions
Alba Jordá 2019, Spain[35]	FA	6 (1/5)	38.3	NR	OMA	Pre-OMA	16W OMA (m)	16W	Outcomes: OFC, mild symptoms during OFC
Fiocchi 2019, Italy[36]	FA	15 (12/3)	144 (96–276)‡ (in months)	13	OMA	Pre-OMA	17W OMA (m)	17W	Outcome: Food tolerance threshold, PedsQL, and AEs

*ADEs: adverse drug events; ADRs: adverse drug reactions; AEs: adverse events; CM: cow's milk; FA: food allergy; IgE: immunoglobulin E; IgG4: immunoglobulin G4; NR: not reported; OFC: oral food challenge; OIT: oral immunotherapy; OMA: omalizumab; OMA (m): omalizumab monotherapy; PedsQoL: pediatric quality of life; QoL: quality of life; SPT: skin prick test; §: mean (range); ‡: median (full range); †: median (interquartile range); *: range*

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Table E2. Assessment of immunological parameters in patients with IgE-mediated food allergy

Food (allergen)	Assessment time points	Intervention (OMA or OMA+OIT)	Comparator	Mean difference, IV, random, 95% CI	*P*-value
Specific IgE levels					
Cow's milk, casein, α-lact, and β-lact[1,3]	32–165 weeks	OMA+OIT	Placebo/placebo+OIT	20.13 (1.94; 38.32)	0.35
Peanuts[14,18,21]	26–317 weeks	OMA and/or OMA+OIT	Pre-OMA	−39.48 (−111.27; 32.31)	0.28
IgG4 levels					
Cow's milk, casein, α-lact, and β-lact[1,3]	32–165 weeks	OMA+OIT	Placebo/placebo+OIT	20.29 (5.99; 34.59)	0.005
Peanuts[14,21]	52–317 weeks	OMA+OIT	Pre-OMA	24.50 (−17.32; 66.33)	0.25
Ratio of specific IgE to IgG4					
Peanuts[14]	52–317 weeks	OMA+OIT	Pre-OMA	−0.28 (−0.54; −0.01)	0.04
Total IgE levels					
Cow's milk[3]	32 weeks	OMA+OIT	Placebo	296.25 (−590.51; 1183.01)	0.51

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Peanuts[14,18]	26–317 weeks	OMA and/or OMA+OIT	Pre-OMA	−89.39 (−279.92; 101.14)	0.36
Multifoods[11]	32 weeks	OMA+OIT	Pre-OMA	−160.00 (−855.53; 535.53)	0.65
Responses in SPT					
Cow's milk[3]	32 weeks	OMA+OIT	Placebo	−1.43 [−4.36; 1.49]	0.34
Cow's milk, cashew, ovalbumin[16]	52 weeks	OMA+OIT	Pre-OMA	13.22 [1.89; 92.56]^	0.009
Peanuts[14,18,21]	26–317 weeks	OMA+OIT	Pre-OMA	−4.32 (−5.50; −3.14)	<0.001

α-lact, alpha-lact-albumin, β-lact, beta-lactoglobulin; CI: confidence intervals; IgE, immunoglobulin E; IgG4, immunoglobulin G4; IV, inverse variance; OIT, oral immunotherapy; OMA, omalizumab; SPT, skin prick test.

^Risk ratio, Mantel-Haenszel, Random, 95% CI

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Table E3. Adverse events reported in the studies included in the meta-analysis

Outcome	Variable	Allergen (s)	Studies	Risk Ratio (95% CI)	*P*-value
Any Adverse Events (52 weeks)	Any	Peanuts	MacGinnitie 2017[9]	0.89 (0.79, 1.01)	NS
Any Adverse Events (8 to 16 weeks)	Any	Multifoods	Andorf 2019[8], Andorf 2018[7]	0.99 (0.88, 1.11)	NS
Any Adverse Events (17 to 29 weeks)	Any	Multifoods	Andorf 2019[8]	0.82 (0.62, 0.99)	**0.04**
Any Adverse Events (30 to 36 weeks)	Any	Multifoods	Andorf 2019[8]	1.25 (0.76, 2.06)	NS
Any Adverse Events (17 to 24 weeks)	Any	Multifoods	Andorf 2018[7]	2.75 (1.23, 6.16)	**0.01**
Any Adverse Events (25 to 36 weeks)	Any	Multifoods	Andorf 2018[7]	2.75 (1.23, 6.16)	**0.01**
Any Adverse Events (52/104 weeks)	Any	Peanuts	NCT00932282[10]	1.14 (0.41, 3.19)	NS
Any Adverse Events (52 weeks)	Any	Peanuts	NCT00382148[4]	1.14 (0.6, 2.17)	NS
Any Serious Adverse Events (52 weeks)	Any	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS

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Any Serious Adverse events (28 weeks)	Any	Multifoods	Mehrotra 2012[17]	0.52 (0.04, 7.68)	NS
Any Serious Adverse Events (52 weeks)	Any	Peanuts	MacGinnitie 2017[9]	0.38 (0.11, 1.36)	NS
Mild Adverse Events	NR	Cow's Milk	Arasi 2017[25]	5.00 (0.29, 85.16)	NS
Mild Adverse Events (8 to 16 weeks)	Grade 1*	Multifoods	Andorf 2019[8]	0.93 (0.64, 1.24)	NS
Mild Adverse Events (17 to 29 weeks)	Grade 1*	Multifoods	Andorf 2019[8]	0.85 (0.65, 1.11)	NS
Mild Adverse Events (30 to 36 weeks)	Grade 1*	Multifoods	Andorf 2019[8]	1.06 (0.59, 1.89)	NS
Mild Adverse Events (16 weeks)	Grade 1*	Peanuts	MacGinnitie 2017[9]	0.79 (0.58, 1.09)	NS
Mild Adverse Events (52 weeks)	Grade 1*	Peanuts	MacGinnitie 2017[9]	5.61 (1.47, 21.47)	**0.01**
Mild Adverse Events (24 weeks)	Grade 1*	Peanuts	Sampson 2011[12]	2.89 (0.17, 49.99)	NS

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Moderate Adverse Events (8 to 16 weeks)	Grade 2*	Multifoods	Andorf 2019[8]	1.00 (0.52, 1.93)	NS
Moderate Adverse Events (17 to 29 weeks)	Grade 2*	Multifoods	Andorf 2019[8]	0.95 (0.58, 1.56)	NS
Moderate Adverse Events (30 to 36 weeks)	Grade 2*	Multifoods	Andorf 2019[8]	1.88 (0.72, 4.91)	NS
Moderate Adverse Events (16 weeks)	Grade 2*	Peanuts	MacGinnitie 2017[9]	0.17 (0.07, 0.41)	**<0.001**
Moderate Adverse Events (52 weeks)	Grade 2*	Peanuts	MacGinnitie 2017[9]	2.11 (0.52, 8.63)	NS
Mild to Moderate Adverse Events (24 weeks)	NR	Peanuts	Sampson 2011[12]	0.97 (0.56, 1.7)	NS
Serious Adverse Events (17 to 29 weeks)	Grade 3*	Multifoods	Andorf 2019[8]	1.52 (0.06, 35.66)	NS
Serious Adverse Events (52 weeks)	Grade 3*	Peanuts	MacGinnitie 2017[9]	0.89 (0.04, 20.01)	NS

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Gastrointestinal disorders (≤139 weeks)	Abdominal pain, diarrhoea, vomiting	Peanuts, Cow's Milk	MacGinnitie 2017[9], Wood 2016[1]	1.33 (0.45, 3.96)	NS
Gastrointestinal disorders (52 weeks)	Vomiting	Peanuts	MacGinnitie 2017[9]	0.06 (0.00, 1.13)	NS
Gastrointestinal disorders (52/104 weeks)	Vomiting, abdominal pain		NCT00932282[10]	1.08 (0.37, 3.15)	NS
Gastrointestinal disorders (52/104 weeks)	Vomiting, abdominal pain	Peanuts	NCT00932282[10]	1.08 (0.37, 3.15)	NS
Gastrointestinal disorders (52/104 weeks)	Oropharyngeal itching	Peanuts	NCT00932282[10]	1.29 (0.31, 5.31)	NS
Gastrointestinal disorders (139 weeks)	Abdominal discomfort, abdominal distention, dyspepsia,	Cow's Milk	Wood 2016[1]	0.60 (0.46, 0.79)	**<0.001**

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	dysphagia, oral disorder, oropharyngeal discomfort, oropharyngeal pain				
Gastrointestinal disorders (0 weeks)	Abdomen-related symptoms	Peanuts	Sampson 2011[12]	1.00 (0.74, 1.36)	NS
Gastrointestinal disorders (24 weeks)	Abdomen-related symptoms	Peanuts	Sampson 2011[12]	0.56 (0.24, 1.30)	NS
Gastrointestinal disorders (≤139 weeks)	Nausea	Peanuts, Cow's Milk	MacGinnitie 2017[9], Wood 2016[1]	0.78 (0.18, 3.44)	NS
Gastrointestinal disorders (52 weeks)	Abdominal pain, diarrhoea, vomiting	Peanuts	NCT00382148[4]	2.57 (0.49, 13.36)	NS

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Gastrointestinal disorders (52 weeks)	Nausea, oral pruritis	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Skin and subcutaneous tissue disorders (≤139 weeks)	Maculopapular rash	Peanuts	MacGinnitie 2017[9]	2.09 (0.12, 36.55)	NS
Skin and subcutaneous tissue disorders (52/104 weeks)	Erythematous rash	Peanuts	NCT00932282[10]	0.29 (0.01, 5.94)	NS
Skin and subcutaneous tissue disorders (≤139 weeks)	Pruritis, urticaria	Peanuts, Cow's Milk	MacGinnitie 2017[9], Wood 2016[1]	0.73 (0.15, 3.42)	NS
Skin and subcutaneous tissue disorders (≤139 weeks)	Urticaria, eczema, rash	Peanuts, Cow's Milk	MacGinnitie 2017[9], Wood 2016[1]	0.75 (0.09, 6.36)	NS
Skin and subcutaneous tissue disorders (52/104 weeks)	Itch	Peanuts	NCT00932282[10]	1.71 (0.20, 4.55)	NS
Skin and subcutaneous tissue disorders (139 weeks)	Furuncle, impetigo	Cow's Milk	Wood 2016[1]	6.15 (0.76, 49.68)	NS

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Skin and subcutaneous tissue disorders (24 weeks)	Skin-related symptoms	Peanuts	Sampson 2011[12]	1.39 (0.41, 0.72)	NS
Skin and subcutaneous tissue disorders (0 weeks)	Skin-related symptoms	Peanuts	Sampson 2011[12]	4.05 (0.25, 64.73)	NS
Skin and subcutaneous tissue disorders (52 weeks)	Pruritis	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Respiratory, thoracic, and mediastinal disorders (≤139 weeks)	Cough, nasopharyngitis	Peanuts, Cow's Milk	MacGinnitie 2017[9], Wood 2016[1]	1.28 (0.56, 2.93)	NS
Respiratory, thoracic and mediastinal disorders (52/104 weeks)	Cough	Peanuts	NCT00932282[10]	0.29 (0.01, 5.94)	NS
Respiratory, thoracic, and mediastinal disorders (≤139 weeks)	Allergic rhinitis, asthma, nasal/sinus congestion, sneezing, throat	Peanuts, Cow's Milk	MacGinnitie 2017[9], Wood 2016[1]	0.37 (0.24, 0.57)	**<0.001**

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	tightness, upper respiratory tract congestion, wheezing				
Respiratory, thoracic, and mediastinal disorders (139 weeks)	Influenza	Cow's Milk	Wood 2016[1]	0.30 (0.07, 1.30)	NS
Respiratory, thoracic, and mediastinal disorders (0 weeks)	Nasal-related symptoms	Peanuts	Sampson 2011[12]	0.83 (0.20, 3.44)	NS
Respiratory, thoracic, and mediastinal disorders (24 weeks)	Nasal-related symptoms	Peanuts	Sampson 2011[12]	1.11 (0.13, 4.07)	NS
Respiratory, thoracic, and mediastinal disorders (52/104 weeks)	Wheezing	Peanuts	NCT00932282[10]	0.86 (0.07, 10.96)	NS
Respiratory, thoracic, and mediastinal disorders (52 weeks)	Asthma, rhinorrhoea, nasal congestion, allergic rhinitis	Peanuts	NCT00382148[4]	1.41 (0.33, 5.97)	NS

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Respiratory, thoracic, and mediastinal disorders (52 weeks)	Throat irritation	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Infections and infestations (139 weeks)	Psychiatric	Peanuts	MacGinnitie 2017[9]	0.89 (0.04, 20.01)	NS
Infections and infestations (139 weeks)	Gastroenteritis	Cow's Milk	Wood 2016[1]	0.21 (0.01, 5.94)	NS
Infections and infestations ($\leq$139 weeks)	Sore throat, URTI, ear infection, viral gastroenteritis, otitis media, streptococcal pharyngitis	Peanuts, Cow's Milk	MacGinnitie 2017[9], Wood 2016[1]	1.05 (0.70, 1.55)	NS
General disorders and administration-site conditions (139 weeks)	Chest pain	Cow's Milk	Wood 2016[1]	0.52 (0.10, 2.60)	NS

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General disorders and administration-site conditions (139 weeks)	Chest discomfort, sensation of foreign body	Cow's Milk	Wood 2016[1]	0.20 (0.07, 0.56)	**0.002**
General disorders and administration-site conditions (≤139 weeks)	Pyrexia, influenza-like illness, pain, feeling abnormal	Peanuts, Cow's Milk	MacGinnitie 2017[9], Wood 2016[1]	0.72 (0.34, 1.52)	NS
General disorders and administration-site conditions (0 weeks)	Chest-related symptoms	Peanuts	Sampson 2011[12]	0.19 (0.01, 2.97)	NS
General disorders and administration-site conditions (24 weeks)	Chest-related symptoms	Peanuts	Sampson 2011[12]	1.11 (0.13, 9.42)	NS
Immune system disorders (52/104 weeks)	Hives	Peanuts	NCT00932282[10]	1.71 (0.20, 14.55)	NS
Immune system disorders (52 weeks)	Anaphylaxis	Peanuts	MacGinnitie 2017[9]	0.29 (0.07, 1.15)	**0.01**

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Immune system disorders (≤32 weeks)	Anaphylaxis	Cow's Milk, eggs, peanuts	Salguero 2017[24], Schneider 2013[20]	0.37 (0.00, 67.25)	NS
Immune system disorders (≤139 weeks)	Anaphylaxis	Peanuts, Cow's Milk	MacGinnitie 2017[3], Wood 2016[1]	0.78 (0.13, 4.88)	NS
Immune system disorders (16 weeks)	Anaphylaxis	Cow's Milk	Ruano 2019[29]	0.09 (0.01, 1.28)	NS
Immune system disorders	Anaphylaxis	Cow's Milk	Arasi 2017[25]	5.00 (0.29, 85.16)	NS
Immune system disorders (32 weeks)	Allergic reaction	Peanuts	Schneider 2013[20]	21.00 (1.36, 323.57)	**0.03**
Immune system disorders (52 weeks)	Lip swelling	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Musculoskeletal and connective tissue disorders (52 weeks)	Arthralgia	Peanuts	NCT00382148[4]	0.20 (0.01, 3.94)	NS
Respiratory, thoracic and mediastinal disorders (52 weeks)	Cough	Peanuts	NCT00382148[4]	4.20 (0.28, 63.95)	NS

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Respiratory, thoracic and mediastinal disorders (52 weeks)	Nasopharyngitis	Peanuts	NCT00382148[4]	3.00 (0.18, 49.45)	NS
Respiratory, thoracic, and mediastinal disorders (52 weeks)	Laryngitis	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Skin and subcutaneous tissue disorders (52 weeks)	Eczema, rash	Peanuts	NCT00382148[4]	0.91 (0.14, 6.17)	NS
Infections and infestations (≤139 weeks)	Gastroenteritis	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Infections and infestations (52 weeks)	URTI		NCT00382148[4]	0.20 (0.01, 3.94)	NS
Infections and infestations (52 weeks)	Localized infection, otitis media	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Nervous system disorders (52 weeks)	Dizziness, headache, hypoesthesia, loss of consciousness,	Peanuts	NCT00382148[4]	1.80 (0.53, 6.08)	NS

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	migraine, motion sickness				
Nervous system disorders (139 weeks)	Dizziness	Cow's Milk	Wood 2016[1]	0.21 (0.01, 4.13)	NS
Nervous system disorders (52 weeks)	Pharyngolaryngeal pain	Peanuts	NCT00382148[4]	3.00 (0.18, 49.45)	NS
Injury, poisoning, and procedural complications (52 weeks)	Injection-site bruising	Peanuts	NCT00382148[4]	0.57 (0.05, 6.86)	NS
Injury, poisoning, and procedural complications (52 weeks)	Overdose	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Ear and labyrinth disorders (52 weeks)	Tinnitus	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Ear and labyrinth disorders (139 weeks)	Pruritis	Cow's Milk	Wood 2016[1]	0.35 (0.04, 3.12)	NS
Eye disorders (139 weeks)	Conjunctivitis	Cow's Milk	Wood 2016[1]	5.18 (0.26, 103.17)	NS

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Eye disorders (139 weeks)	Ocular hyperemia		Wood 2016[1]	0.52 (0.05, 5.39)	NS
Psychiatric disorders (52 weeks)	Depression	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Psychiatric disorders (52 weeks)	Abscess	Cow's Milk	Wood 2016[1]	3.11 (0.13, 73.12)	NS
General disorders and administration-site conditions (52 weeks)	Fatigue, pyrexia	Peanuts	NCT00382148[4]	2.36 (0.31, 18.18)	NS
Spleen, lymphatic, and reticuloendothelial system disorders (52 weeks)	Lymphadenopathy	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Endocrine disorders (52 weeks)	Irregular menstruation	Peanuts	NCT00382148[4]	0.20 (0.01, 3.94)	NS
Metabolism and nutrition disorders (52 weeks)	Anorexia	Peanuts	NCT00382148[4]	1.80 (0.09, 35.42)	NS
Vascular disorders (139 weeks)	Flushing	Cow's Milk	Wood 2016[1]	0.26 (0.10, 0.68)	**<0.01**
Ocular infections, irritations, and inflammations (139 weeks)	Pruritis	Cow's Milk	Wood 2016[1]	0.52 (0.14, 1.87)	NS

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Communication disorders, and disturbances (139 weeks)	Dysphonia	Cow's Milk	Wood 2016[1]	0.21 (0.01, 4.13)	NS

**Grade indicates the severity level as per Bock criteria. NS, not significant*

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Table E4A. Author's judgments on risk of bias in the randomized clinical trials included in the current meta-analysis (n = 9)[37]

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Wood 2016[1]	**Unclear Risk** Subjects were randomized 1:1 to receive OMA or placebo. The method of randomization was not reported	**Unclear Risk** Allocation was not described	**Unclear Risk** Double-blind + Open-label OMA/placebo was unblinded after 1 year of OIT	**Unclear Risk** Double-blind + Open-label	**Low Risk** A total of 7 subjects withdrew from the study: 2 OMA-treated, 1 did not want injections, 1 participant decision, and in placebo 5 subjects – 1 due to family emergency, 3	**Low Risk** All prespecified outcomes reported

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					due to dosing reactions	
Takahashi 2017[3]	**Low Risk** Eligible participants were randomly assigned 3:1 to receive OMA + OIT and untreated group. Simple computerized randomization was carried out	**Low Risk** Allocation was sequentially numbered, opaque sealed envelopes by a hospital nurse	**High Risk** Placebo controls were not blinded. It was reported as trial was not blinded	**High Risk** Placebo controls were not blinded. It was reported as trial was not blinded	**Low Risk** No patient was withdrawn after the randomization from the study	**Low Risk** All prespecified outcomes reported
Andorf 2018[7]	**Low Risk**	**Low Risk** Randomization	**Unclear Risk**	**Unclear Risk**	**Low Risk**	**Low Risk**

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	Eligible participants were randomly assigned 3:1 to OMA or placebo, using a computer and 4×4 block randomization	was stratified by sex and prepared by a blinded biostatistician	Double-blind + Open-label	Double-blind + Open-label	No one dropped out of the study; there were only treatment failures which went through the open-label study	All prespecified outcomes reported
Andorf 2019[8]	**Low Risk** Eligible patients were randomized. Randomization was carried out as 1:1:1 to 1-g,	**Low Risk** Randomization was stratified by site and prepared by a blinded statistician, but	**Unclear Risk** Open-label + Randomized double-blind	**Unclear Risk** Open-label + Randomized double-blind	**Low Risk** During the open-label phase, 10 were out of the study: 4 due to withdrawal of consents, 1 non-compliant with	**Low Risk** All prespecified outcomes reported

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	300-mg, or 0-mg arm using a computer and block randomization	only after they were confirmed to be eligible for Week 30 food challenge			reaction medications, 5 desensitization failures. During randomization phase, a total of 7 were out of the study. In 1-g arm: 1 due to non-compliance, 1 due to withdrawal of consent; 1 from 300-mg arm due to withdrawal of consent, 2 in 20-mg arm due to	

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					withdrawal of consent, and 2 due to non-compliance with reaction medications were out of the study. Blinded discontinuation arm was followed up for efficacy and safety outcomes.	
MacGinnitie 2017[9]	**Unclear Risk** Patients were randomized in a 3.5:1 ratio to receive OMA (n =29) or placebo	**Unclear Risk** Allocation was not described	**Unclear Risk** Double-blind + Open-label	**Unclear Risk** Double blind + Open-label	**Low Risk** Total of 2 participants from the OMA group withdrew: 1 before commencing OMA	**Low Risk** All prespecified outcomes reported

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	(n = 8) in conjunction with peanut OIT. The method of randomization was not given				therapy and 1 before OIT due to eating disorder judged to be unrelated to the study drug, and zero participants withdrew from the placebo group	
NCT00932282[10]	**Unclear Risk** Subjects were randomized to receive OMA and peanut OIT. The method of randomization was not reported	**Unclear Risk** Allocation was not described	**High Risk** Masking was none (Open-label)	**High Risk** Masking was none (Open label)	**Low Risk** There were no dropouts and 13 subjects had efficacy and safety outcomes	**Low Risk** All prespecified outcomes reported

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NCT03181009[11]	**Unclear Risk** Subjects were randomized 1:1 to either group A or group B along with OMA The method of randomization was not reported	**Unclear Risk** Allocation was not described	**Low Risk** All subjects and study personnel will be blinded to group A vs. B	**Low Risk** Double-blind	**Low Risk** There were no dropouts and 60 subjects had efficacy and safety outcomes	**High Risk** Prespecified outcomes were "Change in Allergen-specific serum IgG4 and IgE," but only serum IgE was reported
Sampson 2011[12]	**Unclear Risk** Subjects were randomized 2:1 to receive OMA	**Unclear Risk** Allocation was not described	**Low Risk** Double-blind	**Low Risk** Double-blind	**Low Risk** There were no dropouts and only 14 subjects reached the	**Low Risk** All prespecified

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	or placebo to double-blind treatment. The method of randomization was not reported				study's primary endpoint before the discontinuation of the trial	outcomes reported
Sindher 2020[13]	**Unclear Risk** Randomized 1:1 to receive individualized mOIT containing 2–5 allergens and escalate to a maintenance dose of either 300 mg (Group	**Unclear Risk** Allocation was not described	**Unclear Risk** No information reported on blinding on participants	**Unclear Risk** No information reported on blinding of outcome assessors	**Low Risk** There were no dropouts	**Low Risk** All prespecified outcomes reported

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	A) or 1200 mg (Group B) of total food protein. The method of randomization was not reported					

IgE, immunoglobulin E; IgG, immunoglobulin G; OIT, oral immunotherapy; OMA, omalizumab

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Table E4B. Risk of bias in the CCTs and observational studies using ROBINS-I scale included in the current meta-analysis[38]

Study	Domain						
	Bias due to judgment confounding	**Bias in selection of participants**	**Bias in measurement of interventions**	**Bias due to departures from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of reported results**
Crisafulli 2019[2]	**No Information** No information on whether confounding is present	**No Information** No information is reported about selection of participants into the study	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No Information** No information is reported about the methods of	**Low Risk** All prespecified outcomes were reported

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						outcome assessment	
NCT00382148[4]	**No Information** No information on whether confounding is present	**No Information** No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide.	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**Moderate Risk** Open label	**Low Risk** All prespecified outcomes were reported
Azzano 2021[5]	**Moderate Risk** Omalizumab dosage adjusted for both weight and IgE and dosage	**Low Risk** Patients with either recent IgE-mediated reaction to their food allergen(s) or allergy test results	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** Dropouts are clearly reported. Three discontinued	**No information** No information is reported	**Low Risk** All prespecified outcomes were reported

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	adjusted for weight alone	higher than the 95% positive predictive value for IgE-mediated allergy			OIT and 2 switched to dupilumab, 1 terminated by physician due to poor observance, 1 discontinued due to food aversion, 1 for logistical considerations	about the methods of outcome assessment	

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Hernández 2020[6]	**No Information** No information on whether confounding is present	**Low Risk** Patients with a diagnosis of CMA from childhood who had SPT positive to cow's milk (9 mm; median) and casein (11 mm; median); specific IgE for casein and cow's milk was >100 kU/L.	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No information** No information is reported about the methods of outcome assessment	**Low Risk** All prespecified outcomes were reported
Yee 2019[14]	**No Information** No information on whether	**Low Risk** Patients with positive peanut skin prick test, peanut IgE ≥20 kU/L, and reactivity to ≤50-	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** One patient withdrew because of persistent	**Moderate Risk** Open label	**Low Risk** All prespecified outcomes were reported

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	confounding is present	mg peanut protein on entry DBPCFC			nausea and vomiting, and 1 patient experienced 2 allergic reactions so stopped intake of peanut but agreed to participate in the LTFU study		
Peloche 2011[15]	**No information** No information on whether	**Moderate Risk** Patients suffered with milk and egg allergy; 5	**Low Risk**	**Low Risk** Single-arm study	**Moderate Risk**	**Moderate Risk**	**Moderate Risk**

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	confounding might be present	patients had a positive SBFC at baseline and 2 had a previous history of food transgressions with reactions in last 6 months	Intervention status is well defined		One patient rejected SBFC out of 7	Masking was none (Open-label)	SPT and SBFC were performed in which SBFC was only reported
Bedoret 2012[16]	**No Information** No information on whether confounding might be present	**Moderate Risk** Patients with history of significant IgE-mediated milk allergy were enrolled. Ten of 11 subjects had a past or current history of eczema, asthma, or both, 10 had a history of at least 1 other food	**Low Risk** Intervention status is well defined	**Low Risk** Single-arm study	**Low Risk** One subject voluntarily discontinued the study after the 5th oral dose due to vomiting, later diagnosed as	**Moderate Risk** Open-label	**Low Risk** All prespecified outcomes were reported

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		allergy, and 6 had 2 or more additional food allergies			abdominal migraines		
Mehrotra 2012[17]	**No Information** No information on whether confounding might be present	**Low Risk** Patients with positive DBPCFC with positive skin prick test and/or positive food specific IgE >7kU/L	**Low Risk** Intervention status is well defined	**Low Risk** Co-intervention s were balanced across intervention groups, and there were no deviations from the intended	**Low Risk** There were no dropouts	**No information** No information is reported about the methods of outcome assessment	**Moderate Risk** Safety outcomes were reported; patients reaching 4000 mg of each allergen were not reported

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				interventions			
Savage 2012[18]	**Low Risk** Basophil hyporesponsiveness to allergen assessed either as complete suppression of reactivity or as a shift in allergen sensitivity might be an indicator of the	**Low risk** Patients with clinical history of early-onset peanut allergy, serum total IgE level of 30 to 700 IU/mL, weight within the dosing guidelines for OMA. Peanut-specific IgE level of >0.35 IU/mL, and peanut skin prick test wheal size of 3 mm greater than that	**Low Risk** Intervention status is well defined	**Low Risk** Single-arm study	**Low Risk** No missing data	**Moderate Risk** Open-label	**Low risk** All prespecified outcomes were reported

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	changing threshold in the OFCs	elicited by the saline control					
Dominguez 2013[19]	**No Information** No information on whether confounding might be present	**Moderate Risk** Patients with either peanut and/or egg and/or milk and/or tree nut and/or seed through skin prick test, allergen-specific IgE levels were selected	**Moderate Risk** Intervention status is defined clearly but some aspects of the intervention were not clear due to the presented single-arm	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No Information** No information is reported about the methods of outcome assessment	**Low Risk** All prespecified outcomes were reported

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			conference abstract				
Schneider 2013[20]	**No Information** No information on whether confounding might be present	**Moderate Risk** Six of the 13 patients had a past or current history of eczema, asthma, or both, 6 had a history of at least 1 other food allergy, and 4 had 2 or more additional food allergies	**Low Risk** Intervention status is well defined	**Low Risk** Single-arm study	**Low Risk** One subject withdrew after developing persistent nausea and vomiting associated with increased oral mucus production	**Moderate Risk** Open-label	**Low Risk** All prespecified outcomes were reported

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					after reaching the 1250-mg dose		
Begin 2014[21]	**No Information** No information on whether confounding might be present	**Low Risk** Participants older than or equal to 4 years old; had proven sensitivity to at least 2 food allergens documented by both a skin prick greater than 3 mm (wheal) and food-specific IgE greater than 0.35 kU/L, and who had clinical	**Low Risk** Intervention status is well defined	**Low Risk** Single-arm study	**Low Risk** Three participants withdrew because of non-compliance with study medication	**Moderate Risk** Open-label	**Low Risk** All prespecified outcomes were reported

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		reactivity to those foods proven by positive allergic reaction in a double-blind placebo-controlled oral food challenge					
Loizou 2015[22]	**Moderate Risk** Patients were divided into subgroups based on co-localization of IL-5 and IgE to tryptase-	**Moderate Risk** Patients with IgE-mediated allergy to at least 1 food allergen, based on skin prick testing. Patients were placed into subgroups based on co-localization of IL-5 and	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** Two participants were excluded from the analysis because they failed to	**Moderate Risk** Open-label, unblinded	**Low Risk** All prespecified outcomes were reported

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	positive mast cells	IgE to tryptase-positive mast cells			obtain end of study endoscopies on time		
Pajno 2015[23]	**No Information** No information on whether confounding might be present	**Low Risk** Patients had severe or life-threatening events during up-dosing protocol with cow's milk	**Low Risk** Intervention status is well defined	**Low Risk** Single arm study	**Low Risk** There were no dropouts	**No Information** No information is reported about the methods of outcome assessment	**Low Risk** All prespecified outcomes were reported

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Salguero 2017[24]	**No Information** No information on whether confounding is present	**No Information** No information is reported about selection of participants into the study	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No Information** No information is reported about the methods of outcome assessment	**Low Risk** All prespecified outcomes were reported
Arasi 2017[25]	**No Information** No information on whether confounding is present	**Moderate Risk** Patients with severe cow's milk allergy were enrolled; 4 children had concomitant allergic	**Low Risk** Intervention status is well defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No Information** No information is reported	**Low Risk** All prespecified outcomes were reported

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		asthma and 1 had atopic dermatitis				about the methods of outcome assessment	
Brandstrom 2017[26]	**Moderate Risk** The treatment will be monitored by basophil cell stimulation (CD-sens)	**Low Risk** Peanut-induced anaphylaxis with IgE-ab >0.35 kUA/L to peanut and either Ara h 1, h 2, or h 3, and positive CD-sens and SPT to peanut	**Low Risk** Intervention status is well defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**Moderate Risk** Masking was none (open-phase study)	**Low Risk** All prespecified outcomes were reported
Mennini 2017[27]	**No Information** No information on whether	**Low Risk** Children with severe asthma and anaphylactic reactions	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No Information**	**Low Risk** All prespecified

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	confounding is present	to 2 or more foods were selected with baseline IgE between 30 and 1500 IU/ml and body weight not more than 150 kg				No information is reported about the methods of outcome assessment	outcomes were reported
Demir 2018[28]	**No Information** No information on whether confounding is present	**No Information** No information is reported about selection of participants into the study	**Moderate Risk** Intervention status is not clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No Information** No information is reported about the methods of	**Low Risk** All prespecified outcomes reported

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						outcome assessment	
Ruano 2019[29]	**No Information** No information on whether confounding is present	**Moderate Risk** Patients were diagnosed a concomitant allergic pathology: 80% asthma, 40% food allergy (60% egg, 20% nuts, and 20% peach), 40% atopic dermatitis. 40% had a family history of atopy	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No Information** No information is reported about the methods of outcome assessment	**Low Risk** All prespecified outcomes were reported
Sindher 2019[30]	**No Information**	**No Information** No information is reported about	**Serious Risk** Each participant's	**Low Risk** co-intervention	**Low Risk** There were no dropouts	**No Information**	**Low Risk** All prespecified

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	No information on whether confounding is present	selection of participants into the study	standardized OMZ dose was calculated by dividing their 150 mg dose by weight and total IgE	s were balanced across intervention groups, and there were no deviations from the intended interventions		No information is reported about the methods of outcome assessment	outcomes reported
Gernez 2011[31]	**Low Risk** Subjects with nut allergy	**Low Risk** Clinical nut or apple allergy was diagnosed by clinical history of	**Low Risk** Intervention status is clearly defined	**Low Risk** Co-interventions were	**Low Risk** There were no dropouts	**Moderate Risk** Open-label	**Low Risk** All prespecified

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	show an increase of basophil CD203c levels at baseline and following rapid *ex vivo* stimulation with nut allergen. Both can be reduced by OMA therapy. These results highlight the potential of using basophil	food allergy reaction, nut-specific IgE ≥15 kUA/L and/or positive skin prick test to nut allergen and severity was graded based on published scores of anaphylaxis symptom		balanced across intervention groups, and there were no deviations from the intended interventions			outcomes were reported

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	CD203c levels for baseline diagnosis and therapeutic monitoring in subjects with nut allergy.						
Rafi 2010[32]	**No information** No information on whether confounding might be present	**Low Risk** Patients treated with OMA for moderate to severe persistent asthma had a history of an allergic food reaction, were SPT positive to foods, and had unintended	**Low Risk** Intervention status is well defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**Moderate Risk** Masking was none (Open-label)	**Low Risk** All prespecified outcomes reported

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		consumption of these sensitized foods while on OMA					
Lefevre 2016[33]	**No Information** No information on whether confounding might be present	**Moderate Risk** Highly allergic patients to milk, peanut, and fish were enrolled	**Low Risk** Intervention status is well defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No Information** No information is reported about the methods of outcome assessment	**Low Risk** All prespecified outcomes were reported
Sousa 2020[34]	**No Information**	**Low Risk** Patients with persistent IgE-mediated cow's	**Low Risk**	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No information**	**Low Risk** All prespecified

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	No information on whether confounding is present	milk allergy with eosinophilic esophagitis diagnosed	Intervention status is clearly defined			No information is reported about the methods of outcome assessment	outcomes were reported
Alba Jordá 2019[35]	**No Information** No information on whether confounding is present	**Low Risk** Patients with the diagnosis of food allergy either as the main indication or as an associated diagnosis (3 with off-label indication for food	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**No informatio n** No information is reported about the methods of	**Low Risk** All prespecified outcomes were reported

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		allergy; 1 chronic urticaria, 2 asthma)				outcome assessment	
Fiocchi 2019[36]	**No Information** No information on whether confounding is present	**Low Risk** Patients with severe asthma and immediate reactions to foods. Total IgE was measured and patients exceeding the level of 1500 kU/L	**Low Risk** Intervention status is clearly defined	**Low Risk** Single-arm study	**Low Risk** There were no dropouts	**Moderate Risk** Open-label	**Low Risk** All prespecified outcomes were reported

CCT, controlled clinical trial; CMA, cow's milk allergy; DBPCFC, double-blind placebo-controlled food challenge; IgE, immunoglobulin E; IL, interleukin LTFU, long-term follow up; OFC, oral food challenge; OIT, oral immunotherapy; OMA, omalizumab; SBFC, single-blind food challenge; SPT, skin prick test

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