Article

Discovery Medicine 2023; 35(176): 233–241
https://doi.org/10.24976/Discov.Med.202335176.24

Safety and Tolerability of Omalizumab in Children with Allergic (*IgE*-Mediated) Asthma: A Systematic Review and Meta-Analysis

Dandan Lang[1], Zhengmin Liu[2], Dejun Li[3,*]

[1]Department of Paediatrics, Zhuhai People's Hospital, Zhuhai Hospital of Jinan University, The First Hospital of the Faculty of Medicine of Macau University of Science and Technology, 519000 Zhuhai, Guangdong, China
[2]Department of Neurosurgery, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, 317000 Taizhou, Zhejiang, China
[3]Department of Pediatrics, Taizhou Cancer Hospital, 317502 Taizhou, Zhejiang, China
*Correspondence: ldj19782022@163.com (Dejun Li)
Published: 2 June 2023

Background: Omalizumab is a recombinant humanized monoclonal antibody against immunoglobulin E., which can specifically bind to *IgE* in blood and inhibit the release of inflammatory mediators to improve the symptoms of *IgE*-mediated asthma effectively. This meta-analysis was used to retrieve the studies in recent years to provide a clinical reference for the omalizumab in treating allergic asthma (AA).

Methods: The databases Ovid, Embase, Pubmed, the Cochrane Library of clinical trials, CNKI (China National Knowledge Infrastructure) (China), and Wangfang Data (China) were searched for all studies on omalizumab involvement in treating allergic childhood asthma up to January 2022. Effectiveness, rate of exacerbation within 24 weeks (and 52 weeks), and the incidence of adverse reactions and serious adverse reactions were used as the primary data analysis indicators.

Results: Seven eligible pieces of literature were included. Meta-analysis indicated that omalizumab could significantly improve the treatment efficacy in children with asthma [*RR* (Risk Ratio) = 1.24, 95% CI (Confidential Interval) (1.09, 1.41), $Z = 3.30$, $p = 0.001$], reduced the incidence of significant clinical exacerbation in children with asthma within 24 weeks [*RR* = 0.55, 95% CI (0.35, 0.85), $Z = -2.67$, $p = 0.001$], reduced the incidence of significant clinical exacerbation in children with asthma within 52 weeks [*RR* = 0.52, 95% CI (0.39, 0.71), $Z = -4.2$, $p < 0.0001$], and the incidence of total serious adverse reactions was not statistically different from placebo [*RR* = 1.00, 95% CI (0.98, 1.03), $Z = 0.71$, $p = 0.479$], the incidence of serious adverse reactions was significantly decreased [*RR* = 0.53, 95% CI (0.36, 0.77), $Z = -3.35$, $p = 0.001$].

Conclusions: In treating *IgE* (immunoglobulin E)-mediated asthma in children, adding oral (or subcutaneous) omalizumab to a glucocorticoid regimen can enhance the effectiveness of treatment, reduce the probability of significant exacerbation during treatment, and reduce the incidence of serious adverse reactions.

Keywords: omalizumab; allergic asthma; *IgE* mediated

Introduction

Asthma is the most common chronic airway disease in children, with recurrent wheezing, cough, shortness of breath, and chest tightness as clinical symptoms. There are about 300 million asthmatics worldwide, and the mortality of asthma has shown an increasing trend and has become a serious public health problem in recent years [1,2]. At present, for children with chronic persistent asthma, inhaled corticosteroids (ICS), ICS combined with long-acting β2 receptor agonists (ICS-LABA), leukotriene receptor antagonists (LTRA) and other drugs are usually given for control, but 5%–20% of children still have symptoms that cannot be well controlled and gradually develop refractory asthma [3,4]. Allergic asthma (AA) is the most common manifestation of childhood asthma, and type I allergy mediated by immunoglobulin *IgE* (immunoglobulin E) plays a key role in the onset of asthma [5,6]. Omalizumab is a recombinant humanized anti-immunoglobulin E (*IgE*) monoclonal antibody that can specifically bind to *IgE* in the blood and inhibit the release of inflammatory mediators, thereby effectively improving asthma symptoms [7–9]. With the clinical application of omalizumab, its clinical efficacy has been gradually concerned, but there are still few clinical studies evaluating its use in children with AA. We performed a meta-analysis of the literature on omalizumab in treating children and adolescents with AA to provide a reference for its clinical application in this study.

Method

Inclusion Criteria

We established the inclusion criteria according to the PICOS (Patients, Intervention, Control, Output, Study) principle: (a) Study Type: We only included RCTs (randomized controlled trials) only in Chinese and English languages. We excluded the literature involving case-control studies, case reports, reviews, and meeting minutes. (b) Patients: All patients were children (<18 years old and >6 years old) with asthma, total serum immunoglobulin *IgE*-mediated, serum *IgE* positive, the severity of the disease was moderate and severe. (c) Intervention: Cause the included studies was RCT studies, there must be an experimental group and a control group in the study, the two groups of children were given the same dose of ICS (Inhaled corticosteroids) treatment, on this basis, the observation group of children was given oral omalizumab (or subcutaneous injection intervention), the control group was only given a placebo, the dose of omalizumab was not fixed, should be adjusted according to the weight of children and baseline total serum *IgE*. (d) Control: The included studies was RCT studies, if the grouping method in the study was not randomized, inhaled was excluded, we did not specify the allocation concealment, blind method, and outcome measurement of the study in detail. However, the bias of the study was analyzed. (e) Outcomes: We measured omalizumab's efficacy, tolerability, and safety in children with asthma as the primary outcomes. The efficacy was evaluated by GETE (the Global Evaluation of Treatment Effectiveness), including 5 rates: Excellent, good, moderate, poor, or worsening. The GETE response rate was calculated as (excellent + good) cases/total number of cases. For the tolerability of children, we measured by the incidence of significant exacerbations over 24 or 52 weeks, the criterion of significant exacerbations: Worsening of asthma symptoms, need to double the basal ICS dose, and use of systemic corticosteroids for more than 3 days. As for the safety concern, we measured the incidence of adverse events (AEs) and serious adverse events (SAEs) as indicators. The incidence of AEs was defined as the patients with AEs like nasopharyngitis, upper respiratory tract infection, sinusitis, pyrexia, etc. The incidence of SAEs was defined as the patients with AEs that were fatal or life-threatening, requiring different surgeries and a prolonged hospital stay.

Search Strategy

From January to February 2022, 2 investigators collaborated to search the following databases: Ovid (https://ovidsp.ovid.com/), Embase (https://www.embase.com/), Pubmed (https://pubmed.ncbi.nlm.nih.gov/), the Cochrane library of clinical trials (https://cochranelibrary.com), CNKI (China National Knowledge Infrastructure) (China) (https://cnki.net), Wangfang Data (China) (https://wanfangdata.com.cn). The publication time range of the searched literature was from database establishment to January 2022. The search strategy was a keyword search. The keyword combination was: [*omalizumab*] AND [*Children*] AND [*allergic asthma*].

Literature Screening and Data Extraction

Two staff members were assigned to screen the articles independently. Articles that did not meet the requirements of this study were excluded after the duplicate articles were removed and the full texts of the remaining articles were obtained. Two staff members extracted data from the literature included in this study, including title, first author, publication date, grouping, samples, and intervention method in each group; Age, gender, FEV_1 (the forced expiratory volume in the first one second) estimate before the intervention, and serum total *IgE* level; Implementation time and outcome data. If no data were available in the literature, attempts were made to contact the original author to obtain.

Bias Analysis and Quality Evaluation of Literature

Using Cochrane Rob 2.0 tool provided by Cochrane Collaboration, London, UK to analysis, the revised Cochrane tool to assess the risk of bias in randomized trials (RoB 2) and to perform bias analysis and quality evaluation of the included literature. This tool contains 5 evaluation dimensions: (1) Bias in the randomization process, (2) bias from established interventions, (3) bias from missing outcome data, (4) bias from outcome measurements, (5) and bias from selective reporting of results. The risk of bias in each dimension can be divided into 3 levels: "Low risk of bias", "some concerns", and "high risk of bias". We denote high quality by "low risk" for all 5 assessments in the literature, which is marked as Level A; If there is no "high risk" for 5 assessments, the quality is fair, which is marked as Level B; And if there is "high risk" for one of the 5 assessments, which is denoted as Level C.

Statistical Analysis

(a) Effect Size. As all measures in this study were binary variables, Risk Ratio (*RR*) with 95% CI was used as the effect size. (b) STATA16.0 (released by STATA Corp LLC, College Station, TX, USA) was used for analysis, and the results were presented using forest plots; Literature heterogeneity was analyzed using the I^2 method and *Q*-test, and I^2 >50% or $p < 0.1$ indicated the heterogeneity of the results. (c) If there was no heterogeneity between the articles, the fixed-effect model was used; If there was heterogeneity between the articles, the random-effect model was used. (d) Publication bias analysis. Publication bias was quantified using Egger's test. (e) Sensitivity analysis: Literature culling was performed one by one.

Table 1. Baseline information of literature.

Author	Year	Number of patients	Number of cases (E/C)	Age (years)	Method (E/C)	Dose	Observation time (weeks)	Outcome indicators	Quality Level
Kulus M *et al*. [10]	2010	235	159/76	9.1 (6–12)	*Omalizumab*/ Placebo	75–375 mg once or twice a month by subcutaneous injection	52	(a) (b) (c) (d) (g)	A
Lanier B *et al*. [11]	2009	576	384/192	8.7 (6–12)	*Omalizumab*/ Placebo	75–375 mg sc, q2 or q4 weeks	52	(a) (b) (c) (d) (g)	B
Lemanske RF Jr *et al*. [12]	2002	334	225/109	9.4 (6–12)	*Omalizumab*/ Placebo	at least 0.016 mg/kg/*IgE* (IU/mL) per 4 weeks	28	(e)	B
Berger W *et al.* [13]	2003	332	223/109	9.4 (6–12)	*Omalizumab*/ Placebo	150 or 300 mg every 4 weeks	52	(b) (c)	A
Massanari M *et al.* [14]	2009	146	76/70	14.2 (12–17)	*Omalizumab*/ Placebo	at least 0.016 mg/kg per *IgE* IU/mL per month	28	(a) (c) (d) (g) (h)	B
Milgrom H *et al.* [15]	2011	926	624/302	14.2 (6–12)	*Omalizumab*/ Placebo	75–375 mg sc, q2 or q4 weeks	52	(b) (d)	A
Zhang Q *et al.* [16]	2021	133	67/66	9.14 (6–12)	*Omalizumab*/ Placebo	150–600 mg sc, q2 or q4 weeks	16	(c) (d) (f) (g) (h)	B

Abbreviations: E/C, Experimental group/Control group; GETE, the Global Evaluation of Treatment Effectiveness. Outcomes: (a), The rate of significant exacerbations over 24 weeks; (b), The rate of significant exacerbations over 52 weeks; (c), Adverse event; (d), Serious adverse event; (e), Quality of Life; (f), Effective rate; (g), GETE rating; (h), FEV1.

Table 2. Literature bias assessment based on Cochrane Rob 2.0's Handbook for the Evaluation of Randomized Interventions.

Study	Randomization Bias in Process	Bias from established interventions	Bias in Missing Outcome Data	Bias in outcome measurements	Bias in selective reporting of results
Kulus M *et al.* [10]	L	-	L	L	L
Lanier B *et al.* [11]	L	L	L	SC	L
Lemanske RF Jr *et al.* [12]	L	L	SC	L	L
Berger W *et al.* [13]	L	L	L	L	L
Massanari M *et al.* [14]	L	L	L	SC	L
Milgrom H *et al.* [15]	L	L	L	L	L
Zhang Q *et al.* [16]	L	L	L	SC	L

Abbreviations: L, Low; SC, Some concerns.

Table 3. Publication bias Egger's analysis of the incidence of serious adverse events.

Std effect	Coef	Std err	t	$p > \|t\|$	95% CI
Slope	–0.386	0.151	–2.57	0.083	[–0.866, 0.091]
Bias	0.589	0.669	0.88	0.443	[–1.540, 2.718]

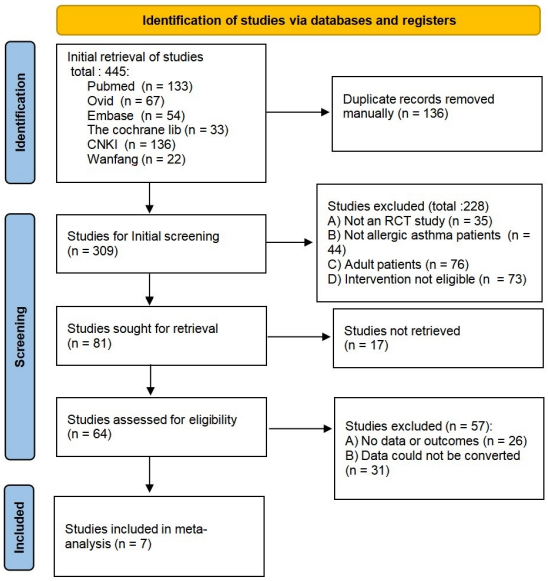

Fig. 1. Flow chart of literature selection. 445 studies were identified, 309 studies were screened and 7 was included in the end.

Results

Screening Results

445 articles were initially detected. After deduplication and screening, 7 [10–16] articles met the criteria and entered the final meta-analysis, comprising 2682 participants. Fig. 1 shows the flow chart of the literature selection.

Baseline Information of Literature

The baseline information of the literature is shown in Table 1 (Ref. [10–16]).

Literature Bias Assessment

As shown in Table 2 (Ref. [10–16]), all literature was mentioned using the random grouping method to assess the risk of bias based on Cochrane's Rob 2.0. All literature showed no bias in the intervention method. Still, the literature [12] showed bias due to the incompleteness of data, while the literature [11,14,16] showed a possible bias for measuring outcomes without selective reporting bias.

Meta-Analysis Results

The GETE Response Rate

As shown in Fig. 2 (Ref. [10,11,14,16]), four pieces of literature reported the effective rate of omalizumab and placebo for children with asthma. The effect size was expressed as *RR*-heterogeneity test results: $I^2 = 54\%$, $p = 0.09$. The results indicated that omalizumab could significantly improve the treatment efficacy for children with asthma with the GETE response rate using fixed effect model analysis [$RR = 1.24$, 95% CI (1.09, 1.41), $Z = 3.30$, $p = 0.001$].

Incidence of Significant Clinical Exacerbation (24 Weeks)

As shown in Fig. 3 (Ref. [10,11,14]), three pieces of literature reported the incidence of significant clinical exacerbation within 24 weeks with heterogeneity test results: $I^2 = 86\%$, $p < 0.01$. The results indicated that omalizumab could significantly reduce the incidence of significant clinical exacerbation in children with asthma within 24 weeks using random effects model analysis [$RR = 0.55$, 95% CI (0.35, 0.85), $Z = –2.67$, $p = 0.001$].

Incidence of Significant Clinical Exacerbation (52 Weeks)

As shown in Fig. 4 (Ref. [10,11,13]), three pieces of literature reported the incidence of significant clinical exacerbation within 52 weeks with heterogeneity test results: $I^2 = 80\%$, $p < 0.01$. The results indicated that omalizumab could significantly reduce the incidence of significant clin-

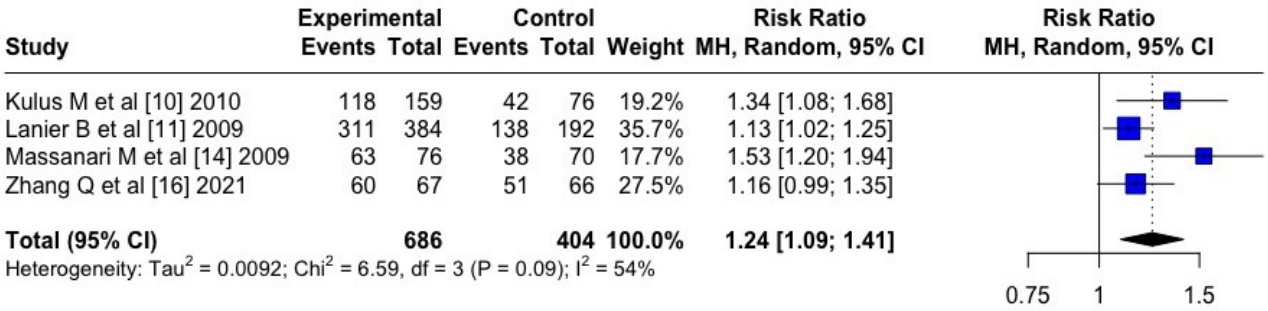

Fig. 2. Effect of omalizumab on clinical response rate in children with asthma. A forest plot of pooling model of *RR*, 4 studies included. The pooling effective size (*RR*) was 1.07 with 95% CI (1.00, 1.14) from MH model. MH, Mantel-Haenszel; *RR*, Risk Ratio; CI, Confidential Interval.

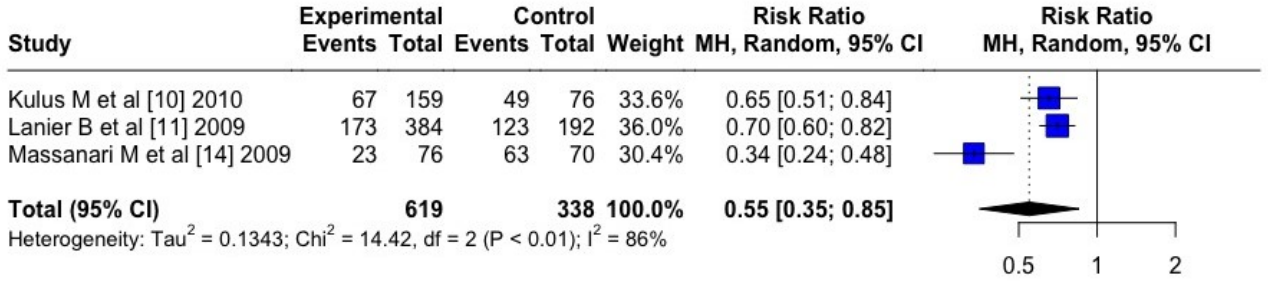

Fig. 3. Effect of omalizumab on the incidence of significant clinical exacerbation within 24 weeks in children with asthma.

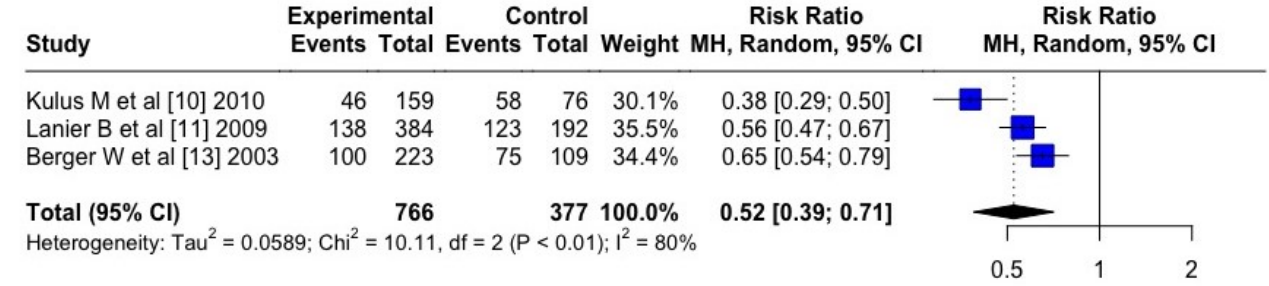

Fig. 4. Effect of omalizumab on the incidence of significant clinical exacerbation within 52 weeks in children with asthma.

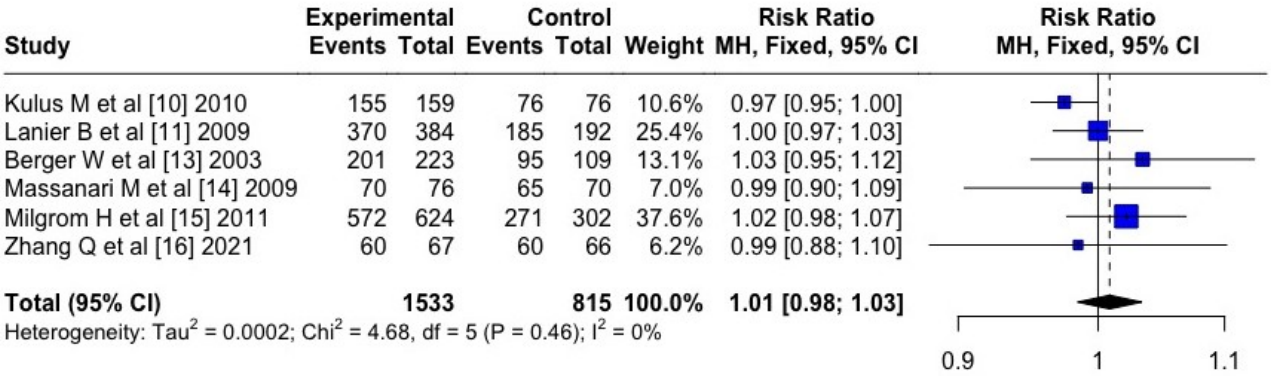

Fig. 5. Effect of omalizumab on the incidence of total adverse reactions in children with asthma.

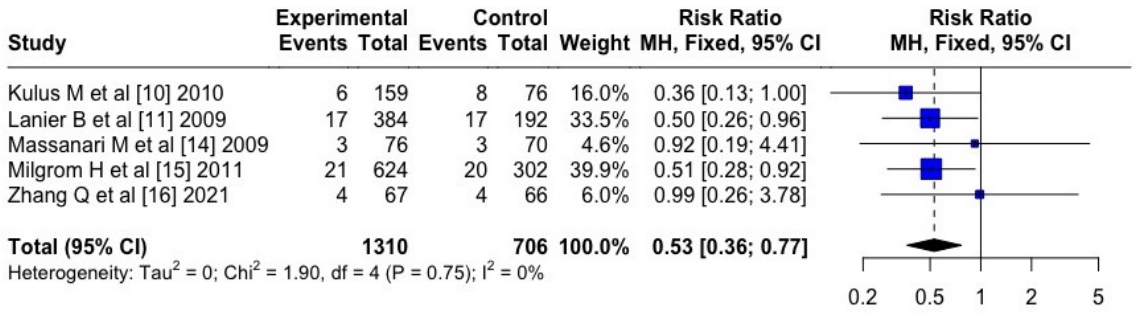

Fig. 6. Effect of omalizumab on the incidence of serious adverse reactions in children with asthma.

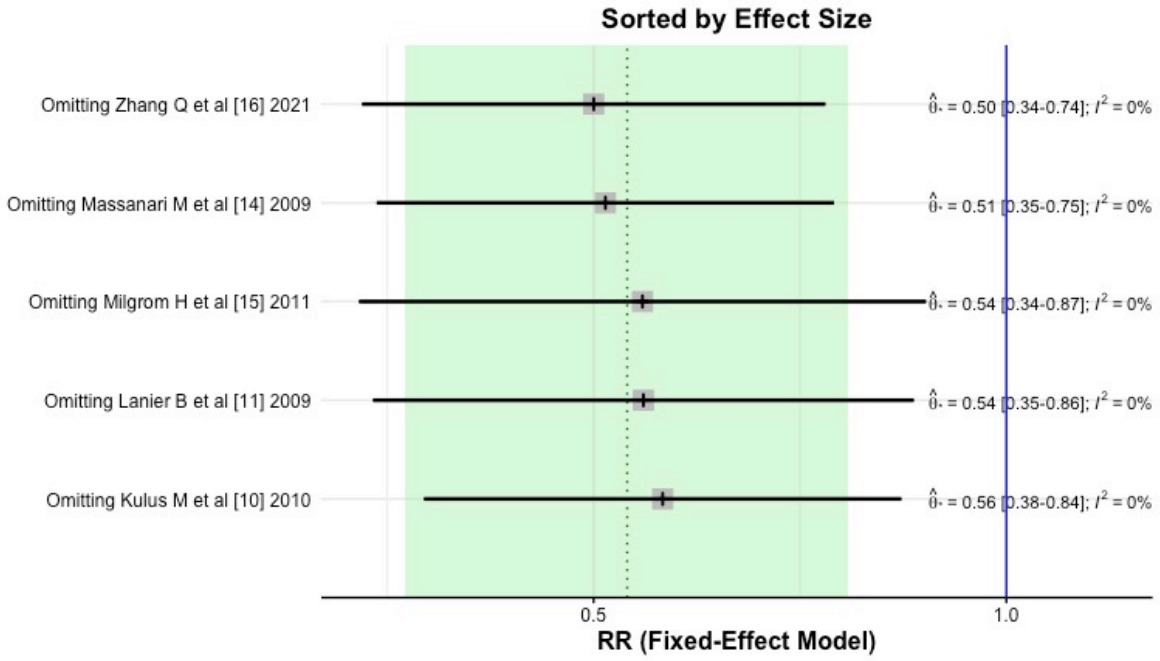

Fig. 7. Sensitivity analysis of the incidence of serious adverse reactions. The studies were omitted one by one out of the group and the pooling effect size of the left studies was calculated.

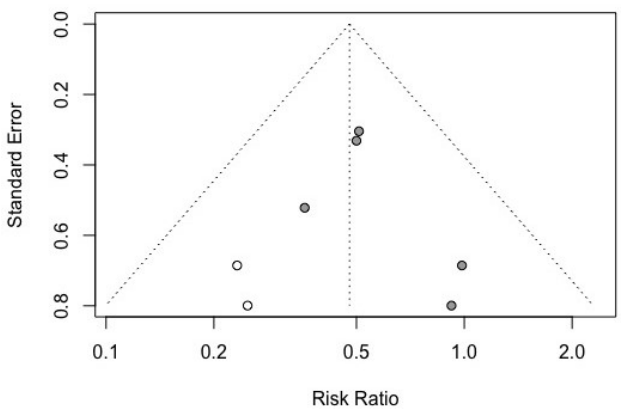

Fig. 8. Funnel plot analysis (Trim-filled mode). The horizontal axis represents Risk Ratio, and the vertical axis represents Standard Error.

ical exacerbation in children with asthma within 52 weeks using fixed effect model analysis [*RR* = 0.52, 95% CI (0.39, 0.71), *Z* = –4.20, $p < 0.0001$].

Total Incidence of Adverse Reactions

As shown in Fig. 5 (Ref. [10,11,13–16]), six pieces of literature reported the incidence of adverse reactions between omalizumab and placebo in children with *IgE*-mediated asthma. Heterogeneity test results: $I^2 = 0\%$, $p = 0.46$, The results indicated no significant difference in the incidence of total adverse reactions between omalizumab and placebo using fixed effect model analysis [*RR* = 1.00, 95% CI (0.98, 1.03), *Z* = 0.71, *p* = 0.479].

Incidence of Serious Adverse Reactions

As shown in Fig. 6 (Ref. [10,11,14–16]), five pieces of literature reported the incidence of serious adverse reactions in children with *IgE*-mediated asthma treated with

omalizumab and placebo. Heterogeneity test results: I^2 = 0%, p = 0.879. The results indicated that the incidence of total serious adverse reactions was lower with omalizumab than with placebo using fixed effect model analysis (Fig. 7, Ref. [10,11,14–16]) [*RR* = 0.53, 95% CI (0.36, 0.77), Z = –3.35, p = 0.001].

Heterogeneity Investigation and Sensitivity Analysis

In this study, in the analysis of the outcome indicators of the incidence of serious adverse reactions, the one-by-one omition method was adopted, and pooling effect size of the remaining literature didn't reverse the result, indicating that the result of this outcome indicator was stable.

Publication Bias Analysis

Using the incidence of serious adverse reactions as the outcome indicator, Egger's test: $p = 0.443 > 0.05$, which suggested the absence of publication bias, as shown in Table 3 and Fig. 8.

Discussion

Asthma is a hypersensitivity disease, and the increase of total *IgE* in serum is closely related to airflow limitation, airway hyperreactivity, and symptom occurrence in asthmatic patients [17]. *IgE* is the main immunoglobulin mediating type I allergic reaction. There is a high-affinity *IgE* Fc receptor FcϵRI on basophils, mast cells, and dendritic cells, but a low-affinity *IgE* Fc receptor FcϵRII on eosinophils, monocytes, lymphocytes, and platelets [18]. After entering the body, meta morphogens activate interleukin-4 receptor, cause the proliferation and differentiation of $CD4^+$, induce the proliferation and differentiation of allergen-specific B lymphocytes, produce *IgE* antibodies, trigger immediate phase type I hypersensitivity and trigger delayed phase hypersensitivity, and cause asthma exacerbations [19].

Omalizumab, a recombinant humanized anti-*IgE* monoclonal antibody, is the first biologically targeted drug for treating asthma worldwide and has been widely used in clinical practice [20]. Clinical studies [21] confirmed that anti-*IgE* monoclonal antibodies could significantly reduce the number of acute attacks in children with asthma and the dosage of glucocorticoids. Simultaneously, it is safe to use and tolerated by children with asthma and has a good application prospect. This meta-analysis analyzed the clinical application of anti-*IgE* monoclonal antibodies in children with AA. The results showed that adding oral (or subcutaneous) omalizumab to the glucocorticoid treatment regimen could enhance the effectiveness of treatment and reduce the probability of significant exacerbation of the disease during treatment.

As an anti-*IgE* antibody, omalizumab treats AA by binding to free *IgE* in the body, reducing the binding of *IgE* to allergen-specific *IgE* receptors, resulting in reduced activation of cytokines such as eosinophils and mast cells, thus playing an anti-allergic role [21]. In the research by Lanier B *et al*. [11], the number of *IgE* receptors on the effector cell surface could be reduced by 86% after omalizumab treatment, directly indicating the effectiveness of omalizumab in treating AA. A guideline by Asthma and Respiratory Foundation [22] recommends that omalizumab can be used in children and teenagers aged 6–18 years with refractory asthma. The results of this study indicate that omalizumab can reduce the incidence of severe asthma exacerbation in children and adolescents and provide a clinical reference for the omalizumab in children and teenagers.

Six included literature [10,11,13–16] compared the incidence of adverse reactions between omalizumab and placebo in children with *IgE*-mediated asthma. The results showed that no new or unexpected safety events occurred. The incidence of adverse events was similar to that of placebo. 90% of AEs were mild or moderate. SAEs were rare and occurred less frequently than placebo, indicating that omalizumab is safe in pediatric patients. In the study by Milgrom H *et al*. [15], the authors summarized that the most common serious adverse reactions were appendicitis, pneumonia and bronchitis (omalizumab: 0.6%, 0.5%, 0.3%; Placebo: 0.3%, 2.3%, 0.3%).

The therapeutic dose of omalizumab depends on the patient's pretreatment serum total *IgE* level and body weight. Once the baseline level of serum total *IgE* is determined, it is not necessary to determine the serum total *IgE* level again during treatment. Still, the body weight of patients changes significantly. In that case, the dose needs to be adjusted, which means the pretreatment serum total *IgE* level and new body weight are used to recalculate the therapeutic dose of omalizumab [23]. The appropriate regimen for administering omalizumab is to inject it subcutaneously every 4 weeks or every 2 weeks.

Despite the significant therapeutic effect of omalizumab, its price is still higher, and a study [24] showed that from a pharmacoeconomic point of view, despite the high cost of omalizumab, it can still be better used in AA patients with poor symptom control and save costs in the long run. Another study in Switzerland [25] also supports this view.

The heterogeneity survey indicated that the heterogeneity of included literatures was small. The results of the publication bias assessment indicated that the absence of publication bias. All articles were of good quality. However, the study still has disadvantages: Meta-analysis was not performed for some key indicators in the study, such as *IgE* level before and after omalizumab treatment, pulmonary indicators, respiratory function indicators, immune indicators ($CD4^+$), and quality of life before and after treatment, which can be further explored in subsequent studies.

Conclusions

In conclusion, in treating *IgE*-mediated asthma in children, adding oral (or subcutaneous) omalizumab to a glucocorticoid regimen can enhance the effectiveness of treatment, reduce the probability of significant exacerbation during treatment, and reduce the incidence of serious adverse reactions.

Availability of Data and Materials

Not applicable.

Author Contributions

DDL, DJL—Conception and design; ZML—Administrative support; DDL—Provision of study materials or patients; DJL—Data analysis and interpretation. All authors have participated acquisition and assembly of data. All authors have participated manuscript writing. All authors have participated final approval of manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] D'Amato G, Chong-Neto HJ, Monge Ortega OP, *et al*. The effects of climate change on respiratory allergy and asthma induced by pollen and mold allergens. *Allergy.* 2020;75(9):2219–2228. doi: 10.1111/all.14476

[2] Akar-Ghibril N, Casale T, Custovic A, *et al*. Allergic Endotypes and Phenotypes of Asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):429–440. doi: 10.1016/j.jaip.2019.11.008

[3] Humbert M, Bousquet J, Bachert C, *et al*. IgE-Mediated Multimorbidities in Allergic Asthma and the Potential for Omalizumab Therapy. *J Allergy Clin Immunol Pract.* 2019;7(5):1418–1429. doi: 10.1016/j.jaip.2019.02.030

[4] Oliveria JP, Agayby R, Gauvreau GM. Regulatory and IgE$^+$ B Cells in Allergic Asthma. *Methods Mol Biol.* 2021;2270:375–418. doi: 10.1007/978-1-0716-1237-8_21

[5] Burch J, Griffin S, McKenna C, *et al*. Omalizumab for the treatment of severe persistent allergic asthma in children aged 6-11 years: a NICE single technology appraisal. *Pharmacoeconomics.* 2012;30(11):991–1004. doi: 10.2165/11597160-000000000-00000

[6] Chapman KR, Cartier A, Hébert J, McIvor RA, Schellenberg RR. The role of omalizumab in the treatment of severe allergic asthma. *Can Respir J.* 2006;13 Suppl B(Suppl B):1B–9B. doi: 10.1155/2006/279435

[7] Sandström T. Omalizumab in the management of patients with allergic (IgE-mediated) asthma. *J Asthma Allergy.* 2009;2:49–62. doi: 10.2147/jaa.s3116

[8] Berghea EC, Balgradean M, Pavelescu C, *et al*. Clinical Experience with Anti-IgE Monoclonal Antibody (Omalizumab) in Pediatric Severe Allergic Asthma-A Romanian Perspective. *Children (Basel).* 2021;8(12):1141. doi: 10.3390/children8121141

[9] Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy.* 2004;59(7):701–708. doi: 10.1111/j.1398-9995.2004.00533.x

[10] Kulus M, Hébert J, Garcia E, Fowler Taylor A, Fernandez Vidaurre C, Blogg M. Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. *Curr Med Res Opin.* 2010;26(6):1285–1293. doi: 10.1185/03007991003771338

[11] Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol.* 2009;124(6):1210–1216. doi: 10.1016/j.jaci.2009.09.021

[12] Lemanske RF Jr, Nayak A, McAlary M, Everhard F, Fowler-Taylor A, Gupta N. Omalizumab improves asthma-related quality of life in children with allergic asthma. *Pediatrics.* 2002;110(5):e55. doi: 10.1542/peds.110.5.e55

[13] Berger W, Gupta N, McAlary M, Fowler-Taylor A. Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol.* 2003;91(2):182–188. doi: 10.1016/S1081-1206(10)62175-8

[14] Massanari M, Milgrom H, Pollard S, *et al*. Adding omalizumab to the therapy of adolescents with persistent uncontrolled moderate–severe allergic asthma. *Clin Pediatr (Phila).* 2009;48(8):859–865. doi: 10.1177/0009922809339054

[15] Milgrom H, Fowler-Taylor A, Vidaurre CF, Jayawardene S. Safety and tolerability of omalizumab in children with allergic (IgE-mediated) asthma. *Curr Med Res Opin.* 2011;27(1):163–169. doi: 10.1185/03007995.2010.539502

[16] Zhang Q, Hou RX, Zhang C, *et al*. Clinical study of omazumab combined with budesonide formoterol powder inhalation in the treatment of children with moderate and severe allergic asthma. *Chinese Journal of Clinical Pharmacology.* 2021,37 (19): 2577–2580. doi: 10.13699/j.cnki.1001-6821.2021.19.008

[17] Tarraf HN, Masoud HH, Zidan M, Wahba B. Effectiveness and safety of omalizumab in severe, persistent IgE-mediated asthma in pediatric and adult patients: a real-world observational study in Egyptian population. *J Asthma.* 2020;57(2):160–166. doi: 10.1080/02770903.2018.1553051

[18] Andorf S, Purington N, Block WM, *et al*. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. *Lancet Gastroenterol Hepatol.* 2018;3(2):85–94. doi: 10.1016/S2468-1253(17)30392-8

[19] Kamin W, Kopp MV, Erdnuess F, Schauer U, Zielen S, Wahn U. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol.* 2010;21(1 Pt 2):e160-e165. doi: 10.1111/j.1399-3038.2009.00900.x

[20] Tortajada-Girbés M, Bousquet R, Bosque M, *et al*. Efficacy and effectiveness of omalizumab in the treatment of child-

hood asthma. *Expert Rev Respir Med.* 2018;12(9):745–754. doi: 10.1080/17476348.2018.1507740

[21] Kopp MV, Brauburger J, Riedinger F, *et al*. The effect of anti-IgE treatment on in vitro leukotriene release in children with seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2002;110(5):728–735. doi: 10.1067/mai.2002.128804

[22] Beasley R, Beckert L, Fingleton J, *et al*. Asthma and Respiratory Foundation NZ Adolescent and Adult Asthma Guidelines 2020: a quick reference guide. *N Z Med J.* 2020;133(1517):73–99.

[23] Sorkness CA, Wildfire JJ, Calatroni A, *et al*. Reassessment of omalizumab-dosing strategies and pharmacodynamics in inner-city children and adolescents. *J Allergy Clin Immunol Pract.* 2013;1(2):163–171. doi: 10.1016/j.jaip.2013.01.011

[24] Oba Y, Salzman GA. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. *J Allergy Clin Immunol.* 2004;114(2):265–269. doi: 10.1016/j.jaci.2004.05.049

[25] Dewilde S, Turk F, Tambour M, Sandström T. The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden. *Curr Med Res Opin.* 2006;22(9):1765–1776. doi: 10.1185/030079906X132389