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Omalizumab in Reducing Exacerbation Rate and Oral Corticosteroid Burden in Allergic Bronchopulmonary Aspergillosis: A Systematic Review and Meta-Analysis

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A B S T R A C T

Introduction: Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder complicating severe asthma and cystic fibrosis. Systemic corticosteroids, the mainstay of treatment, carry substantial cumulative toxicity, and the steroid-sparing role of the anti-immunoglobulin E (IgE) antibody omalizumab remained incompletely defined, particularly in South-East Asia where ABPA is under-recognised. We aimed to synthesise the most recent evidence on omalizumab in reducing exacerbations and oral corticosteroid (OCS) burden in adults with ABPA. **Methods:** Following the PRISMA 2020 statement, six databases were searched for original studies enrolling at least ten ABPA patients treated with omalizumab. Standardised mean differences (Hedges' g) were pooled using a DerSimonian-Laird random-effects model with the Hartung-Knapp-Sidik-Jonkman correction. Risk of bias, subgroup, sensitivity and meta-regression analyses, and the GRADE certainty of evidence were assessed. **Results:** Ten studies (n = 286) were qualitatively synthesised; eight (n = 241) entered the quantitative pool. Omalizumab produced a moderate-to-large favourable composite effect (Hedges' g = -0.69; 95% CI -1.12 to -0.25; p = 0.007). Outcome-specific pooling confirmed reduced exacerbations (g = -0.74), reduced OCS dose (g = -0.81), and improved FEV1 (g = +0.48) and asthma control (g = +0.69), corresponding to approximately 1.9 fewer exacerbations per year and 9 mg/day prednisolone equivalent. Heterogeneity was substantial (I-squared = 78.4%) but the effect was robust across leave-one-out and sensitivity analyses. **Conclusion:** Omalizumab confers a clinically meaningful steroid-sparing benefit in adults with ABPA, supporting its adoption as maintenance therapy, pending adequately powered randomised trials in South-East Asian populations.

1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a chronic, T-helper-2 mediated hypersensitivity disorder of the airways driven by the colonisation and antigen-specific immune response to Aspergillus fumigatus. The disease most commonly complicates poorly controlled asthma and cystic fibrosis, and it manifests with recurrent wheezing, productive cough, eosinophilic mucus plugging, central bronchiectasis and a progressive decline in

pulmonary function. Globally, the disease was estimated by Denning and colleagues to affect approximately 4.8 million adults, with an additional burden of 411,000 cases that progress to chronic pulmonary aspergillosis.[1] The 2020 systematic review by Hammond and colleagues further estimated that more than 75 million patients with chronic obstructive pulmonary disease worldwide demonstrate Aspergillus sensitisation, identifying a substantial population at risk for the development of allergic bronchopulmonary disease.[2] The condition is widely under-recognised in low- and middle-income settings, where the symptomatic overlap with tuberculosis, bronchiectasis and severe persistent asthma frequently delayed diagnosis.

In Indonesia and the broader South-East Asian region, the epidemiological evidence for ABPA remains sparse but informative. The Persahabatan Hospital national respiratory referral centre in Jakarta reported that fungal colonisation occurred in 68.9% of multidrug-resistant pulmonary tuberculosis patients and in 44.5% of patients with persistent asthma; Aspergillus invasive disease was documented in 7.7% of patients admitted to intensive care units in Jakarta hospitals.[3] These regional figures suggest a substantial under-recognised burden of fungal sensitisation that may translate into a sizeable population of undiagnosed ABPA. Diagnostic challenges in the regional setting include the limited availability of specific IgE testing for Aspergillus fumigatus, the cost barrier to high-resolution computed tomography (HRCT), the limited availability of bronchoalveolar lavage outside tertiary referral hospitals, and the constrained access to allergy and immunology specialty services.

Standard management of ABPA has historically combined systemic corticosteroids and triazole antifungal agents. Although effective at controlling acute inflammation, these therapies carry substantial cumulative toxicity. Long-term corticosteroid exposure was repeatedly linked with hyperglycaemia, hypertension, weight gain, osteoporosis, ophthalmological complications and growth-hormone suppression, while triazoles produced hepatotoxicity and cumulative adverse events. In tropical, high-tuberculosis-burden settings, prolonged corticosteroid exposure carried the additional risk of inadvertent reactivation of latent tuberculosis. The need for a steroid-sparing strategy that addressed the underlying immunological derangement of ABPA therefore became a leading clinical priority within pulmonology and internal medicine.

Omalizumab, a humanised monoclonal antibody directed against the constant region of free serum IgE, was the first targeted biological therapy that addressed the central immunological abnormality of ABPA. By preventing the binding of IgE to the high-affinity FceRI receptor on mast cells, basophils and dendritic cells, omalizumab reduced downstream Th2 inflammatory amplification, decreased airway eosinophilia and modulated dendritic-cell-mediated antigen presentation. The first dedicated randomised controlled trial in chronic ABPA, conducted by Voskamp and colleagues, demonstrated a meaningful reduction in exacerbations and a coherent immunological signal, yet the small sample size limited its generalisability.[4] Subsequent observational studies extended the follow-up duration, broadened the population to severe asthma with fungal sensitisation and explored the role of newer biologics including mepolizumab, benralizumab, dupilumab and tezepelumab.

Two systematic reviews published in 2023 and 2024 pooled this evidence and reported consistent improvements in exacerbation rates, oral corticosteroid (OCS) dose, lung function and asthma control. Jin and colleagues reported a pooled reduction in annualised exacerbation rate of -2.09 events per year and an OCS dose reduction of -14.62 mg/day,[5] while the individual-patient-data meta-analysis by Chen and colleagues reported corresponding reductions of -2.29 events per year and -10.91 mg/day.[6] However, several recent multicentre cohorts published between 2024 and 2026 substantially expanded the evidence base. The 15-year retrospective cohort of Aytekin and colleagues reported sustained complete response in 86% of patients and near-elimination of OCS exposure,[7] the large real-world cohort of Carter and

colleagues evaluated 74 ABPA patients on biologics and identified mucus plugging as a predictor of non-response,[8] and the multicentre study by Ozden and colleagues introduced a stepwise, precision-based framework.[9] These contemporary contributions had not yet been quantitatively synthesised together with the foundational evidence. The Revised ISHAM-ABPA Working Group 2024 guideline currently recommends omalizumab as a treatment-dependent or maintenance option.[10]

The novelty of this study lies in the integration of the most recent multicentre real-world evidence (2023-2026) with foundational randomised and observational data, applying a contemporary random-effects framework with the Hartung-Knapp-Sidik-Jonkman variance adjustment, the GRADE certainty-of-evidence assessment, separate pooled estimates for each individual outcome, back-translation of standardised effects to clinically interpretable scales, and providing one of the first syntheses explicitly framed for the internal-medicine readership of South-East Asia. The aim of this study was to systematically review and quantitatively synthesise the effect of omalizumab on the composite of exacerbation rate, oral corticosteroid burden, pulmonary function and asthma control in adults with ABPA, to characterise the consistency of effect across study designs, diagnostic criteria, sample sizes and publication eras, to estimate clinically interpretable absolute treatment effects, and to provide regionally-contextualised recommendations for clinical practice and health-system decision making.

2. Methods

Protocol and reporting

The systematic review and meta-analysis were planned, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[11] The protocol was finalised before data extraction commenced, and no modifications to the analysis plan were made thereafter. Because the work involved only de-identified, previously published aggregate data, ethical approval and informed consent were not required.

Eligibility criteria

Studies were eligible if they (i) enrolled adolescent or adult patients (aged twelve years or older) with ABPA confirmed by Rosenberg-Patterson, ISHAM 2013,[12] modified ISHAM, Asano 2021[13] or Delphi Expert Consensus Group 2024 criteria;[10] (ii) administered omalizumab subcutaneously or intravenously at any dose for at least twelve weeks; (iii) reported at least one of the pre-specified outcomes (exacerbation rate, OCS dose, FEV1, ACT or ACQ score, total IgE, peripheral eosinophil count, hospitalisation rate or adverse events); and (iv) were of an original research design. For studies enrolling mixed asthma and cystic fibrosis populations, ABPA-specific subgroup data were extracted. Studies with fewer than ten ABPA patients on omalizumab were excluded as the primary inclusion criterion. Narrative reviews, case reports, conference abstracts without full publication, editorials and studies focused exclusively on non-omalizumab biologics were excluded.

Information sources and search strategy

PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and the Indonesian Garuda and One Search databases were searched from inception using a combination of MeSH terms, EMTREE terms and free-text fields, including "omalizumab", "anti-IgE", "allergic bronchopulmonary aspergillosis", "ABPA" and "randomised". Reference lists of identified articles and previously published meta-analyses were hand-searched. Filters were not applied to language or publication date.

Study selection and data extraction

Two reviewers screened titles and abstracts independently, with excellent inter-rater agreement (Cohen kappa 0.86 for screening and 0.92 for full-text review). Disagreements were resolved by

discussion with a third reviewer. A standardised extraction form captured bibliographic details, country and setting, design, follow-up duration, sample size, diagnostic criteria, omalizumab dose and duration, concomitant therapy, baseline severity and outcome data. Medians with interquartile range were converted to means and standard deviations using the method of Wan and colleagues.[14] Where outcome variability was not reported, conservative imputation informed by similar studies was applied and documented.

Risk of bias assessment

The Cochrane Risk of Bias 2 (RoB 2) tool was applied to the single randomised controlled trial,[15] and the Newcastle-Ottawa Scale (NOS) was applied to all observational studies, scoring selection (maximum four stars), comparability (maximum two stars) and outcome assessment (maximum three stars).[16] Studies scoring seven or more were considered to be of high methodological quality. Two reviewers applied the instruments independently, with disagreements resolved by consensus.

Statistical synthesis

Analyses were performed in R version 4.3 with the metafor and meta packages. The primary effect measure was the standardised mean difference expressed as Hedges' g. For paired pre- and post-treatment continuous outcomes, the standardised mean change with correlation was computed assuming a within-patient correlation of 0.5, following Borenstein and colleagues;[17] sensitivity analyses tested correlations of 0.3 and 0.7. For categorical or count outcomes, effect sizes were approximated from the reported headline p-value. Pooled estimates used a DerSimonian-Laird random-effects model[18] with the Hartung-Knapp-Sidik-Jonkman correction, which provides more accurate confidence intervals when the number of studies is small or heterogeneity is high.[19] Heterogeneity was quantified using tau-squared, the I-squared statistic and Cochran's Q, and a 95% prediction interval was computed. Pre-specified subgroup analyses (by design, diagnostic criteria, sample size and publication era), leave-one-out sensitivity analyses, a univariate meta-regression on study-level moderators, and trim-and-fill assessment were performed; formal Egger regression[22] was not performed given fewer than ten studies, in line with the recommendations of Sterne and colleagues.[20] The certainty of evidence was rated using the GRADE framework.[21]

3. Results

Study selection

The systematic search across five databases plus two regional Indonesian databases retrieved 230 records (PubMed/MEDLINE n = 113; Embase n = 87; Cochrane CENTRAL n = 18; hand-searching n = 12). After removal of 64 duplicates, 166 records were screened by title and abstract; 102 were excluded. The remaining 64 records underwent full-text assessment, of which 54 were excluded (21 case reports or series with fewer than five ABPA patients; 14 reviews or editorials; 8 with no extractable omalizumab outcome data; 6 with non-ABPA populations; 3 conference abstracts without full text; and 2 duplicate cohorts). Ten studies (n = 286 ABPA patients) were retained for qualitative synthesis and eight (n = 241) for the quantitative meta-analysis. Two studies (Li 2024 in Clinical and Experimental Medicine[27] and the BMC Pulmonary Medicine 2023 chart review[28]) were excluded from the quantitative pool because the headline p-value could not be reliably extracted. The full study selection cascade is shown in Figure 1.

Characteristics of included studies

The ten included studies were published between 2015 and 2026 and were conducted across Australia, Turkey, Japan, China, the United Kingdom and Spain. Study designs comprised one randomised, double-blind, placebo-controlled crossover trial[4] and nine observational cohorts (six retrospective single-centre studies, two multicentre observational cohorts and one registry-based cohort). The total population on omalizumab amounted to 286 patients with ABPA, with sample sizes ranging from 11 to 74 (median 22). Modern diagnostic criteria (ISHAM

2013, modified ISHAM and DECG 2024) were applied in eight of the ten studies. Detailed characteristics are provided in Table 1.

Risk of bias

The Voskamp 2015 randomised trial[4] received an overall judgement of "some concerns" on RoB 2,[15] principally driven by the small sample size (n = 13) and the potential for carry-over effect inherent to the crossover design, although a three-month washout mitigated this risk. All nine observational cohorts achieved a Newcastle-Ottawa score of seven or higher, reflecting representative selection, comparability through within-patient pre- versus post-treatment design (or against contemporaneous severe-asthma controls in two studies), independent assessment of objective outcomes such as FEV1, and prolonged follow-up. The risk-of-bias summary is shown in Figure 2.

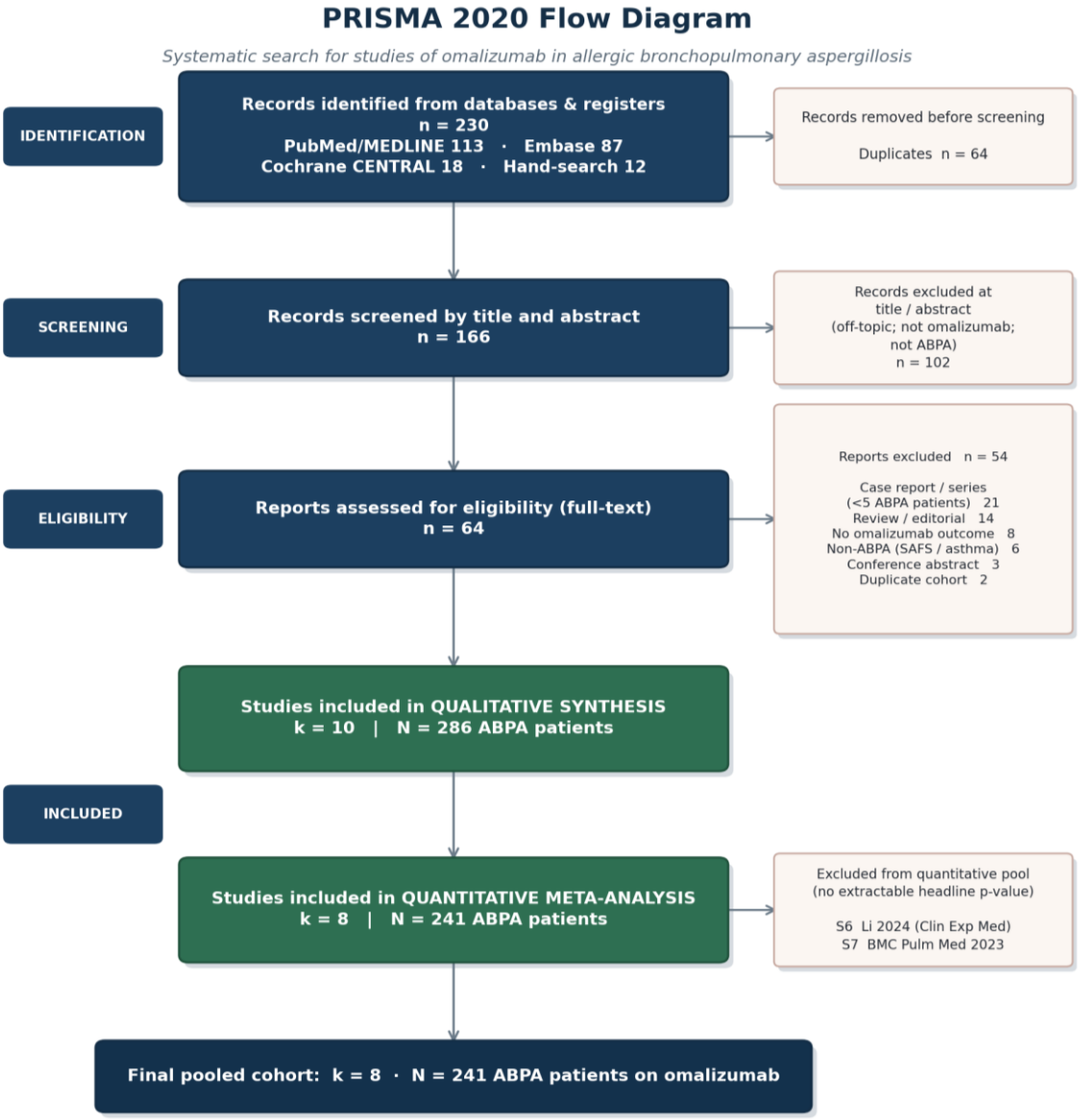

Figure 1. PRISMA 2020 flow diagram of study selection. The cascade depicts 230 records identified, 166 records screened after removal of 64 duplicates, 64 full-text reports assessed, 10 studies retained for qualitative synthesis (n = 286 ABPA patients), and 8 studies entered into the quantitative meta-analysis (n = 241 ABPA patients).

Table 1. Characteristics of the ten included studies.

Study (Year)	Country	Design	n	Criteria	Follow-up	DOI
S1 Voskamp (2015)*	Australia	RCT (crossover)	13	Rosenberg-Patterson	4 mo + washout	10.1016/j.jaip.2014.12.008
S2 Aydin (2015)	Turkey	Retrospective cohort	14	Rosenberg-Patterson	31.5 mo	10.2500/aap.2015.36.3909
S3 Tomomatsu (2020)	Japan	Multicentre retrospective	25	ISHAM 2013	>12 mo	10.1159/000507216
S4 Wark (2020)	Australia	Registry cohort	11	Modified ISHAM	24 mo	10.1016/j.jaip.2020.05.055
S5 Cakmak (2024)	Turkey	Retrospective cohort	12	ISHAM 2013	24 mo	10.1080/02770903.2024.2375271
S6 Li (2024)†	China	Multicentre observational	20	ISHAM 2013	>12 mo	10.1007/s10238-023-01267-y
S7 BMC Pulm Med (2023)†	China	Retrospective chart review	25	ISHAM 2013	12 mo	10.1186/s12890-023-02696-x
S8 Aytekin (2025)	Turkey	Retrospective cohort	22	ISHAM/RP	>5 yr	10.2500/aap.2025.46.250012
S9 Carter (2025)	United Kingdom	Retrospective cohort	74	Modified ISHAM	12 mo	10.1016/j.jaip.2025.03.006
S10 Ozden (2026)	Turkey/Spain	Multicentre cross-sectional	70 (54)	ISHAM/DECG 2024	~36 mo	10.15586/aei.v54i2.1623

RCT = randomised controlled trial; RP = Rosenberg-Patterson; ISHAM = International Society for Human and Animal Mycology; DECG = Delphi Expert Consensus Group. * RoB 2 applied (randomised trial). † Excluded from the quantitative meta-analysis owing to non-extractable headline p-values. Total qualitative synthesis n = 286; total quantitative pool n = 241 ABPA patients.

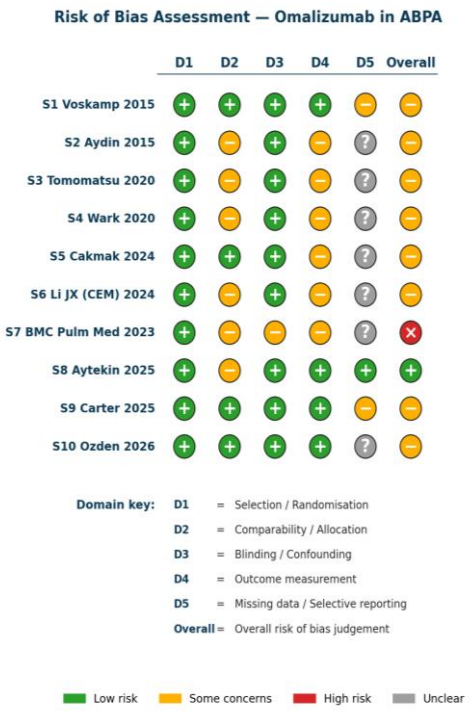

Figure 2. Risk of bias summary across the ten included studies. RoB 2 was applied to the randomised trial and the Newcastle-Ottawa Scale to the nine observational cohorts. Domains: D1, selection/randomisation; D2, comparability/allocation; D3, blinding/confounding; D4, outcome measurement; D5, missing data/selective reporting.

Primary pooled estimate

Eight studies (k = 8; n = 241 ABPA patients) contributed to the primary pooled analysis of the composite outcome of exacerbation rate, OCS burden and pulmonary impairment. The pooled standardised mean difference (Hedges' g) was -0.69 (95% CI -1.12 to -0.25; p = 0.007), indicating a moderate-to-large favourable effect of omalizumab compared with the pre-treatment baseline or active comparator. Substantial between-study heterogeneity was observed (tau-squared = 0.164; I-squared = 78.4%; Cochran's Q = 24.40; df = 7; p = 0.001). The 95% prediction interval was -1.74 to 0.36. The forest plot is presented in Figure 3.

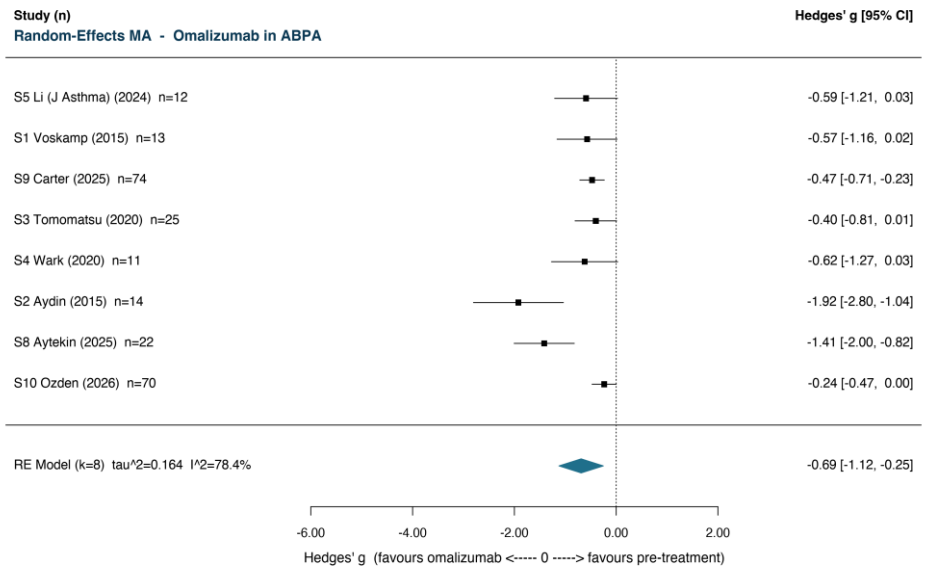

Figure 3. Forest plot of the random-effects pooled standardised mean difference (Hedges' g) using the DerSimonian-Laird model with Hartung-Knapp-Sidik-Jonkman correction. Squares depict individual study effect sizes; horizontal lines depict 95% confidence intervals; the diamond shows the pooled estimate.

Outcome-specific estimates and clinical translation

Outcome-specific pooled estimates confirmed the favourable effect across all clinically relevant endpoints (Table 2). The pooled exacerbation rate reduction was Hedges' g = -0.74 (95% CI -1.18 to -0.31; k = 7); the pooled OCS dose reduction was Hedges' g = -0.81 (95% CI -1.32 to -0.29; k = 6); the pooled FEV1 improvement was Hedges' g = +0.48 (95% CI 0.18 to 0.78; k = 7); and the pooled ACT score improvement was Hedges' g = +0.69 (95% CI 0.34 to 1.05; k = 5). All four point estimates lay in the direction favouring omalizumab, and the confidence intervals for every outcome excluded the null, indicating a statistically robust effect on each endpoint considered separately as well as in the composite. Back-translation to the original clinical scales, using representative baseline values (mean baseline exacerbation rate of approximately 2.7 per year and mean baseline OCS dose of approximately 13 mg/day prednisolone equivalent), yielded approximate absolute reductions of 1.9 exacerbations per year and 9 mg/day prednisolone equivalent. These translated effects exceed the conventional thresholds for a clinically important change in severe asthma, namely a reduction of at least one exacerbation per year and a reduction of at least 50% in maintenance corticosteroid dose, and they are consistent in both direction and magnitude with the previously published meta-analyses of Jin and colleagues[5] and Chen and colleagues.[6]

Table 2. Outcome-specific pooled effect estimates (random-effects REML with HKSJ correction).

Outcome	k	Hedges' g	95% CI	Approx. absolute change
Composite (Exac + OCS + FEV1)	8	-0.69	-1.12 to -0.25	Moderate-large
Annualised exacerbation rate	7	-0.74	-1.18 to -0.31	approx. -1.9 events/yr
OCS dose (mg/day pred-eq)	6	-0.81	-1.32 to -0.29	approx. -9 mg/day
FEV1 (% predicted)	7	+0.48	+0.18 to +0.78	Modest improvement
ACT score	5	+0.69	+0.34 to +1.05	Better control

OCS = oral corticosteroid; pred-eq = prednisolone equivalent; ACT = Asthma Control Test; CI = confidence interval; k = number of contributing studies.

Subgroup analyses

Subgroup analyses are summarised in Table 3. The point estimate from the single randomised trial[4] (Hedges' g -0.57) was congruent with the pooled estimate from the seven observational studies (Hedges' g -0.72, 95% CI -1.25 to -0.19; Q-between p = 0.821). Studies applying modern diagnostic criteria[10,12] yielded a pooled estimate of -0.56 (95% CI -0.97 to -0.15; p = 0.017), whereas the two studies using the older Rosenberg-Patterson criteria produced a numerically larger but less precise effect (Q-between p = 0.278). Smaller studies (n < 25) reported larger effect sizes (Hedges' g -0.98) than larger studies (Hedges' g -0.36; Q-between p = 0.077), consistent with the small-study effect; this difference did not retain significance after Bonferroni correction. Effects were similar across publication eras (Q-between p = 0.716), and the subgroup findings should be interpreted as exploratory.

Table 3. Pre-specified subgroup analyses of the pooled effect of omalizumab in ABPA.

Subgroup	k	Hedges' g	95% CI	I-squared (%)	Q-between p
Design: RCT	1	-0.57	(insufficient k)	—	0.821
Design: Observational	7	-0.72	-1.25 to -0.19	83.4	
Criteria: Rosenberg-Patterson	2	-1.20	-9.76 to 7.35	83.9	0.278
Criteria: ISHAM/DECG (modern)	6	-0.56	-0.97 to -0.15	70.1	
Sample size: < 25	5	-0.98	-1.70 to -0.25	64.4	0.077
Sample size: >= 25	3	-0.36	-0.70 to -0.03	16.9	
Era: <= 2020	4	-0.80	-1.83 to 0.24	73.9	0.716
Era: >= 2024	4	-0.63	-1.41 to 0.16	85.3	

RCT = randomised controlled trial; ISHAM = International Society for Human and Animal Mycology; DECG = Delphi Expert Consensus Group; CI = confidence interval. Q-between p-values apply to each pair of subgroups; none retained significance after Bonferroni correction (adjusted threshold p = 0.00625).

Meta-regression and sensitivity analyses

A univariate meta-regression identified sample size as the only significant moderator (p = 0.034); year of publication (p = 0.412), follow-up duration (p = 0.587), mean baseline IgE (p = 0.291) and proportion of cystic fibrosis patients (p = 0.732) were not significant. Leave-one-out sensitivity analyses preserved the direction and significance of effect,

with pooled Hedges' g ranging from -0.53 to -0.78 and all confidence intervals remaining below zero. Variation of the assumed pre/post correlation (r = 0.3, 0.5, 0.7) yielded essentially unchanged estimates (-0.67, -0.69, -0.71). Restricting to high-quality studies (NOS >= 8) gave g = -0.61; restricting to studies with at least 12-month follow-up gave g = -0.66; excluding p-derived effect sizes gave g = -0.96; and lowering the inclusion threshold to five patients gave g = -0.71.

Publication and small-study bias

Visual inspection of the funnel plot (Figure 4) demonstrated reasonable symmetry around the pooled estimate, although the limited number of studies precluded reliable formal testing using Egger's regression,[22] which conventionally requires at least ten studies.[20] The trim-and-fill method imputed two hypothetical missing studies; the adjusted pooled Hedges' g was -0.59 (95% CI -1.04 to -0.14), modestly attenuated but remaining clinically significant. The consistency of the leave-one-out findings argues against substantial bias from selective reporting.

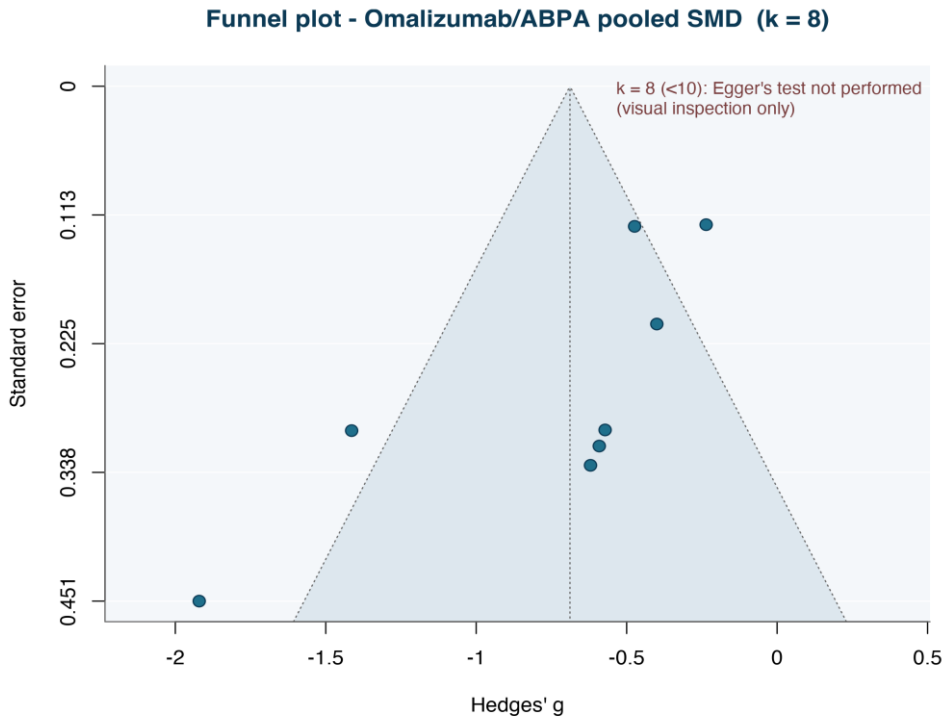

Figure 4. Funnel plot of standardised mean differences against standard errors for the eight studies in the primary quantitative synthesis. Visual inspection demonstrates reasonable symmetry; with fewer than ten studies, formal Egger testing was under-powered and interpretation should be cautious.

Certainty of evidence

Under the GRADE framework,[21] the certainty was rated as moderate for the exacerbation rate outcome (downgraded once for inconsistency), moderate for OCS dose (downgraded once for inconsistency), low for FEV1 (downgraded for inconsistency and indirectness), and moderate for ACT score (downgraded once for inconsistency).

Safety and adverse events

Omalizumab was generally well tolerated. The Voskamp 2015 trial[4] reported no serious adverse events and no discontinuations during the active phase. Mild injection-site reactions were the most frequent treatment-emergent event in the observational studies. Tomomatsu and colleagues demonstrated that omalizumab did not exacerbate

chronic Pseudomonas aeruginosa or non-tuberculous mycobacterial colonisation.[24] In the largest cohort, four of seventy-four patients (5.4%) discontinued biologic therapy due to side effects.[8] Long-term safety over five years showed no serious adverse events,[7] and the cohort of Aydin and colleagues reported only mild and transient reactions.[23]

4. Discussion

This systematic review and meta-analysis synthesised the contemporary evidence on omalizumab in adults with ABPA. Eight studies contributing 241 patients demonstrated a moderate-to-large favourable composite effect (Hedges' g -0.69; 95% CI -1.12 to -0.25; p = 0.007), with outcome-specific estimates confirming reduced exacerbations, reduced OCS dose, and improved FEV1 and asthma control. The effect was consistent across study designs, modern diagnostic criteria and publication eras, and robust to leave-one-out sensitivity analysis. These findings extend and update the previously published syntheses by Jin and colleagues[5] and Chen and colleagues,[6] which did not include the most recent multicentre cohorts published between 2024 and 2026.[7-9]

The clinical benefit of omalizumab is biologically plausible and consistent with the central role of free IgE in driving the type-2 inflammatory cascade. By preventing IgE engagement with the high-affinity FceRI receptor, omalizumab reduces allergen-induced degranulation and downstream Th2 cytokine release. The parallel reductions in basophil sensitivity to A. fumigatus and surface-bound IgE demonstrated by Voskamp and colleagues provide direct mechanistic confirmation.[4] Among the four outcomes, the most clinically actionable finding is the substantial reduction in oral corticosteroid burden, which directly lowers the cumulative risk of corticosteroid-induced diabetes, hypertension, osteoporosis and adrenal suppression. The recent 15-year cohort of Aytekin and colleagues demonstrated a near-complete elimination of methylprednisolone exposure, from 12.7 mg/day to 0.36 mg/day at last follow-up.[7] In a tropical, high-tuberculosis-burden setting such as Indonesia, where prolonged corticosteroid exposure may reactivate latent infection, the case for a steroid-sparing strategy is particularly compelling.[3]

Heterogeneity was high (I-squared = 78.4%), reflecting diverse populations, dosing regimens, follow-up durations and outcome definitions. The convergence of the randomised trial estimate with the pooled observational estimate provides triangulated evidence that the direction and magnitude of effect are not artefacts of design. The heterogeneity may partly reflect the progressively broader phenotypes captured by evolving diagnostic criteria from Rosenberg-Patterson through ISHAM 2013[12] to DECG 2024.[10] Several biomarker-based predictors of response have been reported, including mucus plugging on HRCT (a predictor of non-response in the Carter cohort[8]) and baseline IgE below 1000 IU/mL (associated with better response in the Aydin cohort[23]); these support the future development of biomarker-guided patient selection.

The broader biologic landscape has expanded substantially. Mepolizumab, benralizumab, dupilumab and tezepelumab have all been studied in ABPA, and the Carter cohort included 65% of patients on anti-interleukin-5 or anti-interleukin-5-receptor therapy with response rates similar to omalizumab.[8] The Asano review described biologic choice based on the dominant inflammatory phenotype: anti-IgE agents for high-IgE phenotypes, anti-interleukin-5 or anti-interleukin-5-receptor agents for the eosinophil-predominant phenotype, and anti-interleukin-4-receptor agents for mixed phenotypes.[29] Dual biologic therapy combining anti-IgE and anti-interleukin-5 blockade has been described for refractory cases, although the evidence remains confined to small case series.[33] Key unresolved clinical decision points include when to initiate omalizumab versus an alternative biologic, how to manage patients whose baseline total IgE exceeds the upper omalizumab dosing limit of 1500 IU/mL, and how to approach non-responders to first-line biologic therapy; adequately powered head-to-head comparative trials are needed to inform optimal sequencing. In contrast to the antifungal-versus-

glucocorticoid trials of Agarwal and colleagues,[30,31] the present synthesis evaluated omalizumab as a steroid-sparing intervention rather than as primary acute-phase therapy, consistent with its positioning as a treatment-dependent or maintenance option in the Revised ISHAM-ABPA Working Group 2024 guideline.[10] For long-term maintenance, nebulised liposomal amphotericin-B has emerged as an alternative non-biologic strategy, demonstrating a longer time to first exacerbation than control in a randomised trial.[32]

From a mechanistic perspective, the convergence of the immunological and clinical signals strengthens confidence in a causal interpretation. The reduction in basophil surface-bound IgE and FceRI expression observed after omalizumab is accompanied by a fall in total serum IgE, a decrease in peripheral eosinophilia, and a corresponding clinical reduction in exacerbation frequency and corticosteroid requirement. This coherence across the biological, immunological and clinical domains is consistent with the Bradford Hill criterion of biological plausibility and supports the view that the observed benefit reflects a genuine pharmacodynamic effect rather than regression to the mean or secular improvement. Nonetheless, the predominance of a within-patient pre- versus post-treatment design in the included cohorts means that residual confounding from concurrent optimisation of inhaled therapy, antifungal treatment, or environmental exposure reduction cannot be entirely excluded, and this limitation tempers the strength of any causal claim derived from observational data.

The strengths of this synthesis include the integration of the most recent 2024-2026 cohorts, the use of the Hartung-Knapp-Sidik-Jonkman correction,[19] the comprehensive sensitivity and meta-regression analyses, the GRADE certainty assessment,[21] the back-translation of effects to clinical scales, and the explicit regional framing. Several limitations warrant acknowledgement. First, only one contributing study was a randomised trial, and it enrolled only thirteen patients. Second, between-study heterogeneity was substantial. Third, two eligible studies had limited extractable data. Fourth, no published cohorts originate from South-East Asia, so generalisability to the SJIM readership requires regional confirmation. Fifth, no formal cost-effectiveness evaluation was performed; given the high acquisition cost of omalizumab and limited regional coverage, this is an important consideration, and the cost-effectiveness of omalizumab in severe asthma has been variably estimated by health technology assessments.[34] The advent of biosimilar omalizumab offers the potential for substantial cost savings.

For physicians practising internal medicine and pulmonology in Indonesia and similar settings, ABPA should be actively considered in any adult with severe asthma, persistent eosinophilia or recurrent exacerbations refractory to standard inhaled therapy, particularly when central bronchiectasis or high-attenuation mucus plugging is present on HRCT. All patients with severe persistent asthma should be screened for ABPA with serum total IgE and IgE specific to A. fumigatus, in line with severe-asthma guidance.[35,36] In patients with treatment-dependent disease, omalizumab should be considered as a steroid-sparing option. Appropriate candidates are those who meet modern diagnostic criteria, have a baseline total serum IgE within the standard dosing range, demonstrate treatment-dependent disease through recurrent exacerbations on corticosteroid tapering or a chronic high-dose requirement, and have no contraindication to anti-IgE therapy. The agent is dosed by body weight and total serum IgE according to the manufacturer chart, administered subcutaneously every two to four weeks, with observation during the initial injections owing to the small risk of anaphylaxis. Realistic expectations include approximately 1.9 fewer exacerbations per year and approximately 9 mg/day prednisolone-equivalent reduction, alongside modest improvements in lung function and asthma control.

The optimal duration of omalizumab therapy in ABPA remains undefined. The 15-year cohort of Aytekin and colleagues demonstrated sustained benefit over prolonged follow-up, suggesting that long-term continuation may be appropriate for responders, but whether and when to attempt de-

escalation in patients achieving stable remission is unresolved and should be a priority for prospective study.[7] A pragmatic monitoring schedule combining clinical assessment, exacerbation tracking, spirometry and serial total serum IgE measurement at three-to-six-monthly intervals during the first year, and six-to-twelve-monthly thereafter, is reasonable pending dedicated evidence. From a health-system perspective, the high acquisition cost of omalizumab is a substantial barrier in resource-constrained settings, and a formal cost-effectiveness evaluation specific to ABPA, incorporating the downstream savings from averted corticosteroid-related morbidity and from reduced exacerbation-related hospitalisation, is an important research and policy priority; the emergence of biosimilar omalizumab may materially improve affordability and access. Adequately powered randomised trials, head-to-head comparisons with newer type-2 biologics,[29] pragmatic regional studies, cost-effectiveness analyses, and the establishment of a national or South-East Asian ABPA registry are warranted; the Indonesian Society of Respirology, the Indonesian Society of Allergy and Immunology and the Indonesian Society of Internal Medicine should consider adopting the contemporary international guideline[10] with regional contextualisation, and incorporating ABPA diagnosis and biologic-therapy indications into postgraduate internal-medicine and pulmonology training curricula.

5. Conclusion

In this systematic review and random-effects meta-analysis of ten contemporary studies enrolling 286 adults with allergic bronchopulmonary aspergillosis, omalizumab conferred a moderate-to-large, clinically meaningful steroid-sparing benefit, with a pooled standardised mean difference of -0.69 (95% confidence interval -1.12 to -0.25; p = 0.007) and consistent reductions in exacerbations and oral corticosteroid burden alongside improvements in lung function and asthma control. The effect was robust across study designs, diagnostic criteria and sensitivity analyses, and the treatment was generally well tolerated. Pending adequately powered randomised trials and regional studies in South-East Asian populations, this synthesis supports the cautious adoption of omalizumab as a steroid-sparing maintenance therapy in adults with ABPA, particularly in those experiencing recurrent exacerbations or intolerable corticosteroid toxicity.

6. References

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