The combination of omalizumab improves the safety and efficacy of allergen immunotherapy

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Abstract

Background: Allergen immunotherapy (AIT)-associated adverse events are a major concern for the safety and efficacy of AIT. Omalizumab is a novel anti-IgE monoclonal antibody for the treatment of allergic diseases. At present, there is no agreement on whether combining omalizumab with AIT could improve such conditions. **Objective:** To identify the superiority of combining omalizumab and AIT in allergic diseases. **Methods:** A thorough search of the Pubmed, MEDLINE, and Cochrane Library databases was conducted to find randomized controlled trials reporting the combination of omalizumab in AIT. A fixed-effects model was used to estimate the safety and efficacy with 95% confidence interval. **Results:** The inclusion criteria for the meta-analysis were met by a total of 10 randomized controlled studies (containing 871 patients). According to a pooled analysis, individuals receiving omalizumab reported significantly fewer episodes of severe systemic adverse reaction compared to control patients (RR 0.36, 95% CI 0.22 to 0.58). Similarly, the addition of omalizumab significantly increased the number of patients achieving target maintenance dose (TMD) and sustained unresponsiveness to allergen (SU) (RR 1.33, 95% CI 1.16 to 1.48; and RR 2.55, 95%CI 1.56 to 4.17, respectively) than the control group. Meanwhile, the improvement in symptom severity score (MD -0.28, 95%CI -0.31 to -0.25), rescue medicine daily means score (MD -0.12, 95%CI -0.22 to -0.09), and the number of patients consuming epinephrine in AIT(RR 0.30, 95%CI 0.15 to 0.63)were also displayed superior to control. **Conclusion:** Omalizumab can significantly enhance the safety and efficacy of AIT by decreasing the frequency of severe systemic adverse events and increasing TMD.

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Keywords: Anti-IgE, Omalizumab, allergen immunotherapy, allergic diseases, meta-analysis

Introduction:

Allergic diseases are a group of diseases including allergic rhinitis, asthma, food allergy, and so on[1]. The incidence has shown an upward trend in the past 20 years, currently affecting about 20% of the world's population[1], resulting in a huge social and economic burden[2]. Moreover, when comorbid allergic asthma worsens, life-threatening situations may occur.

Although the management of allergic diseases includes patient education, allergen avoidance, and pharmacotherapy[3, 4], allergen immunotherapy (AIT) is the only potential disease-modifying treatment among them[5]. It involves the repeated administering of allergen extracts to individuals with an allergy who have symptoms of exposure and IgE-sensitization to otherwise harmless proteins (allergens)[5]. Recently, there is oral immunotherapy (OIT), subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), and rush immunotherapy (RIT) for patients to choose from[6]. However, moderate to severe adverse events especially uncontrolled respiratory or cardiac disorders restrict its employment[7]. IgE is a critical player in allergic response and adverse events in atopic individuals after AIT treatment are associated with it as well[8].

At present, nonspecific immunotherapy with anti-IgE monoclonal antibody become a hot spot for the treatment of allergic diseases[9-11]. As a recombinant humanized monoclonal IgE antibody, omalizumab can bind to free IgE, blocking the interaction between IgE and the high-affinity IgE receptor (FcεRI) expressed on the surface of basophils and mast cells[12], reducing the release of downstream products, for example, inflammatory factors and thereby alleviating clinical symptoms[13].

A combination of omalizumab in AIT might serve as an alternative to improve the safety and efficacy of AIT. However, there is disagreement over how applying omalizumab to AIT will affect its safety and efficacy. This systematic review and meta-analysis aimed to evaluate the safety and efficacy of omalizumab combination therapy in AIT.

Methods

A systematic review and meta-analysis were conducted in compliance with the recommended reporting items for systematic reviews and meta-analyses statement guidelines (PRISMA)[14]. There were no age, gender, or racial restrictions on the study. All allergic diseases including allergic rhinitis, asthma, and food allergy required clinician diagnosis.

Two reviewers independently searched MEDLINE, Pubmed, and Cochrane Library databases up to March 2022, and inconsistencies were resolved by a third reviewer. The search was conducted using the following MeSH terms "immunotherapy" or "desensitization" or "immunologic desensitization" or "hypo sensitization" or "rush allergen immunotherapy" or "allergen-specific immunotherapy" or "subcutaneous immunotherapy" or "sublingual immunotherapy" or "oral immunotherapy" or "conventional immunotherapy" or "accelerated immunotherapy" or "cluster immunotherapy" AND "Omalizumab" or "Anti-IgE" or "anti-immunoglobin E" or "monoclonal antibody" AND Publication Type "randomized controlled trial". All clinical trials that assessed the combination of omalizumab in AIT with allergic diseases were considered eligible. All studies

based on the same population were included only in the first published. In addition, research using an anti-IgE other than omalizumab, non-RCT studies, and studies assessing clinical outcomes unrelated to allergic disorders and AIT were all disregarded.

From each eligible study, we recorded information about the first author, publication year, population characteristics, total and per-arm sample size, treatment indication, omalizumab dose, mode of administration, and omalizumab intervention duration. Moreover, we extracted information on allergic-related outcomes along with their effect estimates. The primary outcomes were combined TMD, SU, rescue medicine, and symptom score. The secondary outcomes were adverse event reports including local and systemic reactions.

Relative Risks (RR) along with their corresponding 95% Confidence Intervals (CI) were calculated for the binary outcomes (TMD, SU, Adverse Events(AE)and the number of patients consuming epinephrine) and standardized mean differences (SMD) for the rescue medicine daily mean score, symptom severity score, and nasal severity score were assessed as continuous outcomes. The quality and risk of bias for the included studies were assessed under the Cochrane Collaboration tool using Review manager version 5.4 software. The degree of heterogeneity was assessed with χ^2 and I^2(ranging from 0% to 100%), with P value less than 0.05 or I^2 greater than 56% would be considered heterogeneity.

Results

A total of 285 records were found in electronic databases (Figure 1). Twenty-two full-text were assessed for eligibility and twelve records were excluded. One trial was excluded from the review due to no full text and three trials did not meet the inclusion criteria. Meanwhile, 8 studies were parts of another of our included articles, they were all excluded from further analyses as they did not contain any outcome of interest. Ten articles were included in the review. The characteristics of the included trials are presented in Table1.

Participants and Intervention

There were 5 trials conducted in the United States[15-18], 4 in Germany[19-21], and 1 in Japan[22], assessing a total of 871 participants, 464 of which were treated with the combination of omalizumab in AIT and 407 controls without omalizumab. Four trials[21]reported a younger age group from 19 years old. All trials mentioned the gender of the participants with a male-to-female ratio of 0.95:1. Furthermore, 3 trials investigated AIT for seasonal allergic rhinitis, 1 for allergic asthma, and 5 for food allergy. The publications of Kamin W et al.,2010[19] and Rolinck-Werninghaus et al.,2004[20] were found to be succeeding trials of the study by Kuehr et al.,2002[21]. Among them, one trial[20] reported SIT-birch and SIT-grass arms at the same time.

With regard to the type of immunotherapy, 4 oral immunotherapy (OIT), 3 specific immunotherapy (SIT), and 1 rush allergen immunotherapy (RIT). None of the studies used omalizumab throughout the whole AIT treatment and the intervention duration of omalizumab ranged from 12 weeks to 28 months. In two trials[15][23], omalizumab was used before the immunotherapy and remained in combination for some time after the start of desensitization. In the remaining six studies[21][16][17][18][22][24], omalizumab was introduced in parallel with immunotherapy, with varying lengths of time for the two combinations. At least 0.016mg/kg/IgE omalizumab every 2 or 4 weeks for every patient in 6 trials while one trial used omalizumab ranging from 300 to 525 mg[22]. Only one trial did not refer to the administration dose[24]. Placebo combined with immunotherapy was used as a control group.

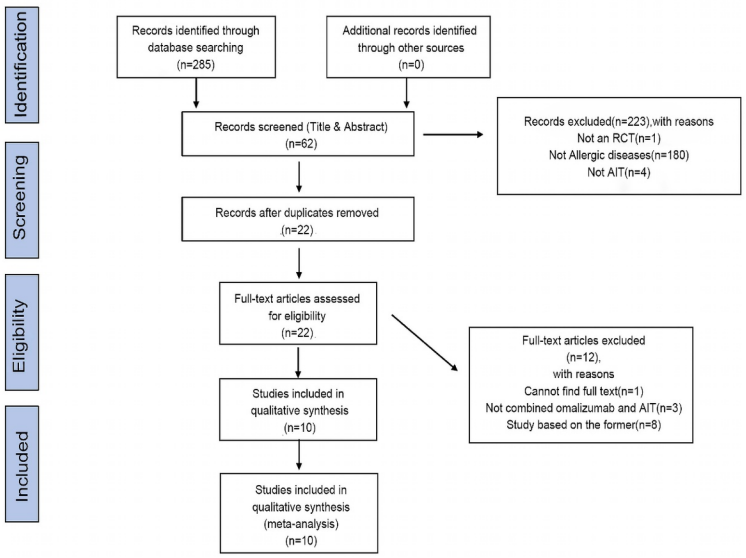


Figure 1. Study flow diagram

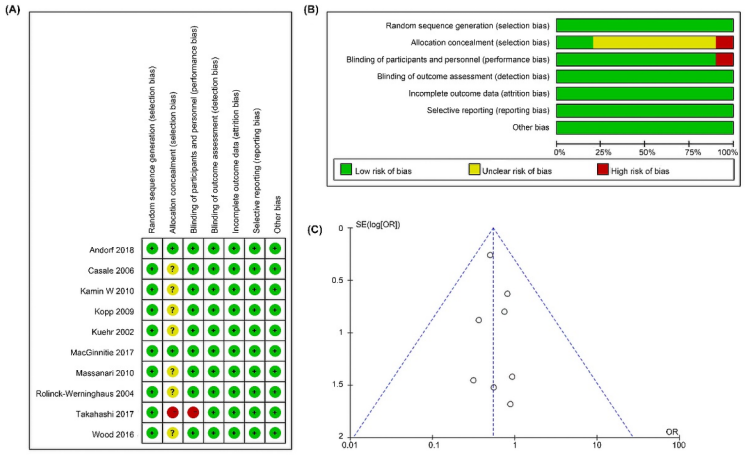


Figure 2. Assessment of risk of bias in the meta-analysis. (A) Quality assessment graph of risk of bias; (B) risk of bias summary; and(C)funnel plots for potential publication bias.

Table 1. General Characteristics of included studies

Study	Location	population age	Sex (M/F)	Indication	allergen	Patients	Patients o/p	arms	TMD o/p	SUN o/p	Omalizumab dose(SC)	Immuno-therapy	Control	Omalizumab Intervention Duration
Kopp, 2009[23]	Germany	12--45	79:61	SARC & SAA	pollen	140	70/70	2			at least 0.016mg/kg/IgE every 4 weeks	SIT	placebo	#20 weeks
Kamin W, 2010*[19] & Rolinck-Werninghaus,2004 *[20]&Kuehr, 2002[21]	Germany	8--15	125:94	SAR	grass or birch pollen	219	113/106	4			at least 0.016mg/kg/IgE every 4 weeks	SIT	placebo	12 to 36 weeks
Casale, 2006[15]	USA	18-50	42:37	SAR	ragweed	79	39/40	4	30/26		at least 0.016mg/kg/IgE every 2 or 4 weeks	RIT	placebo	(-9 to 0 weeks) and (0 to 12 weeks)
Massanari,2010[16]	USA	18-55	88:187	AA	at least 1 of 3 perennial aeroallergen (HDM, dog, cat)	275	139/136	2	110/88		at least 0.016mg/kg/IgE every 2 or 4 weeks	SIT	placebo	0 to 19 weeks
Wood,2016[17]	USA	7-32	40:17	FA	milk	57	28/29	2	24/20	13/10	at least 0.016mg/kg/IgE every 2 or 4 weeks	OIT	placebo	28 months
MacGinnitie,2017[18]	USA	7-19	15:22	FA	peanut	37	29/8	2	23/1	22/1	at least 0.016mg/kg/IgE every 4 weeks	OIT	placebo	12 weeks
Takahashi,2017[22]	Japan	6-14	11:5	FA	milk	16	10/6	2	10/6	10/0	300-525 mg	OIT	placebo	24 weeks
Andorf,2018[24]	USA	4-15	24:24	FA	multifood	48	36/12	2	30/4	30/4	NR	OIT	placebo	16 weeks

SAA: Seasonal Allergic Asthma; SAR:Seasonal Allergic Rhinitis; SARC:seasonal allergic rhinoconjunctivitis;

FA: Food allergy; HDM:house dust mite;NR:NO Reference; SU:sustained unresponsiveness TMD:the number of patients achieving target maintenance dose

RIT:rush allergen immunotherapy; SIT:specific immunotherapy; OIT:oral immunotherapy

*Kamin W, 2010 and Rolinck-Werninghaus,2004 asses the different aspects of Kuer,2002

2-wk run-in and 10-wk pre-seasonal and 8-wk seasonal maintenance

- means pretreatment;

Outcomes

Six trials reported the number of patients achieving target maintenance dose which means they completed AIT successfully[15][16][17][22][24][18]. Meanwhile, four trials reported the number of patients who sustained unresponsiveness to allergen challenges after AIT[17][18][22][24]. No reaction to allergens represents successful desensitization. Three trials reported symptom load score[23][20][15]. Symptom load score was scored on a 0(no symptoms) to 3(severe symptoms) points scale. Among them, one trial[20] further detailed the symptom severity score into ocular and nasal symptoms. Rescue medication score was defined as daily usage on a 4-point scale (0=no rhinitis medication;1=topical nasal, ocular, or lung treatment apart from corticosteroids; 2=systematic antihistamines;3=topical or systematic corticosteroids for nose or lung) in 3 trials[23][16][20]. Epinephrine was given in emergency situations[18][22][17].We calculated the score based on the data supplied on the trials.

All studies enrolled reported secondary outcomes. The adverse events included local reactions (pain, pruritus, and swelling at the site of injection) and severe systematic reactions (mean drop of blood pressure [?] 15 mm, asthma, wheezing and reactions requiring epinephrine). Five trials reported the number of patients with adverse events[15][23][19][18][22]. Four trials reported detailed AE classified in system organ classes[15][23][19][16] (supplementary table 1). Two trials[15][19] reported time-dependent acute allergic reactions based on the percent number of total patients. In one trial[18], allergen sensitivity was measured by the wheel size for allergen skin prick test. Quality of life was measured with Rhinoconjunctivitis of Life Questionnaire (RQLQ) in which higher scores represent worse quality of life[23]. In terms of immunological assessments, one trials[15] reported the base line and post-treatment serum IgE. Subgroup analysis was not performed due to inadequate data.

Risk of Bias

The risk of bias of all included studies is found in Figure 2A and 2B. All reported completed outcome and there was no selective reporting bias or other bias. Most studies referred to "randomized controlled trials", nevertheless, one study demonstrated high risk of performance and selection bias[22]. The author given the reason that it is difficult to recruit participants because none of untreated children pass the double-blind placebo-controlled food challenge from the start of the study, therefore they stopped this trial for an ethical decision and changed it unblind. Funnel plots were prepared to evaluate the potential publication bias. No obvious asymmetry was observed (Figure 2C).

Primary outcomes

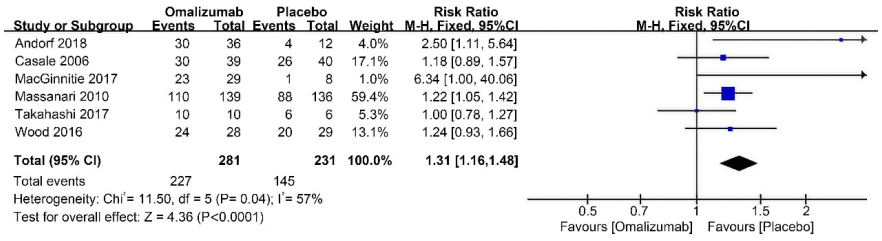
Primary outcomes include target maintenance dose (TMD), sustained unresponsiveness (SU), rescue

medicine score and symptom load score. Six trials[15-18, 22, 24] (n=469) evaluated TMD during AIT. Overall, 80.8% participants in the omalizumab combination treated group achieved TMD (227 of 281) compared with 62.8% (145 of 231) participants in the control group. Statistical analysis reported that comparing with placebo, omalizumab combination significantly increased the number of patients reaching TMD (RR 1.31, 95% CI 1.16 to 1.48; P < 0.0001, I^2 = 57%) (Figure 3A). Sustained unresponsiveness was measured by a rechallenge test using corresponding allergen in 4 trials[17, 18, 22, 24]. Likewise, sustained unresponsiveness also achieved in a greater number of patients after omalizumab combination treated (75 of 103, 78.2%) compared with placebo group (15 of 55, 27.3%) (RR 2.55, 95%CI 1.56 to 4.17; P = 0.0002, I^2 = 51%) (Figure 3B).

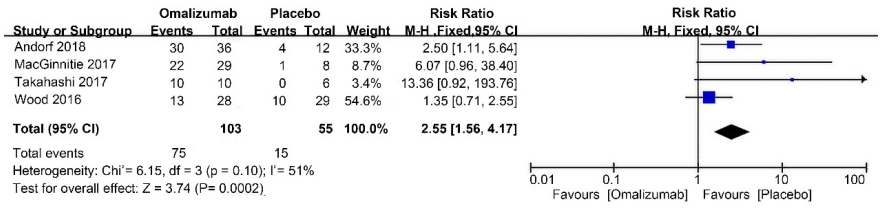
Meanwhile, we also assessed the use of rescue medicine depending on the type of data that eligible studies provided. A total of 736 randomized patients from 3 independent trials[16, 20, 23]included in the evaluation. Rescue medicine score was calculated by adding the total number of different kinds of rescue medications used every day during the treatment divided by the total number of days. It demonstrated that the combination of omalizumab in AIT statistically significantly reduced both the rescue medicine mean score by a summary standardized mean difference of -0.16 points (95% CI, -0.22 to -0.09; P < 0.000001, I^2 = 55%) (Figure 3C).

Two trials[15, 23] reported that reduction of symptom severity score was higher in omalizumab compared to placebo (MD -0.28, 95% CI -0.31 to -0.25; p < 0.00001, I^2 = 0%; 219 participants) (Figure 3D). One trial[20] further compared the reduction of symptom score in nasal which also showed the same results (MD -0.14, 95% CI -0.23 to -0.05; p = 0.002, I^2 = 0%; 221 participants) (Figure 3E). However, one trial[23] showed no difference for RQLQ between two groups (MD -0.32, 95% CI -0.64 to -0.01; p = 0.0537). In terms of immunological assessments,one trial[15] reported that groups receiving pretreatment with omalizumab showed a 10-fold average reduction in serum IgE than immunotherapy-only group.

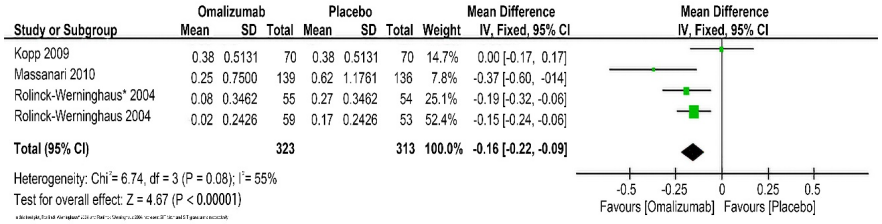
Comparison between omalizumab and placebo combination with immunotherapy for the number of achieving TMD



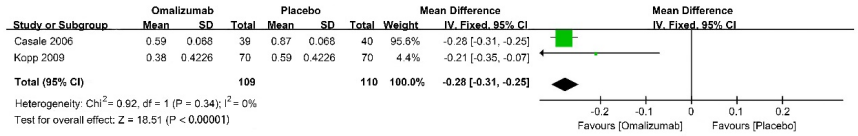
Comparison between omalizumab and placebo combination with immunotherapy for the number of presenting SU



Comparison between omalizumab and placebo combination with immunotherapy for rescue medicine score



Comparison between omalizumab and placebo combination with immunotherapy for symptom severity score



Comparison between omalizumab and placebo combination with immunotherapy for nasal symptom severity score

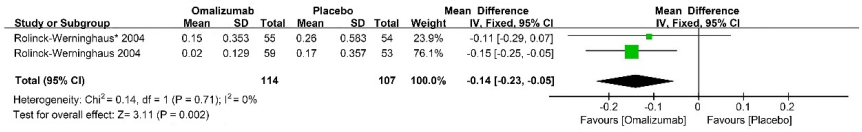
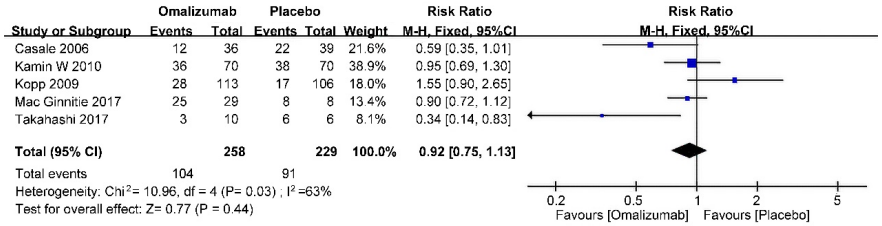


Figure 3. Primary outcomes of the omalizumab combination with immunotherapy versus placebo (Rolinck-Werninghaus*2004 and Rolinck-Werninghaus 2004 represent SIT-birch and SIT-grass respectively)

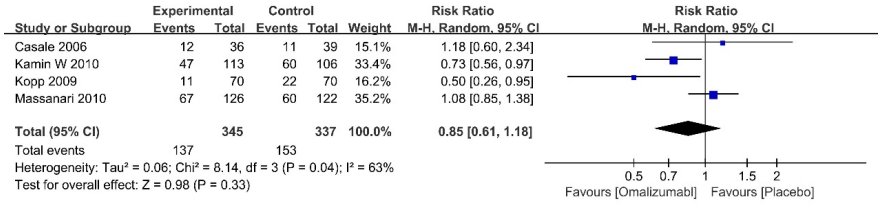
Secondary outcomes

Pooling the data of these studies[15, 18, 19, 22, 23] revealed that the total number of patients with AE showed no difference between two groups (RR 0.92, 95%CI 0.75 to 1.13; P = 0.44, I^2 =63%; 5 trials, 487 participants) (Figure 4A). Likewise, no difference was documented for total topical injection reactions[15, 16, 19, 23] (RR 0.85, 95%CI 0.61 to 1.18 P = 0.33, I^2 = 65%; 4 trials, 682 participants) (Figure 4B). We further compared topical adverse events in swelling and pruritus respectively. In contrast to pruritus[15, 16, 19, 23] (RR 0.82, 95%CI 0.54 to 1.24 P = 0.34, I^2 = 0%; 4 trials, 710 participants) (Figure 4C), there was a significant reduction in the number of patients with swelling in AIT group combined with omalizumab[15, 19, 23] (RR 0.44, 95%CI 0.28 to 0.69 P = 0.0004, I^2 = 0%; 3 trials, 434 participants) (Figure 4D). Six trials[15-19, 23] reported the occurrence of severe systemic adverse events. It was significantly reduced in the combination of omalizumab treated compared with placebo (RR 0.36, 95%CI 0.22 to 0.58 P < 0.0001, I^2 = 0%; six trials, 819 participants) (Figure 4E).

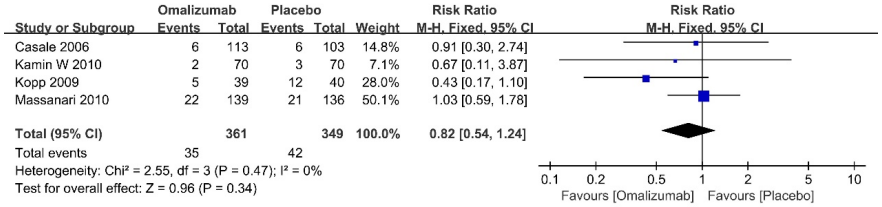
Comparison between omalizumab and placebo combination with immunotherapy for total number of AE



Comparison between omalizumab and placebo combination with immunotherapy for total local injection reactions

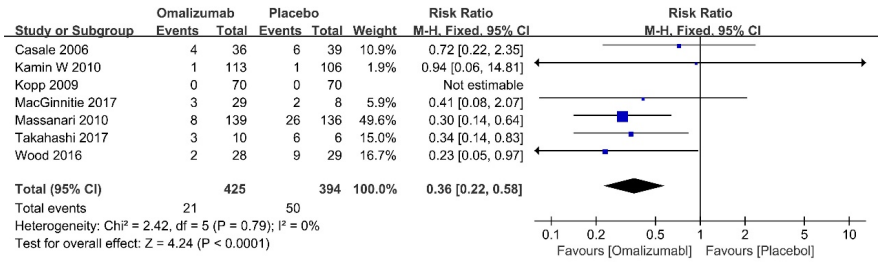


Comparison between omalizumab and placebo combination with immunotherapy for pruritus



Comparison between omalizumab and placebo combination with immunotherapy for swelling

Comparison between omalizumab and placebo combination with immunotherapy for the number of severe system events



Comparison between omalizumab and placebo combination with immunotherapy for the number of patients consuming epinephrine

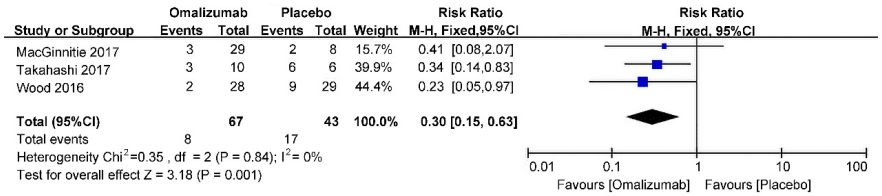


Figure 4. Secondary outcomes (adverse events) of the omalizumab combination with immunotherapy versus placebo

Discussion

In this systematic review and meta-analysis, we calculated the efficacy and safety of omalizumab in allergen immunotherapy in the treatment of allergic diseases. Our systematic review 10 RCTs, with a total of 871 patients. The meta-analysis revealed that treatment with omalizumab combination significantly increased the number of patients achieving the target maintenance dose and passing the responding allergen rechallenge, which also lowering the requirement for rescue medicine and the incidence of severe systematic adverse episodes in patients with allergic diseases.

Significant heterogeneity exists among the results. Influence analysis, in which 1 study is excluded 2 times, was performed to ascertain the impact of removing each of the studies on the heterogeneity. This analysis identified the study conducted by Takahashi et al[22] as largely responsible for the heterogeneity of TMD and the total number with AE. Because the authors selected the patients passing the double-blind placebo-controlled food challenge from the start of the study only showing a better response of TMD thus reduced the possibility with adverse events personally. Removing the study conducted by Takahashi et al[22] from the analysis reduced the degree of heterogeneity within acceptable limits (I^2=44% in TMD and I^2=55% in the total number with AE respectively). Analysis of the substantial heterogeneity of the total local injection reactions in terms of swelling and pruritus, heterogeneity was significantly decreased (I^2 = 0% both in swelling and pruritus).

Someone suggested that the suppression of the basophil response to allergen during treatment with omalizumab is dependent on two competing factors: suppression of allergen-specific IgE on the cell surface versus increased intrinsic sensitivity to IgE-mediated stimulation[25, 26]. A study by Klunker er al.[27] reported that combining immunotherapy with omalizumab block the binding of allergens with IgE to the IgE receptors on mast cells and basophils completely, while immunotherapy alone only partially inhibits. Thus, in comparison to AIT alone, the sulfidoleukotrienes that trigger allergic cascades[28] and the level of nasal inflammatory mediator—tryptase[29] were both dramatically reduced after stimulation with the corresponding allergen, contributing to symptom relief in combination group. It was noted that a high (>10%) specific/total IgE ratio and an increase in the intrinsic response of the basophil to IgE-mediated stimulation resulting to those failed the desensitization treatment[25]. Therefore, it is important to identify those patients who would benefit most from the addition of omalizumab to immunotherapy.

Meanwhile, omalizumab combination has a cumulative effect on inhibition of facilitated antigen presentation both during and after discontinuation of treatment for up to 42 weeks[27]. Acording to Kopp et al.[30], who followed the trials[23] for 3 years, they reported that there was no difference between the two groups in terms of the quality-of-life data but in the first and second year of study extension, investigators' assessment of treatment effectiveness revealed that the combination therapy showed more patients with favorable long-term treatment outcomes than the control. Although[17] further post hoc analyses demonstrated that omalizumab exerts distinct effects on basophil activation beyond those induced by OIT alone[31] leading to successful immunotherapy to food allergens, a percentage of patients relapse with decrease in the clinical reactivity threshold at 2–4 months after suspending omalizumab[32]. More long-term follow-up studies are required to observe the combining therapy's sustained efficacy and serum leukotriene release can be a potential in vitro parameter to monitor therapeutic effects[33].

Another questions to be solved is that the proper dosage and duration of omalizumab to use with immunotherapy. Most eligible trials used omalizumab based on weight and total serum IgE[15-19, 22, 23] while one trial did not refer the specific dosing at all[24]. With regard to duration, some trials added omalizumab before pre-treatment[15], some started some time after treatment[21], others continued the combination therapy through maintenance[17]. Given the expensive price of omalizumab, it is essential to standardize the best dosage and duration in order to maximize effect and minimize costs for patients' benefit.

4.1| Limitations

The sample size in some trials were relatively small, which could potentially contribute to selection bias. Second, the duration of omalizumab from 10 eligible trials, ranging from 12 weeks to 28 months. Whether the length of intervention affects the outcomes is unknown. Similarly, the differences in omalizumab dose and dosing may have limited the accuracy of the study. Furthermore, data for the effect of omalizumab combination in AIT with HDM allergens are presently scare and should be further explored. Finally, there are few randomized controlled trials on this topic which may be a major concern when coping with the efficacy trials.

Conclusion

In this meta-analysis, we have demonstrated that, in comparison to immunotherapy alone, the introduction of omalizumab to AIT with allergic disorders dramatically improved TMD and SU, reduced the need for rescue medicine and the frequency of severe systemic adverse events. Our findings further provided additional evidence for the efficacy and safety of omalizumab used in conjunction with immunotherapy in allergic diseases. It would be a good treatment option for patients with allergic diseases regardless of financial considerations.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTERESTS

The authors have no financial relationships or conflicts of interest to disclose.

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Supplementary Table 1. Reported Adverse Events of included classified in system organ classes

Row Labels	No. of patients		Cardiac disorders		Ear and labyrinth Disorder		Gastrointestinal disorder		General disorders and administration site condition		Infections and infestations		Nervous system disorders		Respiratory, thoracic and mediastinal disorders		Skin and Subcutaneous tissue disorders	
Omalizumab/placebo	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P
Casale, 2006[15]	12/36	22/39	1(1) 2(4)	1(3) 2(3)			2(0),4(0)	2(2),4(3)	6(5)	6(12)			2(2)	2(7)	7(0)	7(3)	3(2),4(5) 5(3)	3(10) 4(16) 5(11)
Kopp, 2009[23]	36/70	38/70							2(7),5(0) 6(2),7(2)	2(12),5(3) 6(3),7(4)	2(8)	2(9)	1(4)	1(7)	1(0),5(2)	1(5),5(3)		
Kamin W, 2010[19]	28/113	17/106			2(2)	2(0)	2+3(3)	(1)	(19)	(13)	(1)	(0)	1(3)	1(3)	(1)	(1)	1+2(2)	1+2(2)
Massanari,2010[16]	139	136	(2)^	(2)^			(2)^	(0)^	2(48),6(43) 7(42)	2(48),6(43) 7(42)					(6)^,4(2) 5(14)	(24)^,4(24) 5(26)	(7)^	(6)^
Wood,2016[17]	28	29	Not specifying how many times each adverse reaction occurred. Reactions requiring epinephrine:2 in omalizumab treated and 9 in placebo-treated															
MacGinnitie,2017[18]	25/29	8/8	Not specifying how many times each adverse reaction occurred. Reactions requiring epinephrine: 3 in omalizumab treated and 2 in placebo-treated															
Takahashi,2017[22]	3/10	6/6	Not specifying how many times each adverse reaction occurred. Reactions requiring epinephrine:3 in omalizumab treated and 6 in placebo-treated															
Andorf,2018[24]	36	12	Not specifying how many times each adverse reaction occurred.															

Cardiac Disorders:	1=Angioedema, 2=Mean drop of BP>=15mm
Ear and Labyrinth Disorders:	1=Earache, 2=Ears/vascular
Gastrointestinal disorder:	1=sore throat, 2=nausea, 3=Diarrhea ,4=Abdominal pain
General disorders and administration site condition:	1=Injection site pain, 2=Injection Site Reaction, 3=Pyrexia, 4=Injection site edema, 5=Peripheral swelling, 6=Injection site pruritus,7=application site reaction
Infections and infestations:	1=Upper respiratory tract infection, 2=Pharyngitis/Nasopharyngitis ,3=Influenza
Nervous system disorders:	1=Headache, 2=lightheadedness
Respiratory, throracic and mediastinal disorders:	1=Cough, 2=Dyspnea, 3=Rhinitis, 4=Asthma, 5=Sinusitis, 7=Wheezing
Skin and subcutaneous tissue disorder:	1=Eczema,2=Pruritus, 3=Anaphylaxis, 4=Flushing, 5=Urticaria
	^experienced a systemic serious allergic reaction within 1 hour of an injection