

Omalizumab in Allergic Bronchopulmonary Aspergillosis: A Systematic Review and Meta-Analysis



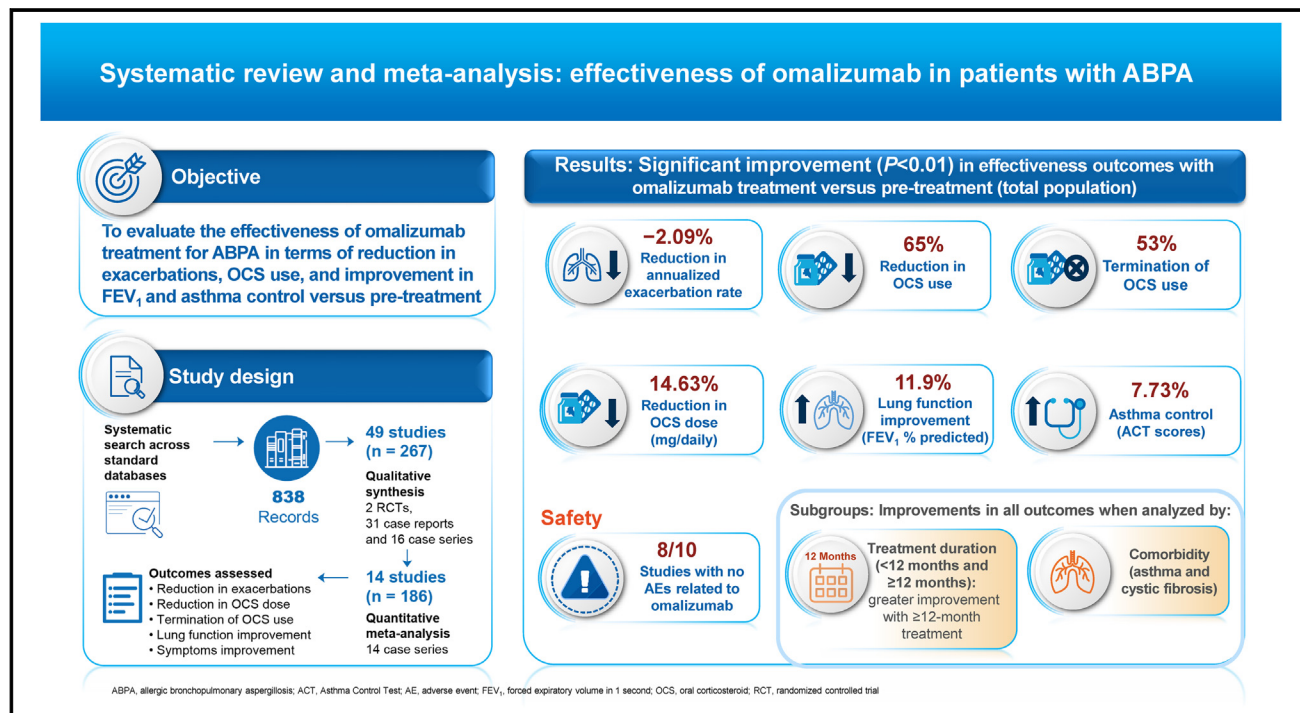
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What is already known about this topic? Omalizumab, an anti-IgE monoclonal antibody, has been used as an off-label therapy for allergic bronchopulmonary aspergillosis (ABPA) over the past 2 decades, along with oral glucocorticoids.

What does this article add to our knowledge? This systematic review and meta-analysis demonstrates that in patients with ABPA, omalizumab reduced exacerbations and oral glucocorticoid use, improved lung function and asthma control, and was well-tolerated.

How does this study impact current management guidelines? This systematic review and meta-analysis adds to the limited data available and demonstrates the effectiveness of omalizumab in improving disease outcomes in patients with ABPA, which may affect treatment decision-making.

GRAPHICAL ABSTRACT



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Abbreviations used

ACT- Asthma Control Test
AE- Adverse event
CF- Cystic fibrosis
CT- Computed tomography
IV- Inverse variance
OCS- Oral corticosteroid
RCT- Randomized controlled trial
RD- Risk difference

BACKGROUND: An unmet clinical need exists in the management of treatment-refractory allergic bronchopulmonary aspergillosis (ABPA). Omalizumab has shown promising effects in case series and cohort studies; however, evidence to support its routine clinical use is lacking.

OBJECTIVE: The aim of this systematic review and meta-analysis was to evaluate the clinical effectiveness and safety of omalizumab in patients with ABPA.

METHODS: We conducted a systematic search across standard databases using specific key words until May 13, 2021. We performed a meta-analysis to compare the effectiveness (exacerbations, oral corticosteroid [OCS] use, lung function, and patient-reported asthma control) and safety of pre- and post-omalizumab treatment. Subgroup analyses were performed for treatment duration and underlying disease.

RESULTS: In total, 49 studies ($n = 267$) were included in the qualitative synthesis and 14 case series ($n = 186$) in the quantitative meta-analysis. Omalizumab treatment significantly reduced the annualized exacerbation rate compared with pre-treatment (mean difference, -2.09 [95% CI, -3.07 to -1.11]; $P < .01$). There was a reduction in OCS use (risk difference, 0.65 [95% CI, 0.46 - 0.84]; $P < .01$), an increase in termination of OCS use (risk difference, 0.53 [95% CI, 0.24 - 0.82]; $P < .01$), and a reduction in OCS dose (milligrams per day) (mean difference, -14.62 [95% CI, -19.86 to -9.39]; $P < .01$) in ABPA patients receiving omalizumab. Omalizumab improved FEV₁ % predicted by 11.9% (95% CI, 8.2-15.6; $P < .01$) and asthma control, and was well-tolerated.

CONCLUSIONS: Omalizumab treatment reduced exacerbations and OCS use, improved lung function and asthma control in patients with ABPA, and was well-tolerated. The results highlight the potential role of omalizumab in the treatment of ABPA. © 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND

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Key words: Omalizumab; Allergic bronchopulmonary aspergillosis; Asthma; Cystic fibrosis; Meta-analysis; Exacerbations; Lung function; Oral corticosteroids; ACT score

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disease resulting from a hypersensitivity reaction to the antigens of *Aspergillus fumigatus*, colonizing the airways of patients with asthma or cystic fibrosis (CF).¹ The small diameter of the *Aspergillus* spores (2-3 μ m) leads to their deposition in the small airways, causing inflammation, bronchiectasis, fibrosis, and eventual loss of lung function.^{1,2} Allergic bronchopulmonary aspergillosis has distinct clinical and radiologic findings compared with other aspergillosis-related allergic conditions, including severe asthma with fungal sensitization and hypersensitivity pneumonitis.³

The worldwide burden of ABPA is estimated to be about 5 million persons, affecting approximately 2.5% of patients with asthma and 9% of patients with CF.⁴⁻⁷

Allergic bronchopulmonary aspergillosis is associated with an elevated serum total IgE level, usually greater than 1,000 IU/mL.^{1,8} Patients with long-standing ABPA have reduced lung function (FEV₁), high rates of hospitalization owing to exacerbations, and worsened respiratory quality of life.^{4,9} Consequently, timely diagnosis of ABPA and treatment that targets inflammation are important to prevent irreversible pulmonary damage.^{5,10}

The main treatment goals of ABPA are to control the symptoms of asthma or CF, manage exacerbations of ABPA, minimize pulmonary inflammation, prevent irreversible lung damage, and restrict the disease progression with further inflammation-mediated lung injury.¹¹ Treatment for ABPA is similar in patients with asthma or CF and primarily includes the use of oral corticosteroids (OCS).^{11,12} Although remission is achieved in most patients receiving OCS, relapse occurs in up to 45% of patients and can progress to chronic corticosteroid dependency,^{13,14} which can be associated with predictable adverse effects.^{2,13} Antifungal therapy is typically used to decrease the fungal burden in the airways and reduce exposure to systemic corticosteroids.¹ However, many patients do not respond successfully to antifungal therapy, and treatment is often associated

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Medical writing support for the manuscript was funded by Novartis Pharma AG, Basel, Switzerland.

Conflicts of interest: M. Jin reports personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Sanofi, and Novartis. J.A. Douglass reports honoraria for educational presentations from AstraZeneca, GSK, Novartis, Alphapharm, Shire, Stallergenes, and CSL in the past 5 years. She has served on advisory boards for Sanofi-Aventis, Novartis, GSK, AstraZeneca, Shire, Immunosis, and CSL. She has undertaken contracted or investigator-initiated research on behalf of GSK, Novartis, Immunosis, AstraZeneca, Sanofi-Aventis, Grifols, CSL, BioCryst, and Equilibrium. She has personal superannuation shareholding in CSL and reports book royalties from *Fast Facts: Asthma*. J.S. Elborn reports grants and personal fees from Vertex; and grants from Gilead and Viartis, Sanofi, Novartis, Polyphor, Alexia, and Ionis. R. Agarwal reports grant support for conducting research in

allergic bronchopulmonary aspergillosis from Cipla Pharmaceuticals, Mumbai, India. W.J. Calhoun reports grant funding from AstraZeneca, Sanofi, and Pulmatrix. He has received consulting fees from Genentech, Sanofi, and Pulmatrix. S. Lazarewicz, X. Jaumont, and M. Yan are or were employees of Novartis during the time of the review and the manuscript writing.

Received for publication August 4, 2022; revised December 9, 2022; accepted for publication December 12, 2022.

Available online December 26, 2022.

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<https://doi.org/10.1016/j.jaip.2022.12.012>

with the emergence of resistance, a wide range of drug–drug interactions, and variations in drug absorption,⁴ necessitating close treatment monitoring.¹

Biologic therapies, especially omalizumab, have been used off-label by physicians over the past 2 decades, primarily based on their effects on the inflammatory cells and mediators that have a fundamental role in the immunologic pathways relevant to ABPA.^{11,12,15,16}

Omalizumab is a humanized monoclonal antibody that binds to free serum IgE and prevents the binding of IgE to FCεRI (high-affinity IgE receptor) on basophils and mast cells, inhibiting the IgE-mediated inflammatory cascade.¹⁷ It is currently approved for treating IgE-mediated diseases such as allergic asthma, chronic rhinosinusitis with nasal polyps, and chronic spontaneous urticaria, with an acceptable safety profile^{17,18} and greater than 1.86 million patient-years of exposure.¹⁹

Published clinical evidence on the use of omalizumab in ABPA is scarce. Studies consist mainly of case series (small uncontrolled prospective studies and retrospective observational studies) and case reports. One double-blind, randomized, cross-over trial demonstrated the clinical benefits and immunologic effects of omalizumab in asthmatic patients with ABPA. However, a key limitation of that trial was the small sample size ($n = 13$).¹⁴ Another randomized controlled trial (RCT) to explore the effect of omalizumab in ABPA in patients with CF ($n = 14$) was terminated early owing to difficulties in patient recruitment.^{20,21} While a few literature reviews are available related to the use of omalizumab in ABPA,^{22–24} none have conducted any form of quantitative analysis to evaluate the qualitative findings that are published.

Hence, we conducted this systematic review and meta-analysis to enhance the current understanding of the potential clinical benefits of omalizumab in patients with ABPA and test the hypothesis that treatment with omalizumab results in clinically meaningful improvement in symptoms, reduces the use of OCS, and improves FEV₁.

METHODS

Protocol and guidance

We report the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.²⁵ The review protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; No. CRD42021268978).²⁶

Information sources and eligibility criteria

We conducted a systematic literature search of PubMed, Embase, Biosis (Ovid), Web of Science, Cochrane Central Register of Controlled Trials, clinical trial databases (<https://clinicaltrials.gov> and www.novartisclinicaltrials.com), and BioRxiv (unpublished literature) from inception to May 13, 2021, to identify publications evaluating omalizumab as monotherapy or in adjunction with systemic corticosteroids or antifungal treatment in patients with ABPA.

We included RCTs, controlled clinical trials, observational studies with the control group (prospective or retrospective), uncontrolled studies such as case reports and case series, letters to the editor, and conference abstracts (published from May 1, 2020 to April 30, 2021). Preclinical studies and consensus reports were excluded.

Medical subject headings and search terms used were “omalizumab” OR “anti-IgE” OR “antiIgE” OR “anti-immunoglobulin E” OR “Xolair” AND “allergic bronchopulmonary aspergillosis” OR “allergic bronchopulmonary mycosis” OR “ABPA”. Studies were

filtered by clinical trial and publication type, without language restrictions.

Outcomes

Primary outcomes were a reduction in annualized exacerbation rate, corticosteroid-sparing effect (reduction in or termination of OCS use, and reduction in OCS dose), lung function improvement (FEV₁ % predicted) from baseline, and asthma control based on Asthma Control Test (ACT).

Secondary outcomes included computed tomography (CT) outcome improvement and safety outcomes (adverse events [AEs] and serious AEs) (Supplemental Material in this article's Online Repository at www.jaci-inpractice.org/ provides additional information on the outcomes).

Study selection and data extraction

After the literature search, two reviewers independently selected the studies based on titles, abstracts, and citations, and any disagreements were resolved by a third reviewer. Each identified study was independently extracted into a predefined extraction form and assessed based on predefined eligibility criteria for population, intervention, study design, and outcomes. Extracted data consisted of patient demographics, baseline clinical characteristics, and pre- and postintervention outcomes.

Assessment of risk for bias in included studies

We assessed the risk for bias using the Cochrane risk of bias tool for RCTs,²⁷ the Moga tool for case series,²⁸ and the Joanna Briggs Institute critical appraisal checklist for case reports.²⁹

Data analysis

R programming software (meta package, version 3.4.1; R Core Team, Vienna, Austria) was used to analyze the data. Binary outcomes are presented as the risk differences (RDs) for single-group estimation analysis or risk ratios for pretreatment versus posttreatment comparisons and 95% CIs, whereas continuous variables are presented as mean differences and 95% CIs. Continuous outcomes such as medians (ranges) or medians (interquartile ranges) were converted to means and SDs, as previously described.³⁰ The analysis used the inverse variance (IV) or Mantel-Haenszel statistical method. Effect measures in the analysis were analyzed using a random-effects model for all outcomes to make optimal use of extracted data, avoid effect size selection bias, and address clinical heterogeneity variation across studies. The weight assigned to each study was determined using the IV method (ie, the inverse of the variance of the effect estimate, which is $1/[SE]^2$). Thus, larger studies that usually have smaller SEs are given more weight than smaller studies. However, when data were reported in terms of event rates, the Mantel-Haenszel method was used, a different weighting scheme that depends on the effect measure used, such as the risk ratio, odds ratio (OR), or RD. For single-group (post–pre) analysis, pre-omalizumab measurements served as the control group for comparisons of the same patients.

Heterogeneity was assessed and quantified using Higgin's inconsistency index I^2 statistics with upper limits of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Sensitivity analysis was conducted for all outcomes by including studies with a sample size of at least 10 patients to confirm the effect measures. In all analyses, P less than .05 (two-tailed test) was considered statistically significant. Subgroup analyses were also performed based on underlying disease (with asthma, with CF and with asthma/CF when not reported separately). Because studies

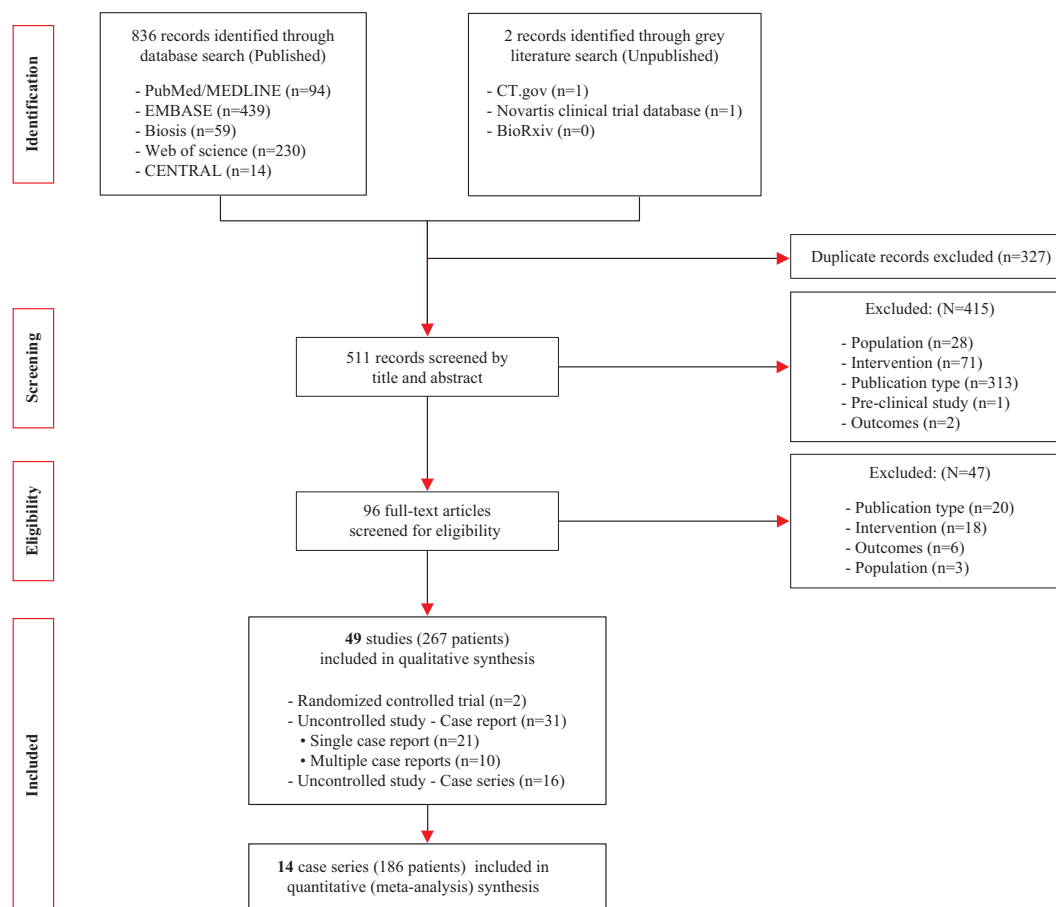


FIGURE 1. Preferred Reporting Items for Systematic Reviews flowchart.

differed in treatment duration, effect measures were analyzed as less than 12 months and 12 months and greater to normalize effect sizes.

RESULTS

A total of 838 studies were obtained from the databases (published and unpublished), 327 of which were excluded as duplicates; 415 were excluded when screened by title and abstract, and a further 47 studies were excluded during full-text screening (Figure 1). A total of 49 studies (n = 267) were included in the qualitative synthesis (two RCTs,^{14,21} 31 case reports,^{24,31-60} and 16 case series).^{8,13,20,61-73}

Fourteen case series^{8,13,20,61-63,66-73} (n = 186) were included in the quantitative (meta-analysis) synthesis (Figure 1), in which 12 studies were retrospective^{8,13,20,61-63,66-68,70,72,73} and two were prospective^{69,71} in design. Although the qualitative and quantitative analysis included 267 and 186 patients, respectively, when stratified for individual outcome, fewer patient data are available for each outcome.

Table I lists the summary characteristics of the included studies. The studies included male and female adolescents and adults. Most studies were conducted in Europe and Asia, but a few included patients from Canada and Australia. In the evaluated case series, asthma^{13,61,63,69-71} and CF^{20,62,66-68,72} were reported as comorbidities of ABPA in six studies each. In one

study,⁷³ both asthma and CF patients with ABPA were included, and in another study,⁸ there was no mention of the underlying disease. Treatment duration with omalizumab ranged between 4 and 36 months.

Details of the included patient populations and study characteristics are presented in Table E1 (in this article's Online Repository at www.jaci-inpractice.org/).

Exacerbation reduction

Qualitative review. Of the nine patients^{31,40,47,49,56,60} with ABPA and a documented exacerbation at baseline (pre-omalizumab), seven^{31,40,49,56,60} treated with omalizumab for 4 to 36 months did not experience a subsequent exacerbation. In the RCT, two of the 13 patients receiving omalizumab experienced an exacerbation each requiring treatment with prednisolone, compared with six of the 13 patients receiving placebo who experienced a total of 12 exacerbations.¹⁴

Quantitative meta-analysis. Exacerbation data were obtained from three studies (n = 37): two^{63,70} included ABPA patients with asthma (n = 19), whereas in the third,⁷³ ABPA patients with both asthma (n = 16) and CF (n = 2) were included. In patients with ABPA, omalizumab significantly reduced the annualized exacerbation rates at 8.3 to 12 months compared with baseline (pre-omalizumab), with a mean

TABLE I. Characteristics of included studies for quantitative meta-analysis

First author	Year	Country	Study type	Patients, n	Age, y	Allergic bronchopulmonary aspergillosis	Treatment duration, mo
Tomomatsu ¹³	2020	Japan	Retrospective	25	Median (IQR): 62 (47-71)	Asthma	Median (IQR): 20 (7.5-45.5)
Koutsokera ²⁰	2020	Canada	Retrospective	11	Median (IQR): 27.8 (21.8-37.7)	CF	12
Wark ⁸	2020	Australia	Retrospective	11	Mean $\pm$ SD: 63.9 $\pm$ 6.60	Not reported	24
Zhao ⁶¹	2020	China	Retrospective	5	Mean: 47	Asthma	≥ 3.68
Ünal ⁶⁹	2019	Turkey	Prospective	5	Mean $\pm$ SD: 48.3 $\pm$ 9.92	Asthma	36
Melscoet ⁷⁰	2019	France	Retrospective	10	Median (IQR): 63 (44.75-77.5)	Asthma	12
Ashkenazi ⁶²	2018	Israel, Belgium	Retrospective	9	Mean $\pm$ SD: 23.0 $\pm$ 9.00	CF	Mean $\pm$ SD: 13.9 $\pm$ 8.6
Perisson ⁶⁸	2017	France	Retrospective	18	Mean $\pm$ SD: 17.1 $\pm$ 4.40	CF	12
Nove-Josserand ⁶⁷	2017	France	Retrospective	32	Median (min, max): 23 (11, 59)	CF	Median (min, max): 18 (3, 50)
Emiraligolu ⁷²	2016	Turkey	Retrospective	6	Mean $\pm$ SD: 16.10 $\pm$ 7.9	CF	Mean $\pm$ SD: 12.5 $\pm$ 5.40
Aydin ⁶³	2015	Turkey	Retrospective	14	Mean $\pm$ SD: 44.2 $\pm$ 13.01	Asthma	Mean $\pm$ SD: 31.5 $\pm$ 3.99
Lehmann ⁶⁶	2014	Germany	Retrospective	6	Mean $\pm$ SD: 19.5 $\pm$ 9.64	CF	Mean $\pm$ SD: 19.7 $\pm$ 19.19
Tillie-Leblond ⁷¹	2011	France	Prospective	16	Median (range): 56 (29-76)	Asthma	12
Pérez-de-Llano ⁷³	2011	Spain	Retrospective	18	Mean $\pm$ SD: 49.0 $\pm$ 17.00	Asthma: 16; CF: 2	3.68

CF, cystic fibrosis; IQR, interquartile range.

difference of -2.09 (95% CI, -3.07 to -1.11 ; $P < .01$ for both subgroups) (Figure 2). Similar findings were reported in the treatment duration subgroup analysis, with a longer duration of treatment resulting in a greater reduction in the annualized exacerbation rate (See Supplemental Material and Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Corticosteroid-sparing effect

Qualitative review. All patients were receiving OCS before treatment with omalizumab. In the case reports that evaluated OCS use,^{31-36,38,40,41,43,45,47,49,52-54,56,58-60} this measure was reduced in all 26 patients treated with omalizumab for 1 to 36 months. A total of 16 of these 26 patients^{31,35,36,43,47,52,54,56,58-60} were completely free from OCS use after omalizumab intervention for 3 to 36 months.

Quantitative meta-analysis

Reduction in percentage of OCS use or termination of OCS. Of the eight studies that evaluated the OCS-sparing effect ($n = 84$), four included ABPA patients with asthma^{13,63,69,71} and four included those with CF.^{20,66,67,72} Data on 20% or greater reduction in OCS use were reported in three studies,^{20,67,71} whereas there was no mention of OCS reduction in three studies.^{13,66,72} Results of the binary outcomes analysis in the total population reported that omalizumab significantly reduced OCS use compared with pre-treatment in 65% of patients (RD, 0.65 [95% CI, 0.46-0.84]; $P < .01$) when patients were treated for 1 to 20 months. Furthermore, a total of 53% of patients terminated OCS use after treatment with omalizumab for 6 to 54 months (RD, 0.53 [95% CI, 0.26-0.80]; $P < .01$) (Figure 3). Findings of the subgroup analyses of treatment duration and comorbidity for these two outcomes are summarized in the Supplemental Material and presented in Figures E2, A, E2, B, E3, A, and E3, B, respectively, in this article's Online Repository at www.jaci-inpractice.org.

Reduction in milligrams per day of OCS dose. Five studies ($n = 64$) evaluated the reduction in daily OCS dose with omalizumab treatment. Three studies^{61,63,71} included ABPA

patients with asthma; one study⁶⁸ included ABPA patients with CF and another study⁸ included ABPA patients for whom the comorbidity status was not documented. A significant reduction in mean daily OCS dose of 14.62 mg (95% CI, -19.86 to -9.39 ; $P < .01$) was observed in ABPA patients treated with omalizumab for 4 or more to 54 months (Figure 4).

Findings of the subgroup analyses of treatment duration and comorbidity for this outcome are summarized in the Supplemental Material and presented in Figures E4, A and B (in this article's Online Repository at www.jaci-inpractice.org). The results indicate that a longer treatment duration (≥ 12 months) with omalizumab showed greater reductions in OCS use and daily OCS dose and increased termination of OCS use relative to those treated for less than 12 months. The corticosteroid-sparing outcomes were more beneficial in ABPA patients with asthma than in those with CF.

Lung function improvement

Qualitative review. A total of 25^{24,31,34-36,38,39,42,44,46,47,49,52,54-56,59} of 31 patients from 17 studies showed improvement in FEV₁ % predicted during omalizumab treatment for 0.5 to 24 months. In contrast, five patients^{33,48,56,57} showed a decrease in FEV₁ % predicted while receiving omalizumab treatment for 1 to 72 months, and one patient⁴³ showed no change in FEV₁ % predicted when treated for 43 months. In the RCT,¹⁴ no significant improvement in FEV₁ % predicted was reported in patients treated with omalizumab for 4 months compared with those treated with placebo (mean $\pm$ SD, 72 $\pm$ 22.5 vs 69 $\pm$ 24.5 for the omalizumab and placebo group, respectively; $P = .12$).

Quantitative meta-analysis. Data on FEV₁ % predicted were available from nine studies ($n = 120$), four of which^{63,69-71} included ABPA patients with asthma and four of which^{66-68,72} included ABPA patients with CF; in one study of 18 patients, two had ABPA with CF and 16 had ABPA with asthma.⁷³

A significant improvement in mean FEV₁ % predicted was reported in patients with ABPA treated with omalizumab for 6 to

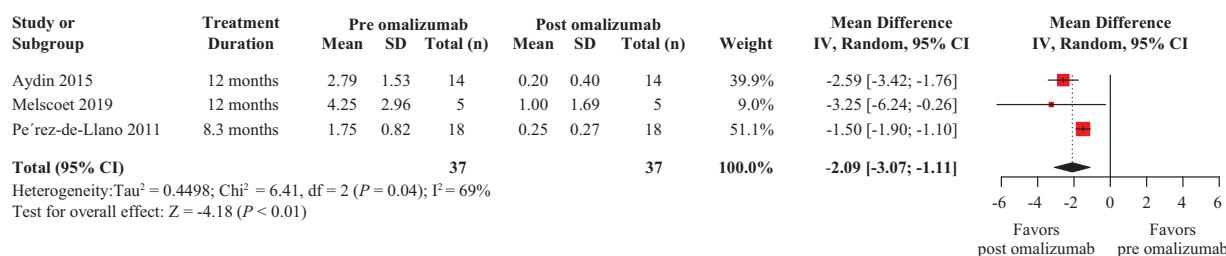


FIGURE 2. Effect of omalizumab on annualized exacerbation rate in patients with allergic bronchopulmonary aspergillosis (total population). Red squares represent mean difference (MD) estimates. Horizontal lines represent 95% CIs of MD estimates. Diamonds represent meta-analysis summary effect estimate. *IV*, inverse variance.

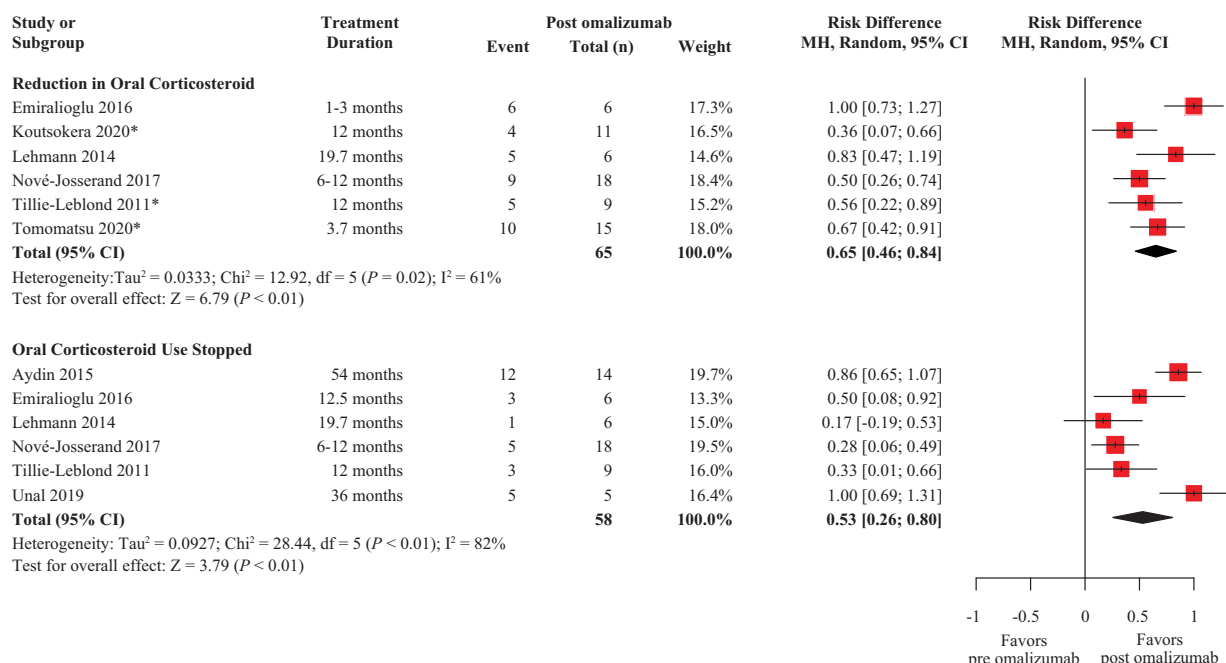


FIGURE 3. Effect of omalizumab on reduction and termination of oral corticosteroid (OCS) use (total population). Red squares represent risk difference estimates. Horizontal lines represent 95% CIs of risk difference estimates. Diamonds represent meta-analysis summary effect estimate. *MH*, Mantel-Haenszel statistic.

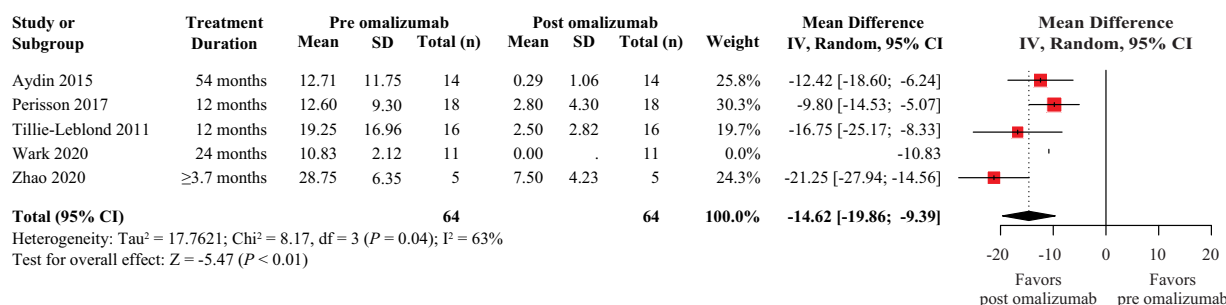


FIGURE 4. Effect of omalizumab on oral corticosteroid dose (mg/d) (total population). Red squares represent estimates. Horizontal lines represent 95% CIs of mean difference estimates. Diamonds represent meta-analysis summary effect estimate. *IV*, inverse variance.

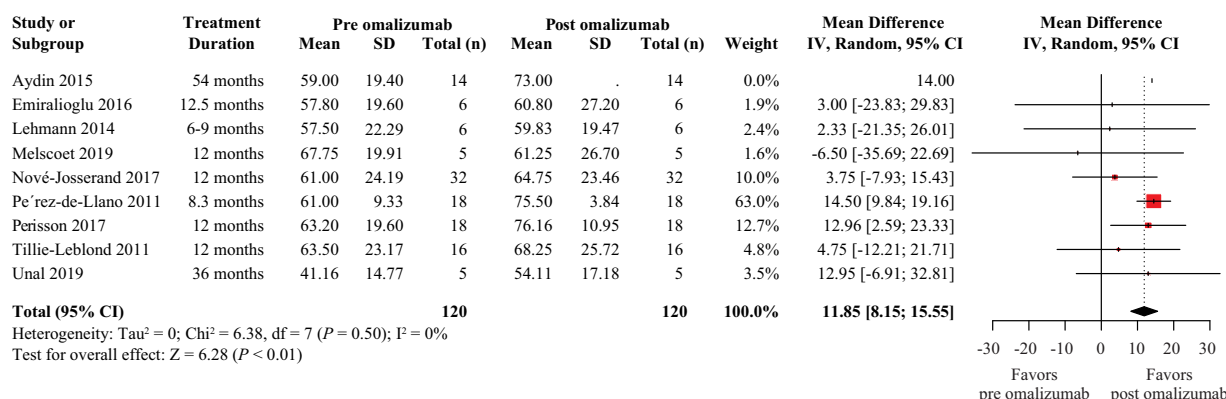


FIGURE 5. Effect of omalizumab on FEV₁ % predicted (total population). Red squares represent mean difference estimates. Horizontal lines represent 95% CIs of mean difference estimates. Diamonds represent meta-analysis summary effect estimate. /V, inverse variance.

54 months (mean difference, 11.9 [95% CI, 8.2-15.6]; $P < .01$) (Figure 5). Findings of the subgroup analyses of treatment duration and comorbidity for this outcome are summarized in the Supplemental Material and presented in the Figures E5, A and B in this article's Online Repository at www.jaci-inpractice.org.

Improvement in ACT scores

Qualitative review. Three^{31,38,45} of four patients reporting ACT scores showed improvement during omalizumab treatment for 4 to 18 months, whereas one patient⁵⁷ showed moderate worsening after 36 months of treatment.

Quantitative meta-analysis. Three studies^{61,63,69} ($n = 24$) reporting ACT scores in 24 patients showed a statistically significant improvement in the ACT score of 7.73 (95% CI, 4.88-10.58; $P < .01$) during omalizumab treatment for 3.7 to 54 months (Figure 6).

Reduction in total IgE levels

Qualitative review. Of 21 patients reporting IgE levels, 12^{24,31,32,35,37,38,41,45,53,57} showed a greater than 5% reduction in total IgE levels during omalizumab treatment for 1.8 to 36 months. For the remaining nine patients,^{33,36,43,54,57} either no change or an increase in IgE levels was observed.

Improvement in CT outcomes

Qualitative review. This was evaluated in two case reports. In one patient⁴⁶ with ABPA and CF, high-resolution CT after 12 months of omalizumab treatment revealed bilateral large cystic bronchiectasis in place of the alveolar consolidations and an improvement in pulmonary opacities in the other case. In the other patient,⁴⁹ after 12 months of omalizumab treatment for ABPA and allergic bronchial asthma, persistent bilateral bronchiectasis at multiple levels with less bronchial wall thickening (indicative of remission of inflammation), a reduced number of micronodular peribronchial opacities (indicative of reduced impaction and inflammation of the distal airways), and overall less bronchiectasis were reported.

Safety

Qualitative review. In the eight studies evaluating safety, no AEs or side effects were documented during omalizumab treatment for 1.4 to 36 months in 10 patients.^{31,38-40,42,51,52,55}

Quantitative meta-analysis. Of 10 studies^{13,20,61,63,66-68,71-73} ($n = 151$) that had data on AEs, eight^{20,61,63,66,68,71-73} ($n = 94$) reported no significant AEs related to treatment with omalizumab. A total of five mild AEs were reported in the remaining two studies: one report of an injection-site reaction,¹³ two mild burns at the injection site, one mild skin eruption coinciding at the injection site, and one of mild tingling and swollen lips.⁶⁷

DISCUSSION

There are no large clinical studies or pooled data on the effectiveness and safety of omalizumab in ABPA. Our systematic review and meta-analysis addresses the gap in evidence regarding the use of omalizumab in ABPA associated with asthma and CF. Omalizumab significantly reduced the annualized exacerbation rate and OCS use or OCS dose and increased the percentage of patients discontinuing OCS use compared with pretreatment in patients with ABPA. Significant improvements in lung function and asthma control were also reported in patients with ABPA treated with omalizumab. Omalizumab was well-tolerated in patients with ABPA.

Whereas the meta-analysis showed significant improvements in the outcomes in patients treated for less than 12 and 12 months or greater compared with baseline values, drug exposure of 12 months or greater showed a greater reduction in exacerbation rate and more patients discontinued OCS use. The improvement with longer duration is consistent with routine clinical practice of treating ABPA patients with asthma, in which omalizumab is usually administered for at least 12 months.

In the comorbidity subgroup analysis, ABPA patients with asthma or CF treated with omalizumab had significantly improved clinical outcomes with respect to a reduction in the exacerbation rate and corticosteroid-sparing effect compared with baseline values. However, only minor improvements in lung function were reported compared with baseline in both of the comorbid groups. Interestingly, the proportion of patients who discontinued corticosteroids and the extent of reduction in

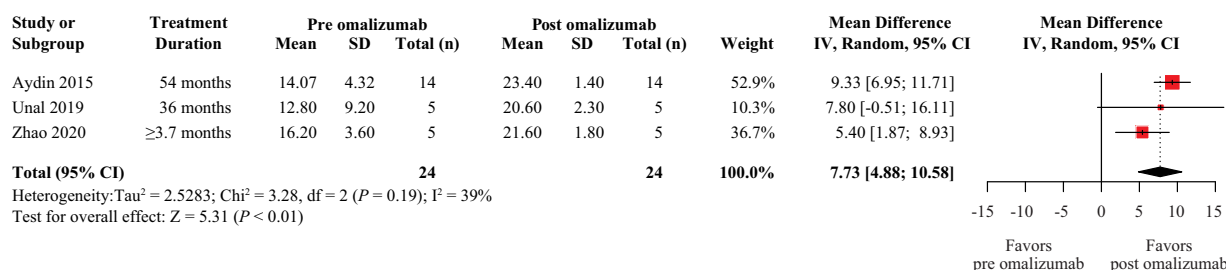


FIGURE 6. Effect of omalizumab on Asthma Control Test score (total population). Red squares represent mean difference estimates. Horizontal lines represent 95% CIs of mean difference estimates. Diamonds represent meta-analysis summary effect estimate. IV, inverse variance.

corticosteroid dose were higher in ABPA patients with asthma than in those with CF. This may be caused by the occurrence of severe lung disease owing to CF *per se* in patients with CF compared with those with asthma. Moreover, the diagnosis of ABPA in patients with CF is often delayed, increasing the severity of ABPA when diagnosed and potentially leading to a worse outcome.⁷⁴ Studies involving patients with CF may also be confounded by changes in underlying treatment, resulting in less beneficial outcomes. Nevertheless, patients with CF may be treated with corticosteroids for reasons other than those used to treat ABPA patients with asthma. Our study results indicate that omalizumab might be a good treatment option in CF-ABPA patients who have steroid dependency or contraindications to steroid use, owing to its steroid-sparing effect.²

In routine clinical practice, lung function may not be a meaningful variable to assess outcomes in patients with ABPA and comorbid asthma, especially in the presence of bronchiectasis. In addition, the specific outcome analyzed here as a measure of lung function (FEV₁ % predicted) does not necessarily reflect the severity of ABPA. Instead, the classification of ABPA based on the extent of bronchiectasis may best reflect the severity of the disease. In line with this, we revisited baseline CT and FEV₁ data to assess the severity of ABPA, especially for those with comorbid asthma. We noted that 34% of patients ($n = 64$ of 186) had ABPA with central or peripheral bronchiectasis. Baseline lung function data showed that in nine of 14 case series, patients had low mean or median FEV₁ (<60% predicted⁷⁵), three studies had patients with FEV₁ greater than 60% predicted, and in two studies, baseline lung function data were not reported. The results of this meta-analysis stratified by the baseline data indicate that omalizumab could be a potential treatment option irrespective of the ABPA severity (the presence or absence of bronchiectasis) and a history of asthma exacerbations.

Current dosing recommendations for omalizumab are based on IgE levels at baseline and body weight and are prescribed up to a dose of 600 mg every 2 weeks.^{17,18} The 49 studies included in the qualitative synthesis and quantitative meta-analysis used doses of omalizumab of 150 to 1200 mg and a frequency ranging from weekly to monthly. The most frequent dosage was 375 mg every 2 weeks. Participants received omalizumab for 1.38 to 36 months; most patients received omalizumab for at least 12 months (Table E1). Most ABPA patients have baseline IgE levels greater than 1,000 IU/mL, and many patients may have IgE levels that are above the dosing table range. Therefore, patients with ABPA generally exceed the current dosing parameters of

omalizumab in clinical practice. However, a randomized, placebo-controlled trial demonstrated that despite high levels of IgE in ABPA patients, the routine dose of omalizumab (375 mg every 2 weeks as a subcutaneous injection) may be sufficient to elicit clinical and immunologic benefits in these patients.¹⁴ This analysis did not assess the dose-response relationship of omalizumab because it was beyond the scope of the study.

Because the frequency of events for all outcomes was not large, we conducted an analysis using the EXACT method (for binary outcomes) of pooling data. The results of primary outcomes using this method were similar to those reported in the random effects model (data not shown). This meta-analysis was confined to data from case series; therefore, it is expected to have high heterogeneity. Sensitivity analysis was conducted for all outcomes using studies with a sample size of 10 or more patients. Although the results (effect measure and significance trend) were not markedly different from the original analysis, the heterogeneity of studies was reduced in a few instances, specifically for the corticosteroid-sparing outcomes (data not shown).

In this meta-analysis, we also explored the effect of omalizumab dosage per month using a meta-regression analysis of the various doses used in the studies. However, this was not feasible because of the lack of adequate patient data in the literature. The relative risk reduction in exacerbations data for studies involving ABPA patients with asthma was extracted, but an analysis was not performed owing to the small sample size. Similarly, the impact of omalizumab on total IgE levels could not be quantitatively evaluated by meta-analysis owing to insufficient IgE data from the included studies.

Although omalizumab is sporadically used off-label in patients with ABPA, to date, no systematic reviews and meta-analyses have been conducted in patients with ABPA treated with omalizumab. A synthesis review of the use of omalizumab in ABPA patients demonstrated that the treatment resulted in clinically important reductions in the serum IgE, exacerbation rate, and corticosteroid requirement and attenuated asthma symptoms, and improved lung function.²³ Our results support the use of omalizumab in patients with ABPA, but double-blind, randomized, placebo-controlled trials are required to substantiate the efficacy and safety of this biologic agent in this patient population. In addition, further clarity is required regarding the optimal dosing and duration of omalizumab treatment before it can be recommended as a routine treatment approach in this population. Our analysis of a pooled population of almost 186 patients provides evidence of the effectiveness and safety of omalizumab in patients with ABPA.

Limitations of our study include the use of case series data leading to selection bias and substantial heterogeneity and the lack of a placebo or control group. Moreover, the sample size of this meta-analysis is relatively small, which may limit the statistical power of the analysis. However, data used in the study are from published real-world evidence available on omalizumab in ABPA. Baseline clinical data with respect to the stage and duration of ABPA and extent of bronchiectasis (ABPA severity) were not available for most enrolled patients. Such data could have further improved the interpretation of the outcomes of the meta-analysis.

Conclusion

The results of this systematic review and meta-analysis show that omalizumab treatment significantly reduced the annual exacerbation rate and use of OCS in patients with ABPA. Omalizumab also significantly improved lung function and asthma control and was well-tolerated. Because many patients with ABPA might be candidates for long-term OCS treatment, the ability of omalizumab to reduce or cease OCS use is clinically meaningful, suggesting a valuable role of the anti-IgE therapy in managing treatment-refractory ABPA.

Acknowledgments

The authors thank Preethi B and Ian Wright (CONEXTS-Medical & Knowledge Solutions, India and UK) for providing medical writing support, which was funded by Novartis in accordance with Good Publication Practice guidelines (<http://www.ismpp.org/gpp3>). The authors also acknowledge Molecular Connections Pvt Ltd for providing support in the data analyses.

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