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Efficacy and safety of omalizumab in children with moderate-to-severe asthma: a meta-analysis

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ABSTRACT

Objective: To assess the efficacy and safety of omalizumab in children with moderate-to-severe asthma.

Data sources: We systematically searched MEDLINE, EMBASE, and Cochrane for randomized controlled trials (RCTs) (inception to January 2020).

Study selections: All RCTs which were conducted in childhood and adolescence with asthma and compared the efficacy or safety of omalizumab were adopted.

Results: Three studies with four publications including 1380 pediatric patients met our criteria. For children with moderate-to-severe asthma, omalizumab decreased asthma exacerbations rate (OR 0.51, 95% CI: 0.44–0.58, $p < 0.001$) compared with placebo with no evidence of heterogeneity. Omalizumab reduced the rate of asthma exacerbations (0.58) with treatment period ≥ 30 weeks (p for heterogeneity = 0.03). Omalizumab treated patients had an excellent or good response rate of treatment effectiveness assessed by physicians (2.75, 2.45–3.09) and a bigger reduction in the dosage of inhaled corticosteroid (ICS) at the end of follow-up. For children with severe asthma, omalizumab also reduced the likelihood of asthma exacerbations and increased the odd of treatment effectiveness rated as excellent or good. Patients receiving omalizumab had a lower incidence of severe adverse events (0.36, 0.22–0.57).

Conclusions: These findings suggested that omalizumab had beneficial effects on moderate-to-severe asthma in children. Patients may benefit more from long-term use of omalizumab. In addition, omalizumab reduces the rate of serious adverse events requiring hospitalizations.

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Omalizumab; children; moderate-to-severe asthma; meta-analysis

Introduction

Asthma is a respiratory disease that affects all ages and it is more prevalent in childhood and adolescence (1,2). Although treatment with doses of inhaled corticosteroids (ICSs) and/or long-acting bronchodilators improves clinical outcomes and disease progression, some children and adolescents continue to experience severe exacerbations and a higher mortality risk (1,3,4).

Immunoglobulin E (IgE) is an immune mediator in asthma which contributes to some clinical manifestations, including mast cell activation, airway remodeling, and irreversible change in pulmonary function. Omalizumab is a recombinant, humanized, monoclonal antibody that can suppress free IgE levels and cure IgE-mediated diseases (5). Omalizumab, in combination with inhaled steroid treatment, has been reported to be effective in adults with moderate-to-severe persistent asthma (6–9). However, few data

on omalizumab treatment in childhood asthma are available. Several studies have been performed to date evaluating the efficacy and safety of omalizumab in pediatric asthma, but the smaller number of patients leads to uncertainty about the effects of omalizumab (10–13). Therefore, we conducted this meta-analysis to assess the efficacy and safety of omalizumab in children with moderate-to-severe asthma.

Methods

Search strategy

We performed an extensive search from the database of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) with language restricted to English. The Mesh headings and text words of all spellings of known “randomized controlled trials (RCTs), controlled clinical study,

omalizumab, rhuMAb-E25, children, pediatrics” were searched from their earliest records to January 2020.

Study selection and inclusion criteria

All RCTs which were conducted in childhood and adolescence with asthma and compared the efficacy or safety with omalizumab *versus* placebo were adopted. The inclusion criteria were defined as follows: (1) studies that aimed at pediatric patients; (2) studies that compared the efficacy and/or safety of omalizumab *versus* placebo; (3) studies identified in asthma; and (4) studies that reported at least one of the following outcomes: number of patients with asthma exacerbations, global evaluation of treatment effectiveness (GETE) assessed by physicians, decrease in ICS dose, and/or drug-related adverse events.

Data extraction and quality of evidence

Two authors extracted data independently using standard data extraction forms, which included study design, interventions, mean age, mean baseline IgE level, study duration, asthma severity, number of patients, and clinical outcomes. We used standard criteria (quantified with Cochrane Collaboration tool for assessing the risk of bias) to assess the quality of the studies. Differences between these two authors were settled through consultation with a third reviewer.

Statistical analysis

We calculated odd risk (OR) and 95% confidence interval (CI) for categorical variables. Weighted mean difference and standard deviation (SD) between groups were used for continuous outcomes. The random-effect model is applied to these analyses. We analyzed heterogeneity by I^2 statistic to describe the percentage of variability. Begg Funnel plot was performed to assess potential publication bias. The results were considered significant with 2-sided $p < 0.05$. STATA version 12.0 (StataCorp, College Station, TX) and Review Manager version 5.1 software (The Nordic Cochrane Centre, Copenhagen, Denmark) were used to perform this meta-analysis.

Results

The literature search yielded 303 articles, eventually; three studies with four publications including 1380 pediatric patients met our criteria (Figure 1). Of these four papers, three compared the efficacy and safety of omalizumab *versus* placebo in patients with moderate-

to-severe asthma; one was conducted in patients with severe asthma. Treatment duration in two papers was within less than 30 weeks, and two was prolonged for more than 30 weeks. The age of the children included ranged from 6 to 12 years old in three papers, and one enrolled patients aged 6–20 years old. The characteristics of the included studies were summarized in Table 1. These studies were performed from 2001 to 2011, with sample sizes ranging from 334 to 627.

Quality assessment

The quality of studies was assessed by Cochrane Collaboration tool. As listed in Table 2, the selection bias of the sequence generation and allocation concealment was unclear in all studies. Two papers had low risk of performance bias, detection bias, and attrition bias, and two were unclear. All studies were unclear in selective outcome reporting bias.

Asthma exacerbations

The data of asthma exacerbations were offered in all studies. Of the 817 patients in the omalizumab group, there were 185 patients with asthma exacerbations (22.6%) and 193 asthma exacerbations occurred in 512 patients in the placebo group (38.2%). Omalizumab therapy decreased asthma exacerbations rate (OR 0.51, 95% CI: 0.44–0.58, $p < 0.001$) compared with placebo with no evidence of heterogeneity ($I^2=30.8\%$, $p = 0.23$, Figure 2).

Treatment duration

These studies had different duration of treatment. Furthermore, we explored the questions whether treatment with long-term omalizumab appeared to be more likely to benefit. Omalizumab reduced the rate of asthma exacerbations by 33% (0.67, 0.53–0.84) within 30 weeks and 50% (0.50, 0.43–0.58) with treatment period ≥ 30 weeks (p for heterogeneity = 0.03, Figure 3). Subgroup analysis revealed that patients may benefit more from long-term use of omalizumab.

Global evaluation of treatment effectiveness (GETE) assessed by physicians

Two studies reported GETE which was assessed by physicians. Omalizumab treated patients showed an excellent or good response rate of GETE assessed by physicians than placebo-treated patients (OR 2.75, 95% CI: 2.45–3.09, $p < 0.001$; Figure 4).

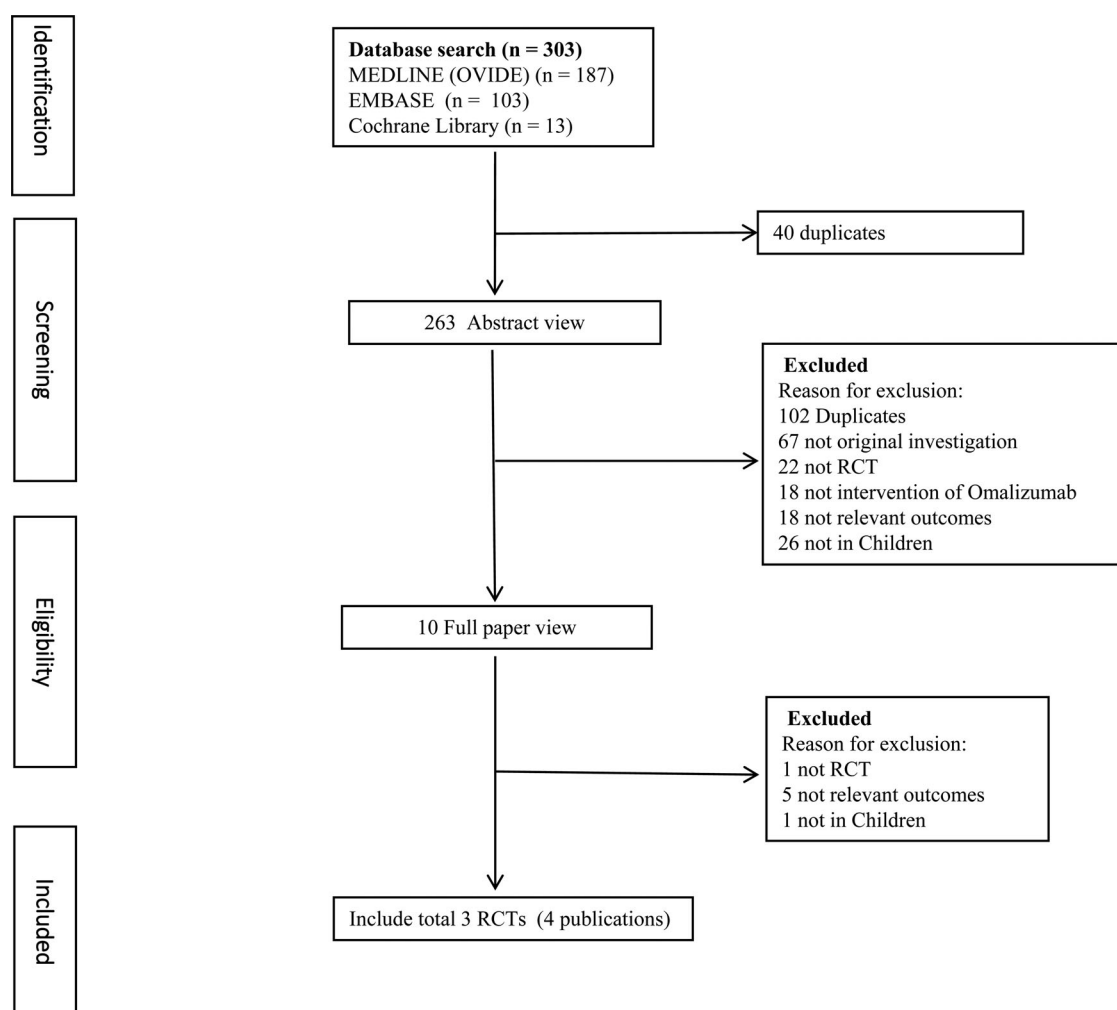


Figure 1. Process for identifying studies eligible for the meta-analysis.

Table 1. Characteristics of included studies.

Study	Study design	Intervention	Mean Age (range)	Mean IgE (IU/ml)	Study duration (weeks)	Asthma severity	Number of patients (Omalizumab/placebo group)
Milgrom 2001 (13)	RCT	Omalizumab + ICS (BDP) Placebo + ICS (BDP)	9.4 years (6–12 years)	335	28	Moderate-severe	225/109
Lanier 2009 (10)	RCT	Omalizumab + ICS Placebo + ICS	8.6 years (6–12 years)	469.7	24, 52	Moderate-severe	421/206
Kulus 2010 (11)	Additional analysis of a RCT (Lanier 2009)	Omalizumab + ICS (BDP) Placebo + ICS (BDP)	9.0 years (6–12 years)	440	24, 52	Severe	159/76
Busse 2011 (12)	RCT	Omalizumab + guideline-based treatment Placebo + guideline-based treatment	10.8 years (6–20 years)	NA	60	Moderate-severe	208/211

RCT: randomized controlled trials; ICS: inhaled corticosteroid; BDP: beclomethasone dipropionate

Table 2. Risk of bias of the eligible studies.

Bias	Milgrom 2001 (13)	Lanier 2009 (10)	Kulus 2010 (11)	Busse 2011 (12)
Random sequence generation (selection bias)	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Allocation concealment (selection bias)	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Blinding (performance bias and detection bias)	Low risk	Unclear risk	Unclear risk	Low risk
Incomplete outcome data (attrition bias)	Low risk	Unclear risk	Unclear risk	Low risk
Selective reporting (reporting bias)	Unclear risk	Unclear risk	Unclear risk	Unclear risk

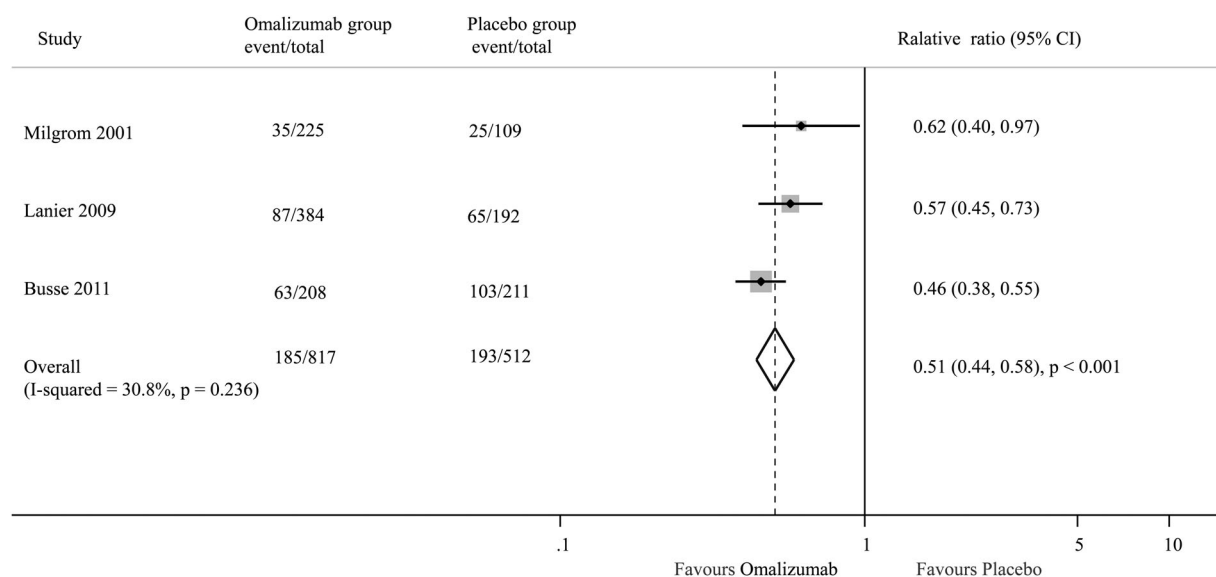


Figure 2. Comparison of number of patients with asthma exacerbations between the omalizumab and placebo group in children with moderate-to-severe asthma.

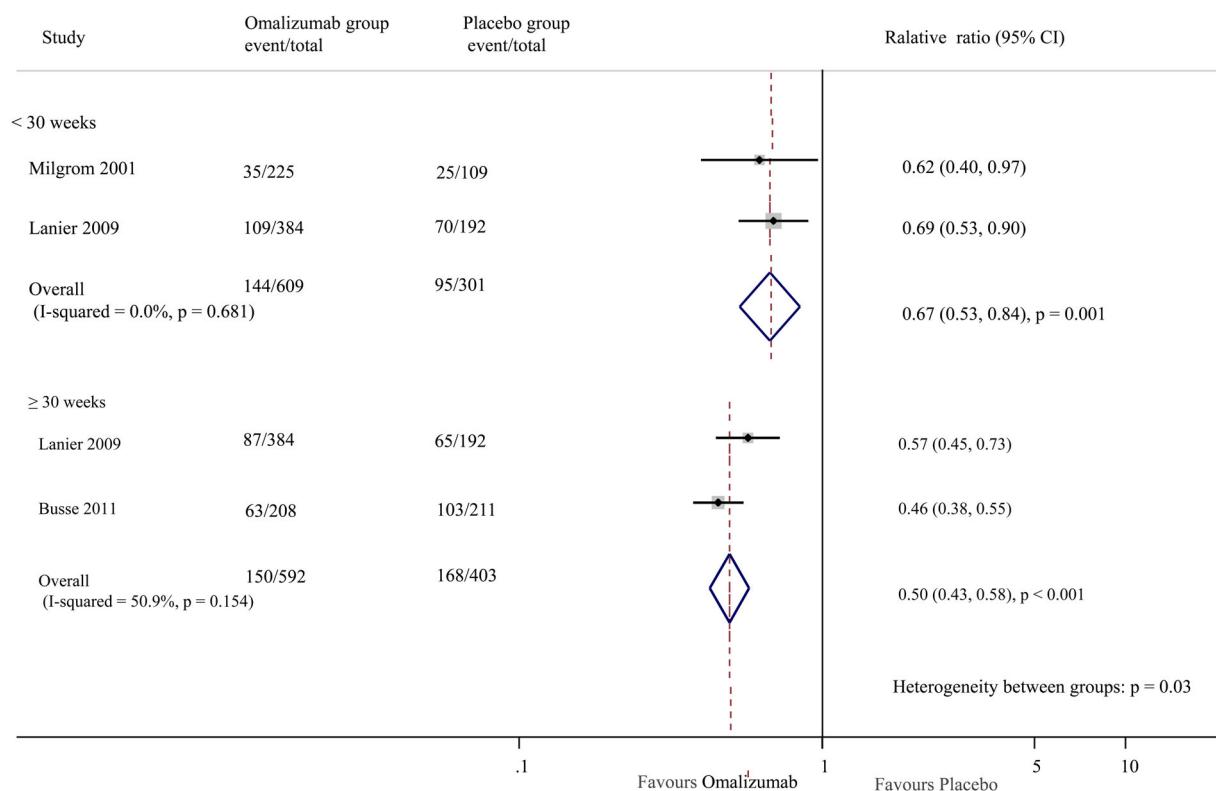


Figure 3. Comparison of number of patients with asthma exacerbations over a period of less than 30 weeks vs. more than 30 weeks between the omalizumab and placebo group in children with moderate-to-severe asthma.

Decrease in inhaled corticosteroid (ICS) dose

Two studies reported mean and SD values of decrease in ICS dose. The results showed people receiving omalizumab had a bigger reduction in the dosage of ICS than placebo group (weighted mean difference, $-108 \mu\text{g/d}$, 95% CI: -151.19 to $-64.81 \mu\text{g/d}$, $p < 0.001$; $I^2 = 0\%$, $p = 1.0$; Figure 5) at the end of follow-up.

Severe asthma

Additional analysis of one study evaluated the efficacy and safety of omalizumab in children with severe asthma. Omalizumab-treated patients experienced significantly lower rates of asthma exacerbations for treatment duration <30 weeks (OR 0.66, 95% CI: 0.44–0.99) or ≥ 30 weeks (OR 0.50, 95% CI:

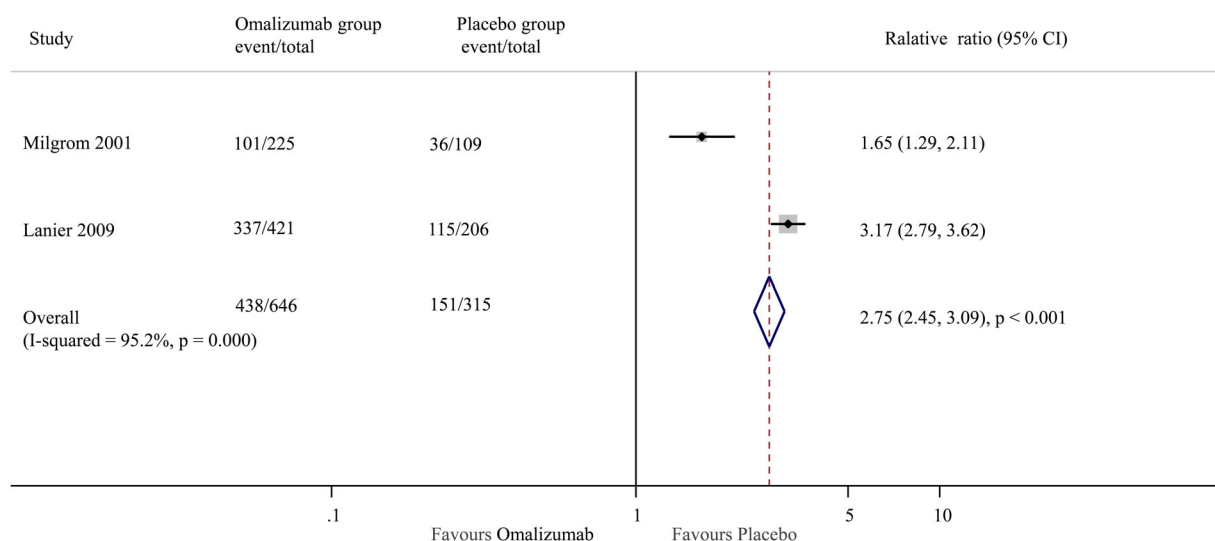


Figure 4. Comparison of global evaluation of treatment effectiveness between the omalizumab and placebo group in children with moderate-to-severe asthma.

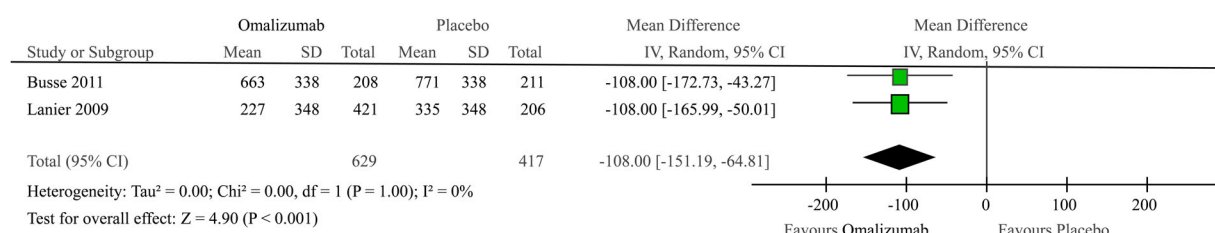


Figure 5. Comparison of decrease in inhaled corticosteroid (ICS) dose between the omalizumab and placebo group in children with moderate-to-severe asthma.

0.35–0.73). Omalizumab also increased the proportion of treatment effectiveness rated as excellent or good (OR 2.33, 95% CI: 1.87–2.91, Figure 6).

Adverse events

Data on adverse events such as any adverse events, severe adverse events, nasopharyngitis, upper respiratory tract infection, gastrointestinal symptom, and skin problem were provided in Table 3. Patients receiving omalizumab had a lower incidence of severe adverse events (OR 0.36, 95% CI: 0.22–0.57). The results of analysis showed that omalizumab therapy had no effects on incidence of any other adverse events (Table 3).

Risk of bias

Statistical testing showed no evidence of publication bias for asthma exacerbations (Begg's test $z = 0.52$, $p = 0.60$), which was displayed in Figure 7.

Discussion

In this meta-analysis, three studies with 1380 children focused exclusively on moderate-to-severe asthma to assess the efficacy and safety of omalizumab were included. We found that patients with omalizumab had a decreased incidence of asthma exacerbation, an excellent or good response rate of GETE assessed by physicians, and a bigger reduction in ICS dose than those receiving placebo. Omalizumab treatment also reduced the likelihood of asthma exacerbations and increased the odd of treatment effectiveness rated as excellent or good in children with severe asthma. Omalizumab-treated children were less likely to experience a serious adverse event. Our study provides evidence supporting the efficacy and safety of omalizumab in children with asthma.

Clinical practice guideline recommends the use of omalizumab in children with persistent allergic IgE-dependent asthma uncontrolled despite optimal pharmacological and non-pharmacological treatment (14). However, this is supported by the low-quality evidence because of limited studies in pediatric population. The present meta-analysis added the support

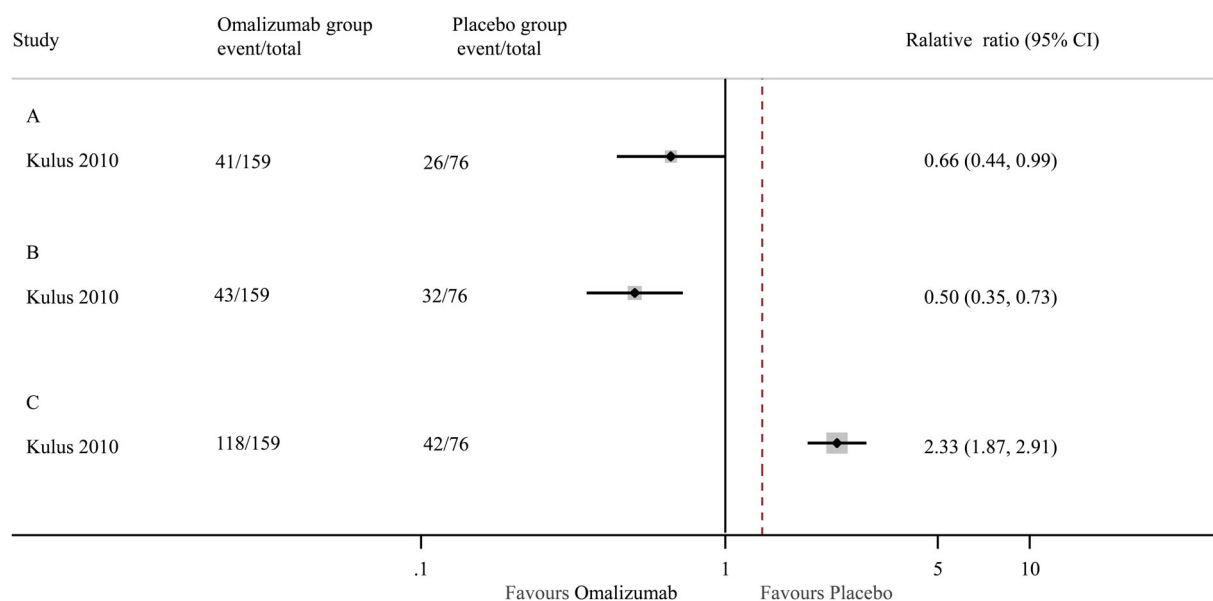


Figure 6. Comparison of number of patients with asthma exacerbations over a period of less than 30 weeks (A), number of patients with asthma exacerbations over a period of more than 30 weeks (B), and global evaluation of treatment effectiveness between the omalizumab and placebo group in children with severe asthma.

Table 3. Adverse events reported in the included studies.

Adverse events	Number of studies reporting	Omalizumab group (n/N)	Placebo group (n/N)	OR (95% CI)	p value
Any adverse events	3	663/854	384/526	1.06 (0.90–1.26)	0.47
Severe adverse events	3	30/854	51/526	0.36 (0.22–0.57)	<0.001
Nasopharyngitis	3	201/854	100/526	1.23 (0.94–1.60)	0.12
Upper respiratory tract infection	3	181/854	132/526	0.84 (0.65–1.08)	0.18
Gastrointestinal disorders	3	100/854	50/526	1.23 (0.86–1.75)	0.25
Skin	2	20/433	19/320	0.78 (0.40–0.48)	0.44
Sinusitis	2	108/646	61/316	0.86 (0.615–1.21)	0.41
Pyrexia	2	98/646	36/316	1.33 (0.88–1.99)	0.17
Headache	2	155/646	66/316	1.14 (0.83–1.57)	0.39
Cough	2	74/646	44/316	0.82 (0.55–1.22)	0.33
Influenza	2	107/646	53/316	0.98 (0.69–1.41)	0.95

for the efficacy of omalizumab to prior studies. The use of omalizumab is associated with reduced risk of asthma exacerbations and excellent or good response rate of GETE assessed by physicians than those receiving placebo. Folqué et al. reported omalizumab therapy in children aged less than 18 years reduced risks of asthma exacerbations and hospitalizations, improved lung function, and decreased the maintenance therapy after 6 months of treatment (15). Most of the results of our study were comparable to those of Gustavo 2015 (16). In their meta-analysis, they did not include the paper of Kulus 2010 and explore the response to omalizumab treatment for children with differing disease severity. In the current analyses, it appeared that patients with severe asthma also benefited from omalizumab treatment, with a reduction of the risk of asthma exacerbations and improved symptoms.

So far, the optimal course of treatment with omalizumab has not been determined. Whether patients

would benefit more from long-term use of omalizumab is still pending. Milgrom et al. found treatment with omalizumab over 28 weeks could protect against asthma exacerbation (13). The results of another RCT from Lanier et al. showed omalizumab-treated patients experienced a 31% reduction in the rate of clinically significant asthma exacerbation over a period of 24 weeks, and a 43% reduction over a period of 52 weeks compared with placebo (10). In the current analysis, long-term treatment with omalizumab over 30 weeks reduced asthma exacerbations to a greater extent. Physicians have questioned whether omalizumab should be discontinued or the dose should be reduced after clinical improvement is seen. Slavin et al. revealed asthma symptom reemerged after omalizumab withdrawal or pharmacokinetic concentrations decrement (17). These data may be reflective of the emergence of a full treatment effect with time, because suppressed free IgE levels lead to

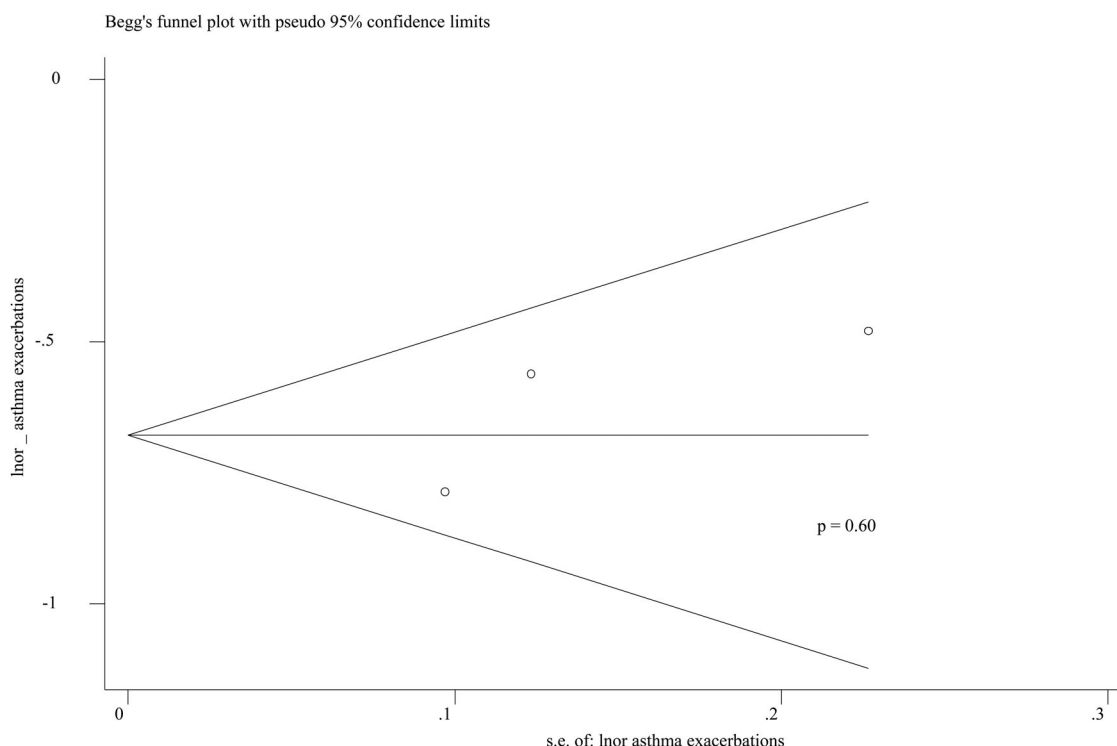


Figure 7. Begg's funnel plot of number of patients with asthma exacerbations.

downregulation of high-affinity IgE (FcεRI) receptors expressed on proinflammatory cells. This implies that treatment needs to be continued for a long time to keep effective.

Some people with more severe asthma depend on high doses of inhaled or oral corticosteroids to control their disease. It is important to underline the risks caused by the administration of steroid in children (18–20). A cohort study which was conducted in children aged 5–12 years who had mild-to-moderate asthma showed multiple oral corticosteroid could produce a dosage-dependent reduction in bone mineral accretion and increase risk for osteopenia (21). Long-term administration of steroid is also associated with many other side effects, including immune suppression, hyperglycemia, and growth failure. Therefore, agents that allow patients to reduce their daily steroid dose are of great interest. We found omalizumab reduced the daily inhaled steroid dose compared with placebo treatment, which consistent with the prior conclusion (22,23). In such situations, omalizumab should be preferred in children with large quantity application of corticosteroid.

Another major issue in omalizumab treatment in children is safety. It appeared that omalizumab-treated patients were less likely to experience a serious adverse event than those with placebo. It was noteworthy that the majority of serious adverse events was asthma exacerbations requiring hospital admission.

No significant difference was observed between groups regarding nasopharyngitis, gastrointestinal disorders, upper respiratory tract infection, skin problem, sinusitis, pyrexia, headache, cough, and influenza. The evidence suggests omalizumab is well tolerated but it has elevated costs.

Strength of this meta-analysis was the rigorous methodology we used. However, our review had a number of limitations. First, to our great pity, only three RCTs were included, all of which were relatively old. Observational studies or cohort studies that reported outcomes with low quality of evidence were not included. Second, because of the lack of sufficient data, a subgroup analysis exploring the efficacy and safety of omalizumab therapy for children in different age groups was not conducted. Third, this study provides a clear proof of beneficial effects of omalizumab therapy in children with moderate-to-severe asthma. However, we do not evaluate whether the effect of omalizumab is superior to other type of medication. The limitations of this study mean that high-quality RCTs with a large sample size are needed to reliably emphasize the efficacy of omalizumab therapy in children with asthma.

Conclusions

These findings suggested that omalizumab had beneficial effects on moderate-to-severe asthma in children.

Patients may benefit more from long-term use of omalizumab. In addition, omalizumab reduces the rate of serious adverse events requiring hospitalizations. Future research should involve large-scale multicenter RCTs with high quality and long-term follow-up durations to realize its full potential in children.

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Ethics approval and consent to participate

Not applicable.

Declaration of interest

The authors declare that they have no competing interests.

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References

1. Boulet LP, Reddel HK, Brightling C, Brusselle G. GINA fosters World Asthma Day 2020 to prevent asthma deaths. *Am J Physiol Lung Cell Mol Physiol*. 2020;318:L998–L1000. doi:10.1152/ajplung.00075.2020.
2. Serebrisky D, Wiznia A. Pediatric asthma: a global epidemic. *Ann Glob Health*. 2019;85:6. doi:10.5334/aogh.2416.
3. Nordon C, Grimaldi-Bensouda L, Pribil C, Nachbaur G, Amzal B, Thabut G, Marthan R, Aubier M. Clinical and economic burden of severe asthma: a French cohort study. *Respir Med*. 2018;144:42–49. doi:10.1016/j.rmed.2018.10.002.
4. Nagase H, Adachi M, Matsunaga K, Yoshida A, Okoba T, Hayashi N, Emoto K, Tohda Y. Prevalence, disease burden, and treatment reality of patients with severe, uncontrolled asthma in Japan. *Allergol Int*. 2020;69(1):53–60. doi:10.1016/j.alit.2019.06.003.
5. Thomson NC, Chaudhuri R. Omalizumab: clinical use for the management of asthma. *Clin Med Insights Circ Respir Pulm Med*. 2012;6:27–40. doi:10.4137/CCRPM.S7793.
6. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma*. 2012;49(2):144–152. doi:10.3109/02770903.2011.648296.
7. Garcia G, Magnan A, Chiron R, Contin-Bordes C, Berger P, Taille C, Devouassoux G, de Blay F, Couderc LJ, Didier A, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. *Chest*. 2013;144(2):411–419. doi:10.1378/chest.12-1961.
8. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;(1):CD003559. doi:10.1002/14651858.CD003559.pub4.
9. Li J, Kang J, Wang C, Yang J, Wang L, Kottakis I, Humphries M, Zhong N. Omalizumab improves quality of life and asthma control in Chinese patients with moderate to severe asthma: a randomized phase III study. *Allergy Asthma Immunol Res*. 2016;8(4):319–328. doi:10.4168/aa.2016.8.4.319.
10. 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.
11. Kulus M, Hebert J, Garcia E, Fowler TA, Fernandez VC, 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.
12. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. 2011;364(11):1005–1015. doi:10.1056/NEJMoa1009705.
13. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, Taylor AF, Rohane P. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics*. 2001;108(2):E36. doi:10.1542/peds.108.2.e36.
14. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleeker ER, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343–373. doi:10.1183/09031936.00202013.
15. Folque MM, Lozano J, Riggioni C, Piquer M, Alvaro M, Machinena A, Giner MT, Dominguez O, Jimenez-Feijoo RM, Dias DCM, et al. Real-life experience in asthmatic children treated with omalizumab up to six-years follow-up. *Allergol Immunopathol (Madr)*. 2019;47(4):336–341. doi:10.1016/j.aller.2018.09.009.
16. Rodrigo GJ, Neffen H. Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents. *Pediatr Allergy Immunol*. 2015;26(6):551–556. doi:10.1111/pai.12405.
17. Slavin RG, Ferioli C, Tannenbaum SJ, Martin C, Blogg M, Lowe PJ. Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations. *J Allergy Clin Immunol*. 2009;123(1):107–113. doi:10.1016/j.jaci.2008.09.050.
18. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling ZJJ, Tran TN. Adverse outcomes from initiation

- of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193–204. doi:[10.2147/JAA.S176026](https://doi.org/10.2147/JAA.S176026).
19. Janjua S, Schmidt S, Ferrer M, Cates CJ. Inhaled steroids with and without regular formoterol for asthma: Serious adverse events. *Cochrane Database Syst Rev*. 2019;9:CD6924. doi:[10.1002/14651858.CD006924.pub4](https://doi.org/10.1002/14651858.CD006924.pub4).
 20. Heffler E, Bagnasco D, Canonica GW. Strategies to reduce corticosteroid-related adverse events in asthma. *Curr Opin Allergy Clin Immunol*. 2019;19(1):61–67. doi:[10.1097/ACI.0000000000000493](https://doi.org/10.1097/ACI.0000000000000493).
 21. Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. *Pediatrics*. 2008;122(1):e53–e61. doi:[10.1542/peds.2007-3381](https://doi.org/10.1542/peds.2007-3381).
 22. Briars LA, Diaz A. Omalizumab: a steroid-sparing option for improving pediatric asthma management? *J Pediatr Health Care*. 2005;19(6):386–391. doi:[10.1016/j.pedhc.2005.09.001](https://doi.org/10.1016/j.pedhc.2005.09.001).
 23. Rees PJ. Review: omalizumab reduces exacerbation and steroid use in chronic asthma. *Arch Dis Child Educ Pract Ed*. 2007;92(4):ep127. doi:[10.1136/ebm.12.1.11](https://doi.org/10.1136/ebm.12.1.11).