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REVIEW



Short- and long-term real-world effectiveness of omalizumab in severe allergic asthma: systematic review of 42 studies published 2008–2018

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ABSTRACT

Introduction: Omalizumab is a recombinant monoclonal anti-IgE antibody approved in the US as add-on treatment in moderate-to-severe allergic asthma (in severe allergic asthma [SAA] in Europe). A 2016 review of 24 real-world effectiveness studies in SAA published between 2008–2015 concluded that omalizumab was associated with significant improvements in objective and subjective outcomes with benefits extending beyond 2 years. Several new real-world studies have been published since, bringing the total to 42 studies.

Areas covered: This systematic review of 42 studies published since 2008 updates and extends the 2016 review on the real-world evidence on omalizumab in SAA. It offers greater granularity as to time windows within which outcomes are reported and includes studies extending well beyond 4 years post omalizumab initiation.

Expert commentary: This review firmly establishes the short-term effectiveness of omalizumab in adolescent and adult patients with SAA at 1 year, and provides strong evidence of long-term effectiveness up to 4 years and emergent evidence of effectiveness beyond 4 years. In the aggregate, these 42 studies underscore the long-term effectiveness of omalizumab in terms of: reducing exacerbations and symptoms, achieving asthma control, improving lung function, enhancing quality of life, decreasing emergency department visits and hospitalizations, and promoting concomitant medication-sparing.

ARTICLE HISTORY

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KEYWORDS

Allergic asthma; IgE; omalizumab; real-world effectiveness; systematic review

1. Introduction

In its 2018 report, the Global Asthma Network estimated that as many as 339 million people worldwide, or 5% of the world population, suffer from asthma [1], with other estimates reaching as high as 16% [2]. Asthma is the 16th leading cause of years lived with disability and the 28th ranked cause of disability-adjusted life years [1]. About 1000 people die of asthma daily [1]. With no cure, asthma management strategies aim to: control the clinical aspects of the disease, including respiratory function; prevent exacerbations and thus reduce unscheduled medical visits, emergency room admissions, and hospitalizations; lower medication burden; and enhance quality of life.

One treatment target concerns the antibody class of immunoglobulin E (IgE), which binds to the high-affinity receptors on the surface of mast cells and causes these cells to release inflammatory mediators [3]. Omalizumab (Xolair®, Novartis, Basel, Switzerland; Genentech, San Francisco, California USA) is a recombinant monoclonal anti-IgE antibody that binds to free IgE and downregulates high-affinity IgE receptors (FcεRI) on mast cells as well as basophils, eosinophils and dendritic cells [4,5]. Omalizumab interrupts the allergic cascade by inhibiting IgE from binding to these receptors [4,5], preventing IgE cross-linking [6], limiting mast cell degranulation [5,6], and

minimizing the release of mediators in the early- and late-phase of allergen response [6,7]. It is administered as add-on treatment to inhaled corticosteroids (ICS) and/or long-acting β₂-agonists (LABA) [8,9]. The efficacy and safety of omalizumab were demonstrated in phase III clinical trials, including its positive impact on asthma symptom management and control, exacerbations, medication burden, and quality of life [9–12]; were confirmed in subsequent studies and a meta-analysis [13]; and have been summarized extensively [14–23].

Following the approval of omalizumab for moderate-to-severe allergic asthma in the US in 2003 and for severe allergic asthma in Europe in 2005, several ‘real-world’ (also referred to as ‘real-life’) studies were initiated to evaluate the effectiveness of omalizumab add-on therapy under conditions of heterogeneity in patients, clinicians, and settings. In a prior independent systematic review of 24 such studies [24–47] published between 2008 and 2015 and covering 4117 unique patients with severe allergic asthma from 32 countries, we concluded that omalizumab was effective in: reducing asthma symptoms, exacerbations, and work/school days lost; improving asthma control; improving lung function; decreasing healthcare utilization; lowering the use of other asthma medications; and enhancing quality of life; while presenting

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 Supplemental data for this article can be accessed [here](#).

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Article highlights

- 42 real-world studies published between 2008 and 2018 were reviewed to confirm the short-term and to evaluate the long-term effectiveness and safety of omalizumab in the treatment of severe allergic asthma.
- Omalizumab treatment is associated with significant short- and long-term improvements in clinical outcomes, quality of life, healthcare resource utilization, and medication-sparing.
- Omalizumab is associated with reduced exacerbations and symptoms; better asthma control; improved lung function; enhanced quality of life; fewer emergency room visits and hospitalizations; and lower use of corticosteroids and other asthma medications.
- Our review establishes the short-term (up to 1 year of treatment) effectiveness of omalizumab, provides strong evidence for its long-term (up to 4 years) effectiveness, and presents emergent evidence for its effectiveness over 4 and more years of treatment.
- The reductions in healthcare resource utilization and concomitant asthma medications are likely to translate into significant cost savings.

This box summarizes key points contained in the article.

a similar safety profile as that of the randomized controlled trials [48]. That systematic review was the basis for an independent meta-analysis [49] of these 24 studies plus one subsequently published investigation [50] that synthesized results for the following outcomes: Global Evaluation of Treatment Effectiveness (GETE); FEV₁ (% predicted); Asthma-related Quality of Life Questionnaire (AQLQ); Asthma Control Test (ACT); oral corticosteroid (OCS) and ICS use; asthma exacerbations; and asthma-related hospitalizations. The meta-analysis demonstrated that, quantitatively, the real-life effectiveness of pharmacotherapy with omalizumab mirrors, complements, and extends the efficacy data from randomized controlled studies.

Several new real-world studies have been reported since our initial systematic review, bringing the total to 42 studies published between 2008 and 2018 and including a total of 9377 patients from 35 countries. In the aggregate, thirty of these studies (n = 3558) included adult patients only, and twelve studies (n = 5819) comprised both adult and adolescent patients. We report here on an updated systematic review of these 42 observational studies of the real-world benefits and harms of omalizumab in the management of severe allergic asthma. Notably, our prior systematic review [48] and meta-analysis [49] provided strong evidence on outcomes up to 1 year with some emergent evidence beyond 1 year. This present systematic review also provides significant evidence for the long-term effectiveness of omalizumab after 2 and 3 years of treatment, with emergent evidence well beyond 4 years.

This present systematic review is part of a broader initiative to synthesize the real-world evidence on omalizumab. In addition to our earlier independent systematic review [48] and meta-analysis [49], two papers commissioned by Novartis have summarized the evidence on omalizumab in childhood asthma [51,52]. We recently published a commissioned systematic review [53] and meta-analysis [54] of omalizumab in the IgE-mediated condition of chronic idiopathic/spontaneous urticaria.

2. Evidence base

This is an update and extension of the Abraham et al. [48] systematic review published in 2016 on the real-world effectiveness of omalizumab in adults with severe allergic asthma. The protocol for the prior systematic review, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [55] guidance, was updated. This review extends our prior review in terms: study designs used; the patients in these studies; the effectiveness of omalizumab therapy in terms of clinical, health resource utilization, quality of life, and medication-sparing outcomes; and safety. However, it does so with greater granularity as to time points at which, and time windows within which, outcomes are reported; specifically, at the fixed time points of 16 weeks and 1 year, and the time windows of 5–9 months (including the 6-month mark), 23 to 32 months (including the 2-year and 2.5-year marks), and 36 months (or 3 years) and beyond. In addition, effectiveness and safety outcomes are presented on standardized scales of percent change; specifically, positive percent change for improvements on positive outcomes, and negative percent change for improvements on negative markers.

2.1. Eligibility

Eligibility for inclusion was defined in PICOS terms:

Participants Male or female adolescents and adults diagnosed with severe allergic asthma.

Interventions Treated with omalizumab for severe allergic asthma.

Comparators Permissible but not required.

Outcomes At least one measure of the following: lung function, exacerbations, daytime or nighttime symptoms, asthma control (Asthma Control Test [ACT] or Asthma Control Questionnaire [ACQ]), quality of life (Juniper Asthma-related Quality of Life [AQLQ] or European Quality of Life Questionnaire 5 Dimensions [EQ-5D]), physician-rated asthma classification (Global Initiative on Asthma [GINA]), physician-rated treatment effectiveness (Global Evaluation of Treatment Effectiveness [GETE]), asthma-related emergency department visits or hospitalizations, use of concomitant anti-asthmatic treatments, or safety.

Studies Any observational method including registry, retrospective chart review, prospective observational study, or pragmatic trial reported as full-text articles.

Note that we also admitted studies that included both adult and adolescent (age 12 years or older) patients, but not children. However, to assure a predominant adult study population, the pooled weighted mean age for the adult/adolescent set of studies could not be statistically significantly lower than that for the adult-only set of studies.

2.2. Search strategy, screening, and data extraction

PubMed, Embase and Cochrane Library databases were searched from initiation on 17 July 2018 using the terms 'IgE', 'immunoglobulin E'; 'omalizumab'; 'asthma'; 'effectiveness', 'real-life', 'real-world'; without date, sample size, or language restrictions. Abstract-only publications were not included due to lack of

sufficiently detailed data. Additional potential sources were identified through citation analysis and general monitoring of the literature. With the search period being from initiation of the databases to 17 July 2018, it was possible to validate the studies in the prior systematic review [48] in addition to identifying studies reported since 2015.

If two or more publications containing the same subjects were identified (either partially or wholly), the publications were assessed for sample size and detail of reporting, and only one publication was selected for inclusion. Likewise, subsequently published pooled analyses comprising one or more samples already selected for this review were excluded. One exception is the eXpeRience Registry in which different outcomes on the entire sample were reported across three different publications [39,56,57]. This registry study is included in this review once but the data were aggregated from the three publications.

An initial pool of 755 publications was identified (Figure 1). Following removal of 61 duplicate citations, 694 studies were retained and screened, of which 625 were rejected. The remaining 69 full-text articles were assessed for eligibility and 27 were excluded: 11 papers reported results on samples previously published and thus included duplicate cases, 10 were ineligible per PICOS criteria, and 6 lacked sufficiently detailed outcome data. This yielded a total of 42 studies.

Data were extracted as reported in the published studies, except where noted, and entered into master tables of evidence (Supplementary Tables S1 through S4).

2.3. Other methodological considerations

Published results in all papers were validated, data permitting, to assess data integrity and derive common metrics for comparisons across studies. Hence, results in our analysis may diverge from originally reported data if recalculations were done using a different formula to permit cross-study comparisons. Changes in outcomes between baseline and each reported time point were transformed into percentage change. The statistical significance associated with changes, if reported, was extracted from the original publications. The reported or standardized data from the individual studies were aggregated where possible to provide pooled weighted estimates (either pooled weighted percentage or pooled weighted mean $\pm$ SD). To minimize bias, non-significant results reported in the original publication were included in our pooled estimates.

3. Review of studies

Table 1 summarizes the 42 studies stratified by 30 adult-only studies [24,26,27,30–37,40–47,58–68] (n = 3558) and 12 adult/adolescent studies [25,38,39,56,57,69–77] (n = 5819). These 42 studies comprised a total of 9377 patients from 35 countries: 25 in Europe (incl. Israel, Russia, and Turkey), 5 in Asia-Pacific (incl. Australia), 3 in North-America, and 2 in South-America.

Detailed data by study are presented in the Supplementary Tables S1 through S4: patient demographics, clinical status, healthcare resource utilization, and asthma treatment at

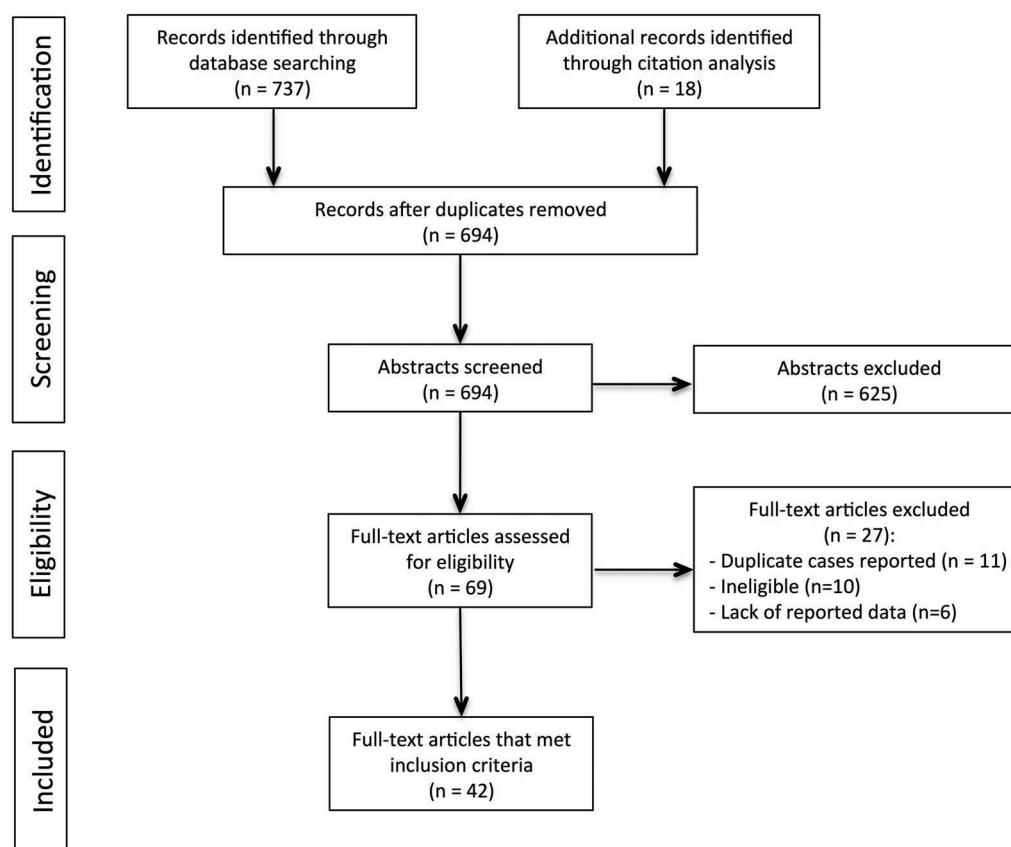


Figure 1. Data identification, screening, eligibility and inclusion.

Table 1. Summary of designs, time points of assessments, and effectiveness outcomes reported.

Studies on adults	Reference number	Design	Retrospective data pre-onalizumab therapy		Country	Evaluable N at baseline (onalizumab-treated)	Time points of assessments reported												
			Physicians/centers	16 weeks			6 months	1 year	Other										
Molimard et al., 2008*	24	Prospective	1 year		France	146		✓	✓	≥ 5 months									
Kom et al., 2009*	26	Prospective	1 year		Germany	280	134	✓											
Cazzola et al., 2010*	27	Prospective	1 year		Italy	142	13		✓										
Bousquet et al., 2011*	30	Prospective	1 year		Various^	272	106	✓		32 weeks									
Costello et al., 2011*	31	Retrospective	6 months		Ireland	63	6	✓											
Dal Negro et al., 2012	58	Retrospective	1 month		Italy	16			✓	3 years									
Rottem et al., 2012*	32	Retrospective	1 year		Israel	33													
Rubin et al., 2012*	33	Prospective	Not specified		Brazil	78				Week 12 & Week 20									
Schumann et al., 2012*	34	Prospective	16 weeks		Germany	195	85	✓	✓										
Sweeney et al., 2012*	35	Retrospective	Not specified		UK	59				Not specified									
Tzortzaki et al., 2012*	36	Retrospective	1 year		Greece, Cyprus	60	4	✓	✓	4 years									
Vennema et al., 2012*	37	Prospective	1 year		Spain	266	30	✓	✓	2 years									
Wittchen et al., 2012	59	Prospective	1 year		Germany	53**				T1: 2 to 3 months T2: 6 to 8 months 1.67 years (mean)									
Grimaldi-Bensouda et al., 2013*	40	Prospective	1 year		France	374	129			5 months									
Kelmenson et al., 2013*	41	Prospective	Not specified		USA	4													
Subramaniam et al., 2013*	42	Retrospective	6 months		Ireland	30		✓											
Alfarroba et al., 2014*	43	Retrospective	1 year		Portugal	26		✓		2 years									
Gaminati et al., 2014	60	Retrospective	Not specified		Italy	59	9			23 ± 16.5 months									
Tajiri et al., 2014*	44	Prospective	1 year		Japan	31		✓	✓										
Vieira et al., 2014*	45	Prospective	1 year		Portugal	15		✓	✓	2 years									
Goudier et al., 2015	61	Prospective	1 year		Malta	22	1	✓	✓	32 weeks									
Novelli et al., 2015*	46	Prospective	1 year		Italy	306	26		✓	32 months									
Tiro et al., 2015*	47	Prospective	1 year		Mexico	47				3 years									
Kuprys-Lipińska et al., 2016	62	Prospective	1 year		Poland	53***	1	✓		18–39 y.o.: 30 ± 22 months 40–64 y.o.: 36 ± 22 months ≥ 65 y.o.: 37 ± 22 months									
Sposato et al., 2016	63	Retrospective	1 year		Italy	105°	18			35.7 ± 17.8 months									
Tat & Cilli 2016	64	Retrospective	Not specified		Turkey	19	1			60.7 ± 30.9 months (range 23–121)									
de Carvalho-Pinto et al., 2017	65	Prospective	Not specified		Brazil	12	1	✓											
Mansur et al., 2017	66	Retrospective	1 year		UK	45			✓	4 to 6 months									
Nygaard et al., 2017	67	Retrospective	6 months		Denmark	24	1	✓											
Humbert et al., 2018	68	Retrospective	1 year		France	723 ^{oo}	78		✓										
Studies with adults and adolescents																			
Brusselle et al., 2009*	25	Prospective	1 year		Belgium	158	35	✓	✓	40 weeks (9.2 months)									
Pelaia et al., 2011	69	Prospective	1 month		Italy	16	1		✓										
Barnes et al., 2013*	38	Retrospective	1 year		UK	136	10	✓	✓										
Braunstaht et al.* [§]	39,56,57	Prospective	1 year		Various^,^	925		✓	✓	8 ms, 18 ms, 2 years									
Özgür et al., 2013	70	Retrospective	1 year		Turkey	26	1		✓	2 years, 3 years, last visit (40.8 ± 8.2 months [range 36–62])									
Ancochea et al., 2014	71	Retrospective	1 year		Spain	214	60			6.3 ± 3.5 months									
Niven et al., 2016	72	Prospective	1 year		UK	258	22	✓	✓	8 months									
DiBona et al., 2017	73	Retrospective	1 year		Italy	91	2			45.6 ± 31.2 months									
Kawamatawong et al., 2017	74	Retrospective	1 year		Thailand	78	10	✓	✓										
Maltby et al., 2017	75	Prospective	1 year		Australia	160¶	21¶¶		✓										
Paganin et al., 2017	76	Retrospective	1 year		France	164~	10		✓	2 years									
Adachi et al., 2018	77	Prospective	1 year		Japan	3593	1001	✓	✓										
Effectiveness assessments reported																			
Studies on adults	Lung function: FEV ₁	Lung function: other (physician-rated)	Lung function: subjective (physician-rated)	Physician-rated effectiveness: GINA	Asthma control: ACT	Asthma control: ACQ	Exacerbations	Day-time symptoms	Night-time symptoms	Work or school days lost	General practitioner visits	Specialist visits	Emergency department visits	Hospitalizations	Hospitalization days	Concomitant corticosteroid use	Other concomitant medications	Adverse events	
			✓				✓	✓	✓	✓			✓	✓	✓	✓		✓	
				✓			✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	
	✓			✓		✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	
	✓	✓					✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	
(Continued)																			

(Continued)

Table 1. (Continued).

	Effectiveness assessments reported																			
	Lung function: FEV ₁	Lung function: other objective	Lung function: subjective (physician-rated)	GINA	Physician-rated effectiveness: GETE	Quality of life (AQLQ, [min]) AQLQ, EQ5D	Asthma control: ACT	Asthma control: ACQ	Exacerbations	Day-time symptoms	Night-time symptoms	Work or school days lost	General practitioner visits	Specialist visits	Emergency department visits	Hospitalizations	Hospitalization days	Concomitant corticosteroid use	Other concomitant medications	Adverse events
Studies on adults																				
Dal Negro et al., 2012	✓						✓		✓				✓	✓	✓	✓		✓		
Rottem et al., 2012*															✓	✓	✓		✓	
Rubin et al., 2012*	✓			✓	✓	✓			✓			✓						✓		✓
Schumann et al., 2012*	✓				✓	✓		✓										✓		✓
Sweeney et al., 2012*																		✓		✓
Tzortzaki et al., 2012*	✓						✓		✓							✓		✓		✓
Vennera et al., 2012*	✓						✓		✓									✓		✓
Witchchen et al., 2012							✓		✓									✓		✓
Grimaldi-Bensouda et al., 2013*															✓	✓		✓		
Kelmonson et al., 2013*	✓	✓			✓	✓	✓													
Subramaniam et al., 2013*	✓			✓					✓							✓		✓		✓
Alfarroba et al., 2014*	✓			✓			✓		✓	✓	✓							✓		✓
Caminati et al., 2014	✓				✓				✓											
Tajiri et al., 2014*	✓	✓		✓		✓		✓	✓						✓	✓		✓		✓
Vieira et al., 2014*	✓						✓		✓				✓		✓	✓		✓		✓
Gouder et al., 2015	✓				✓		✓		✓						✓	✓		✓		✓
Novelli et al., 2015*	✓			✓			✓		✓						✓	✓		✓		✓
Tiro et al., 2015*	✓			✓			✓		✓						✓	✓		✓		✓
Kupryś-Lipińska et al., 2016	✓				✓			✓	✓											
Sposato et al., 2016	✓						✓		✓							✓		✓		
Tat & Cilli 2016	✓						✓		✓							✓			✓	
de Carvalho-Pinto et al., 2017								✓	✓											
Mansur et al., 2017	✓							✓							✓	✓		✓		
Nygaard et al., 2017	✓						✓		✓											
Humbert et al., 2018					✓				✓									✓		
Studies with adults and adolescents																				
Brusselle et al., 2009*	✓			✓	✓	✓			✓	✓	✓		✓	✓	✓	✓		✓	✓	✓
Pelaia et al., 2011	✓								✓	✓	✓		✓	✓	✓	✓		✓	✓	✓
Barnes et al., 2013*	✓	✓			✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Braunstahl et al.*§	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓
Özgür et al., 2013	✓				✓	✓	✓		✓	✓	✓		✓	✓	✓	✓		✓		✓
Ancochea et al., 2014	✓				✓	✓	✓		✓	✓	✓		✓	✓	✓	✓		✓		✓
Niven et al., 2016	✓					✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓		✓
D'Bona et al., 2017							✓		✓						✓	✓		✓		✓
Kawamatawong et al., 2017									✓						✓	✓		✓		
Maltby et al., 2017	✓							✓							✓	✓		✓		
Paganin et al., 2017	✓														✓	✓				
Adachi et al., 2018					✓				✓			✓			✓	✓		✓		✓

*Study included in prior systematic review Abraham et al., 2016 [48]

§ Sample is from eXpense Registry; data are reported in three publications: Braunstahl, Chlumský et al. 2013 [39]; Braunstahl, Chen et al., 2013 [56]; and Braunstahl et al., 2014 [57]

^Belgium, Canada, Denmark, Germany, Hungary, Israel, Italy, Norway, Poland, Spain, Sweden, Switzerland, Turkey, and the United Kingdom

^^ Argentina, Bulgaria, Canada, Cyprus, Czech Republic, Hungary, The Netherlands, Philippines, Portugal, Russia, Slovakia, Slovenia, Spain, Taiwan

** Full sample n = 106, results reported separately for omalizumab-treated group and matched controls receiving usual care without omalizumab; only omalizumab-treated group reported here: effectiveness evaluation n = 53, safety evaluation n = 56

*** Full sample n = 53, effectiveness evaluation conducted on n = 16 de novo patients (remainder of sample were continuing omalizumab patients)

° Stratified results reported by age categories 18–39 years (n = 13), 40–64 years (n = 61), ≥65 years (n = 31)

°° Study also includes a cohort of 149 patients age 6–17 years not reported here.

¶ Study also includes a cohort of 17 patients with overlapping COPD not reported here.

¶¶ Description of Australia Xolair Registry design and eligibility from Gibson et al., 2016 [78]

~ Total sample n = 207 of which 43 (20.8%) were non-responders at 6 months and discontinued omalizumab; results reported over 2 years on n = 164 responders.

y.o. = years old.

enrolment (Table S1); and evolution in clinical outcomes and quality of life (Table S2), healthcare resource utilization (Table S3), and medication and safety outcomes (Table S4). These are subsequently aggregated into summary tables of demographics and baseline characteristics (Table 2) and evolution of outcome measures (Table 3).

Note that evolutions are presented at two fixed time points (16 weeks and 1 year) and in three time windows (5–9 months; 23–32 months; and 36 months and beyond). Not all studies reported on similar time frames, as some studies had shorter and some had longer follow-up durations. Outcomes at different time points may or may not include the same patients, the same samples, and the same studies. Trends over time should therefore be interpreted as trends across studies and their samples. Longer follow-up durations are unlikely to include all initial patients. Various causes of censoring are likely (e.g., attrition, lost-to-follow-up, discontinuation of omalizumab, or death). Analyses at a given time point or time window could be influenced by long-term responders. Findings should be interpreted as pertaining to those persisting in treatment due to, among other reasons, positive treatment response.

3.1. Study designs

Of the 42 studies, 23 (55%) were designed as prospective and 19 (45%) as retrospective studies (Table 1). The prospective studies included 17 (74%) adult-only studies and 6 (26%) adult/adolescent studies. Of the 19 retrospective studies, 13 (68%) studied only adults and 6 (32%) a mixed adult-adolescent sample. Most (36/42; 86%) studies reported retrospective data from prior to the initiation of omalizumab therapy. The majority of these (30/36; 83%) went back 1 year, including 19/24 (79%) adult-only and 11/12 (92%) adult/adolescent studies reporting pre-omalizumab data.

Evaluable sample sizes ranged from 4 to 3593 patients, including from 4 to 723 patients in the adult-only and from 16 to 359 in the adult/adolescent studies. Though only 28/42 (67%) of studies stated the number of physicians or centers contributing patients, the observed range was from 1 to 1001, including 1 to 134 for the adult-only studies and 1 to 1001 for the adult/adolescent studies.

Sixteen weeks is the indicated time point to initially assess treatment response and decide about continuation of omalizumab therapy. Only 11/30 (37%) adult-only and 6/12 (50%) adult/adolescent studies reported fixed 16-week data. A few studies 7/42 (17%) reported fixed 6-month data and 18/42 (43%) reported fixed 1-year data, including the majority (8/12 or 67%) of adult/adolescent but only 10/30 or 33% of adult-only studies. In total, 26/42 (62%) of studies reported data at various other time points ranging from fixed 2 months to 4 years or at averages ranging from 20 to 60.7 months.

In descending order, the clinical outcome variables and instruments most consistently evaluated – across time points but not necessarily at each time point or in each time window – were exacerbations (74% of studies), FEV₁ (% predicted) (71%), concomitant corticosteroid use (69%), hospitalizations (55%), emergency department visits (45%), ACT (43%), concomitant medications other than corticosteroids (36%), GETE

(31%), and AQLQ (26%). All other outcomes were evaluated in fewer than 20% of studies. Adverse events were recorded in 55% of the studies.

3.2. Baseline characteristics of patients

In pooled weighted analyses, mean ($\pm$ SD) age of patients at enrolment across all studies was 52.3 ± 14.6 years across (see Table 2). Mean age was 48.8 years in adult-only versus 54.4 years in adult/adolescent studies, showing that mean age in the adult-adolescent sample was not suppressed by the inclusion of small sub-cohorts of adolescents. Unless marked differences are noted between the adult-only and adult/adolescent studies, we focus on the all-studies results.

About two-thirds (63.2%) of patients were female and 70.9% of patients had never smoked. At baseline, mean weight was 74.8 kg, mean serum total IgE was 374.3 IU/mL, and mean FEV₁ was 64.7% predicted. In terms of asthma control at baseline, mean ACT scores were 14.1 (reported in $n = 13$ studies) and mean ACQ scores were 3.0 ($n = 7$ studies). Quality of life was significantly impaired, as indicated by mean AQLQ scores of 3.8 ($n = 8$ studies). In the year preceding the start of omalizumab therapy, 93.8% of patients had experienced exacerbations (reported in $n = 14$ studies) and the weighted mean number of exacerbations per patients in the preceding year was 4.0 ($n = 25$ studies); 28.6% had required at least one emergency room visit ($n = 5$ studies) and the weighted mean number of ER visits per patient was 2.0 ($n = 7$ studies); and 26.2% were hospitalized at least once ($n = 10$) with a mean of 0.9 hospitalizations per person ($n = 16$). Daytime (90.5%) and nighttime symptoms (79.5%) in the year prior to enrolment were reported in a large majority of patients, though this information was collected in only a small number of studies ($n = 4$ and $n = 5$, respectively). Summarized, patients who comprised the samples in these studies had the hallmarks of severe allergic asthma including high serum concentrations of IgE, poor predicted FEV₁, poor asthma control, frequent emergency department visits and hospitalizations, and impaired quality of life.

Virtually all patients were previously treated with ICSs (98.8%) and LABAs (96.7%), and many (73.2%) with leukotriene receptor antagonists (LTRA). Compared to the adult-only studies, the adult/adolescent studies reported proportionately higher rates of treatment with LTRAs (80.1% vs. 58.0%) and theophylline derivatives (59.1% vs. 25.8%).

Weighted mean omalizumab dose, as reported in 21 studies ($n = 6,084$), was 308 mg/month. Eight studies reported that an aggregated 20.4% of patients were initiated on an omalizumab dose inconsistent with the recommended dosing schedule.

3.3. Effectiveness

Table 3 summarizes the time course of outcomes measures from baseline to the fixed time points of 16 weeks and 12 months, and from baseline to the time windows of 5–9 months, 23–32 months, and through ≥ 36 months. As the first 16 weeks are a trial period to evaluate whether patients

Table 2. Summary of demographics and baseline characteristics.

	Adult-Only Studies (n = 30)				Adult/Adolescent Studies (n = 12)				All Studies (n = 42)			
	Studies	Patients	Mean±SD		Studies	Patients	Mean±SD		Studies	Patients	Mean±SD	
Age (years)	29	3499	48.8 ± 12.3		11	5741	54.4 ± 15.8		40	9240	52.3 ± 14.6	
Weight (kg)	10	950	73.8 ± 16.6		9	1926	75.3 ± 17.6		19	2876	74.8 ± 17.3	
Serum total IgE (IU/mL)	24	3299	393.7 ± 629.2		11	5561	362.7 ± 784.5		35	8860	374.3 ± 737.0	
FEV ₁ (% predicted)	23	1865	66.0 ± 18.9		9	1223	62.6 ± 18.1		32	3088	64.7 ± 18.6	
Asthma symptoms												
Exacerbations in past year (# events)	17	2379	4.1 ± 4.3		8	1826	3.9 ± 2.2		25	4205	4.0 ± 4.0	
ACT at baseline	10	781	16.7 ± 4.7		3	1261	12.5 ± 4.5		13	2042	14.1 ± 4.6	
ACQ at baseline	4	324	3.5 ± 1.2		3	1299	2.9 ± 1.0		7	1623	3.0 ± 1.1	
AQLQ at baseline	3	162	3.4 ± 1.2		5	1715	3.8 ± 1.3		8	1877	3.8 ± 1.3	
Healthcare resource utilization*												
Emergency room visits (# per pt/yr)	4	254	2.9 ± 2.3		3	4009	1.9 ± 10.5		7	4263	2.0 ± 10.4	
Hospitalizations (# per pt/yr)	12	1527	1.5 ± 1.6		4	4145	0.7 ± 3.0		16	5672	0.9 ± 2.7	
Female gender	29	3499	2129	60.8%	12	5819	3763	64.7%	41	9318	5892	63.2%
Never smoked	18	2607	1807	69.3%	8	5365	3848	71.7%	26	7972	5654	70.9%
Asthma symptoms												
Exacerbations in past year (% of pts)	8	1243	1158	93.2%	4	1461	1379	93.9%	14	2704	2536	93.8%
Daytime symptoms (% of pts)	1	280	269	96.1%	3	1297	1158	89.3%	4	1577	1427	90.5%
Nighttime symptoms (% of pts)	2	552	457	82.8%	3	1297	1012	78.0%	5	1849	1469	79.5%
Healthcare resource utilization*												
≥ 1 Emergency room visit (% of pts)	3	625	301	48.2%	2	3751	949	25.3%	5	4376	1250	28.6%
≥ 1 Hospitalization (% of pts)	8	1863	673	36.1%	2	3751	801	21.4%	10	5614	1473	26.2%
Prior treatments at baseline												
Inhaled corticosteroids (% pts)	19	2900	2856	98.5%	6	800	800	100.0%	25	3700	3656	98.8%
Oral corticosteroids (% pts)	22	2958	1283	43.4%	9	5409	2573	47.6%	31	8367	3856	46.1%
Long-acting β ₂ agonists (% pts)	18	2884	2778	96.3%	6	800	734	98.0%	24	3684	3562	96.7%
Leukotriene receptor antagonists (% pts)	14	1921	1115	58.0%	6	4229	3388	80.1%	20	6150	4503	73.2%
Theophylline/derivatives (% pts)	11	1396	360	25.8%	5	4203	2482	59.1%	16	5599	2842	50.8%
Anticholinergics (% pts)	5	508	92	18.1%	2	318	92	28.9%	7	826	184	22.3%

Abbreviations: ACT Asthma Control Test; ACQ Asthma Control Questionnaire; AQLQ Juniper Asthma-related Quality of Life; FEV₁ forced expiratory volume in 1 second; IgE immunoglobulin E; IU international units; kg kilogram; mL milliliters; pt patient; pts patients; yr year

Number of patients reflects number at enrollment.

* In year prior to enrollment.

Table 3. Summary of outcome measures (all studies: n = 42).

	16 weeks				5 to 9 months				12 months			
	Studies		Patients		Studies		Patients		Studies		Patients	
			% change from baseline	range of % change			% change from baseline	range of % change			% change from baseline	range of % change
FEV ₁ (% predicted)	10	1193	12.5%	6% to 22%	10	1207	10.8%	7% to 44%	11	1814	12.4%	0% to 51%
Asthma symptoms												
Exacerbations (# events per pt/yr)	2*	211	-81.5%	-53% to -91%	6	995	-55.3%	-29% to -80%	6	5567	-38.4%	-30% to -90%
Exacerbations (% of pts)	7*	729	-67.3%	-21% to -83%	7	1057	-31.5%	-16% to -82%	13	5712	-62.2%	-45% to -80%
Daytime symptoms (% of pts)	2	438	-66.1%	-61% to -69%	3	520	-68.7%	-53% to -76%	3	1109	-40.5%	-36% to -64%
Nighttime symptoms (% of pts)	2	438	-65.1%	-53% to -72%	4	792	-75.9%	-51% to -84%	3	1109	-59.6%	-49% to -73%
ACT score	8	735	39.1%	14% to 54%	5	363	44.8%	8% to 53%	10	1700	44.5%	23% to 77%
ACQ score	4	291	-41.0%	-31% to -58%	3	569	-34.2%	-17% to -46%	2	956	-32.7%	-32% to -55%
GINA classification	3°	508	63.3%	38% to 81%	2	298	75.4%	61% to 77%	2	184	35.7%	31% to 65%
Quality of Life												
AQLQ score	6°	604	43.8%	19% to 128%	5	714	46.1%	33% to 55%	4	1372	28.4%	21% to 55%
EQ5D VAS	1	258	23.0%	23%	1	258	25.0%	25%	2	416	25.1%	24% to 27%
EQ5D Index Utility	1	258	20.0%	20%	1	258	17.0%	17%	2	416	21.7%	19% to 26%
Healthcare resource utilization [§]												
Emergency room visits (# events per pt/yr)	1	78	-90.0%	-90%					5	1320	-80.6%	-33% to -93%
≥ 1 Emergency room visit (% of pts)					2	418	-64.1%	-61% to -70%	1	3593	-55.0%	-55%
Hospitalizations (# events per pt/yr)	2	344	-79.8%	-69% to -83%	2	93	-74.7%	-67% to -91%	8	1753	-76.1%	-34% to -86%
≥ 1 Hospitalization (% of pts)					3	698	-74.5%	-55% to -90%	2	3735	-61.4%	-60% to -96%
Other anti-asthma treatments												
ICS (% pts DC or dose reduced)	2*	248	-1.6%	0 to -2%	4	443	-35.7%	-7% to -67%	2	749	-48.1%	-17% to -49%
ICS dose	3	153	-15.9%	-12% to -21%	2	42	-25.5%	-19% to -36%	7	745	-21.5%	-10% to -40%
OCS (% pts DC or dose reduced)	4*	341	-43.4%	-25% to -48%	5	469	-58.8%	-22% to -71%	6	1099	-57.7%	-27% to -76%
OCS dose	2	3646	-51.4%	-51% to -80%	2	79	-55.1%	-45% to -95%	5	4967	-68.6%	-12% to -79%
LABA (% pts DC or dose reduced)	2*	248	-17.8%	-2% to -76%	3 ^{oo}	293	-47.7%	-13% to -76%				
LABA dose									3 [¶]	310	-21.4%	-10% to -34%
LTRA (% pts DC or dose reduced)	3*	326	-23.5%	-18% to -30%	2	267	-36.0%	-20% to -40%	3	378	-28.0%	-9% to -50%
Theophylline (% pts DC or dose reduced)	2	273	-21.1%	-18% to -29%	1	214	-60.0%	-60%	4	404	-31.5%	-5% to -50%
GETE: good or excellent	8	5290	63.4%	58% to 100%	3	959	67.9%	67% to 100%	5	4181	64.5%	62% to 95%
Safety												
Adverse events (% pts)	3*	514	16.2%	5.4% to 25.6%	5	740	23.7%	0% to 36%	4	4039	31.6%	8% to 56%
Serious adverse events (% pts)	2	273	5.1%	3.8% to 5.6%	4	714	13.3%	0% to 24%	4	4151	15.0%	7% to 24%
≥ 36 months												
FEV ₁ (% predicted)	7	1508	8.5%	0.1% to 44%	8	305	26.0%	19% to 42%				
Asthma symptoms												
Exacerbations (# events per pt/yr)	4	1303	-63.5%	-55% to -80%	4	165	-60.0%	-29% to -90%				
Exacerbations (% of pts)	4	1232	-83.9%	-71% to -88%	3	95	-70.7%	-54% to -87%				
Daytime symptoms (% of pts)	2	951	-41.2%	-40% to -83%								
Nighttime symptoms (% of pts)	2	951	-68.6%	-68% to -90%	7	260	55.6%	24% to 109%				
ACT score	6	1271	45.7%	39% to 90%								
ACQ score	2 ^Δ	970	-31.6%	-31% to -43%								
GINA classification	1	26	69.2%	69%								
Quality of Life												
AQLQ score					2	951	20.2%	16% to 170%				
EQ5D VAS					1	26	24.0%	24%				
EQ5D Index Utility					1	26	19.0%	19%				
Healthcare resource utilization [§]												
Emergency room visits (# events per pt/yr)	4 ^Δ	1012	-90.6%	-32% to -94%								
≥ 1 Emergency room visit (% of pts)	2 ^{ΔΔ}	353	-86.1%	-80% to -87%								
Hospitalizations (# events per pt/yr)	2	1191	-81.8%	-67% to -86%	4	106	-81.1%	-71% to -100%				
≥ 1 Hospitalization (% of pts)	2 ^{ΔΔ}	353	-87.2%	-86% to -90%								
Other anti-asthma treatments												
ICS (% pts DC or dose reduced)	4	395	-57.2%	-8 to -100%								
ICS dose	3	307	-29.8%	-5% to -33%	2	107	-31.9%	-13% to -56%				
OCS (% pts DC or dose reduced)	4 ^{**}	1340	-53.1%	-12% to -81%	5	160	-83.1%	-51% to -100%				
OCS dose	2	970	-63.6%	-63% to -77%								

(Continued)

Table 3. (Continued).

	23 to 32 months				≥ 36 months			
	Studies	Patients	% change from baseline	range of % change	Studies	Patients	% change from baseline	range of % change
LABA (% pts DC or dose reduced)	1	26	–8.0%	–8%				
LABA dose								
LTRA (% pts DC or dose reduced)	1	266	–66.0%	–66%				
Theophylline (% pts DC or dose reduced)	1	266	–69.0%	–69%				
	Studies	Patients	% of patients	% range	Studies	Patients	% of patients	% range
GETE: good or excellent	2	325	80.8%	77% to 82%				
Safety								
Adverse events (% pts)	2	325	4.6%	3% to 13%	6	259	9.2%	0% to 12%
Serious adverse events (% pts)	3	999	6.5%	0% to 7%	4	152	0.7%	0% to 1.1%

Abbreviations: ACT Asthma Control Test; ACQ Asthma Control Questionnaire; AQLQ Juniper Asthma-related Quality of Life; DC discontinued; EQ5D European Quality of Life Questionnaire 5 Dimensions; FEV₁ forced expiratory volume in 1 second; GETE Global Evaluation of Treatment Effectiveness; GINA Global Initiative on Asthma; IgE immunoglobulin E; ICS inhaled corticosteroids; IU international units; kg kilogram; LABA Long-acting β_2 agonists; LTRA leukotriene receptor antagonists; mL milliliters; OCS oral corticosteroids; pt patient; pts patients; VAS visual analog scale; yr year

Number of patients reflects number at enrollment.

\$ Comparing year preceding baseline to each follow-up timepoint annualized.

* Follow-up ranged from 8 to 16 weeks.

^ Follow-up was ≥ 23 months.

° Follow-up ranged from 12 to 16 weeks.

^^ Follow-up ranged from 32 to 36 months.

** Follow-up ranged from 20 to 24 months.

°° Follow-up ranged from 6 to 12 months.

¶ Follow-up ranged from 9 to 12 months.

¶¶ Follow-up ranged from 16 to 20 weeks.

respond to omalizumab, and a decision to continue or discontinue treatment is made at this time, we focus mainly on outcomes in patients in whom treatment is continued.

Figure 2 depicts the standardized outcomes where improvement is expressed as a positive percentage from baseline. Figures 3 and 4 present the standardized outcomes where improvement is expressed as a negative percentage from baseline. For a given outcome, the diamond represents the point estimate of the pooled weighted mean percent of change over baseline. The bar denotes the lowest and the highest percent change reported by singular studies and also reflects the relative variation in rates reported across studies.

3.3.1. Clinical outcomes

In terms of objective lung function, FEV₁ (% predicted) improved consistently from baseline by an average of 8.5% to 12.4% between 5 and 32 months, and by an average of 26.0% from baseline to ≥ 36 months. Some studies reported improvements from baseline as high as 42% and 51%.

Major reductions in exacerbations were identified. At the 5–9 month time window, exacerbations declined by an average of 55.3% compared to the year prior to omalizumab treatment. At 12 months, the rate was 38.4% lower than the 12 months pre-omalizumab and this trend continued over time to eventually reach declining averages of 60%. Singular studies reported decreases in exacerbations beyond the initial 16 weeks as high as 80% and 90%.

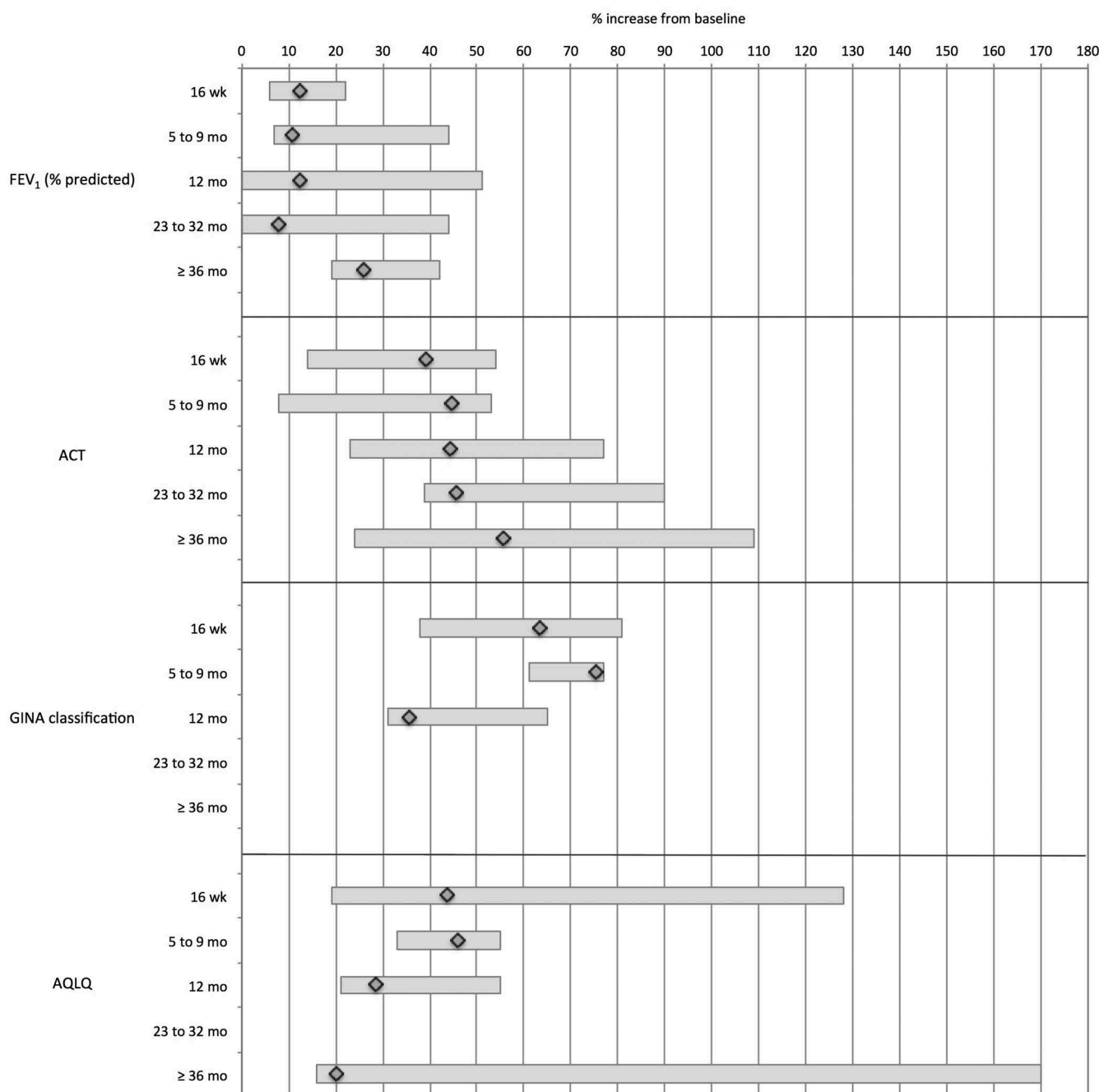


Figure 2. Effectiveness outcomes: % increase from baseline for FEV₁, ACT, GINA and AQLQ.

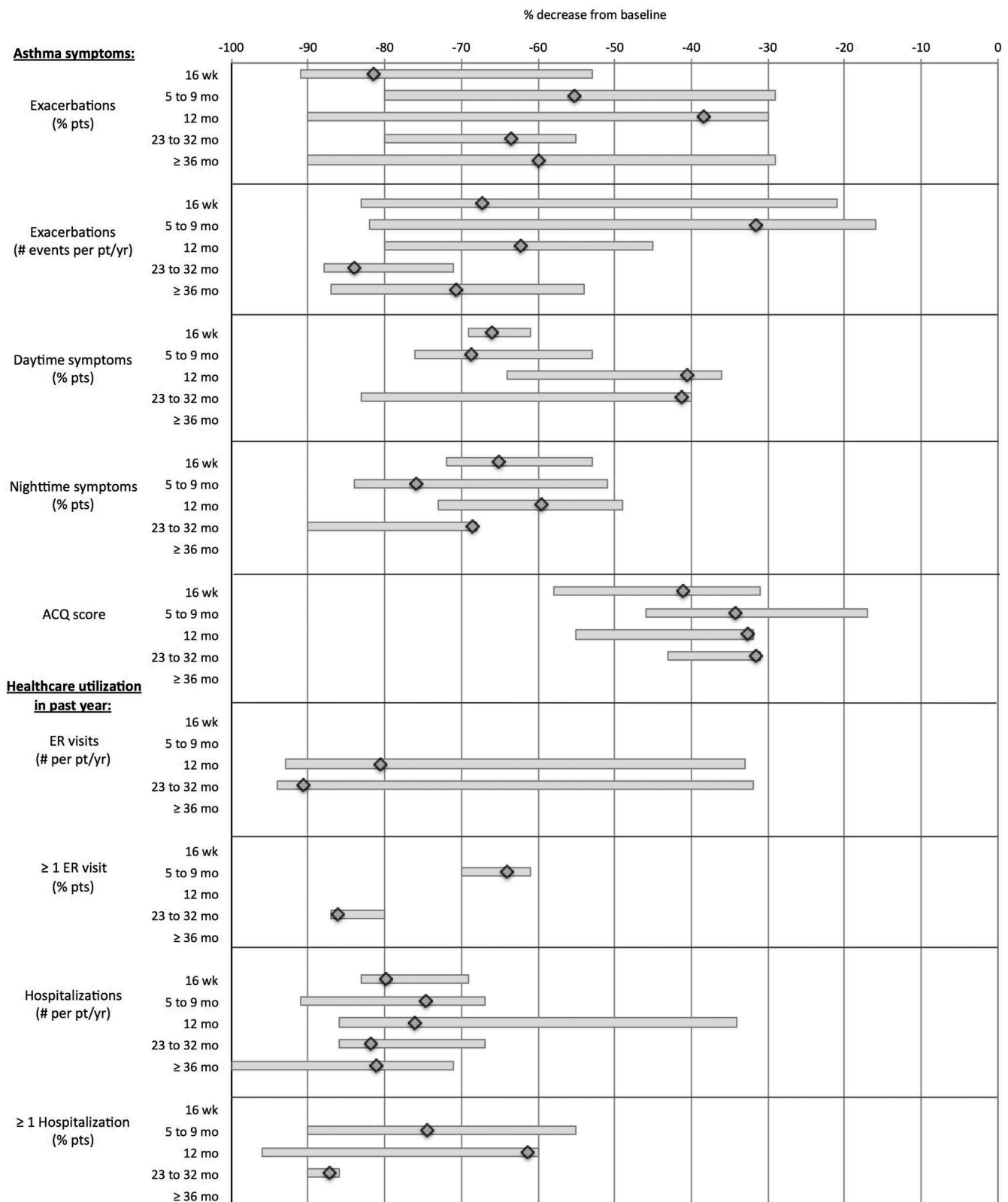


Figure 3. Effectiveness outcomes: % decrease from baseline for asthma symptoms and healthcare utilization.

parallel, the annual number of exacerbations per patient declined on average by 31.5% at 5–9 months, and this decline continued steadily to 62.2% at 12 months and 83.9% at 23–32 months; to settle at a 70.7% decline at 36 months and beyond. Singular studies reported

percentages of decline in exacerbation events between 80% and 88%.

Whereas daytime symptoms had decreased by an average 68.7% by the 5–9 month time window, later on the reported decreases averaged slightly above 40%. Singular

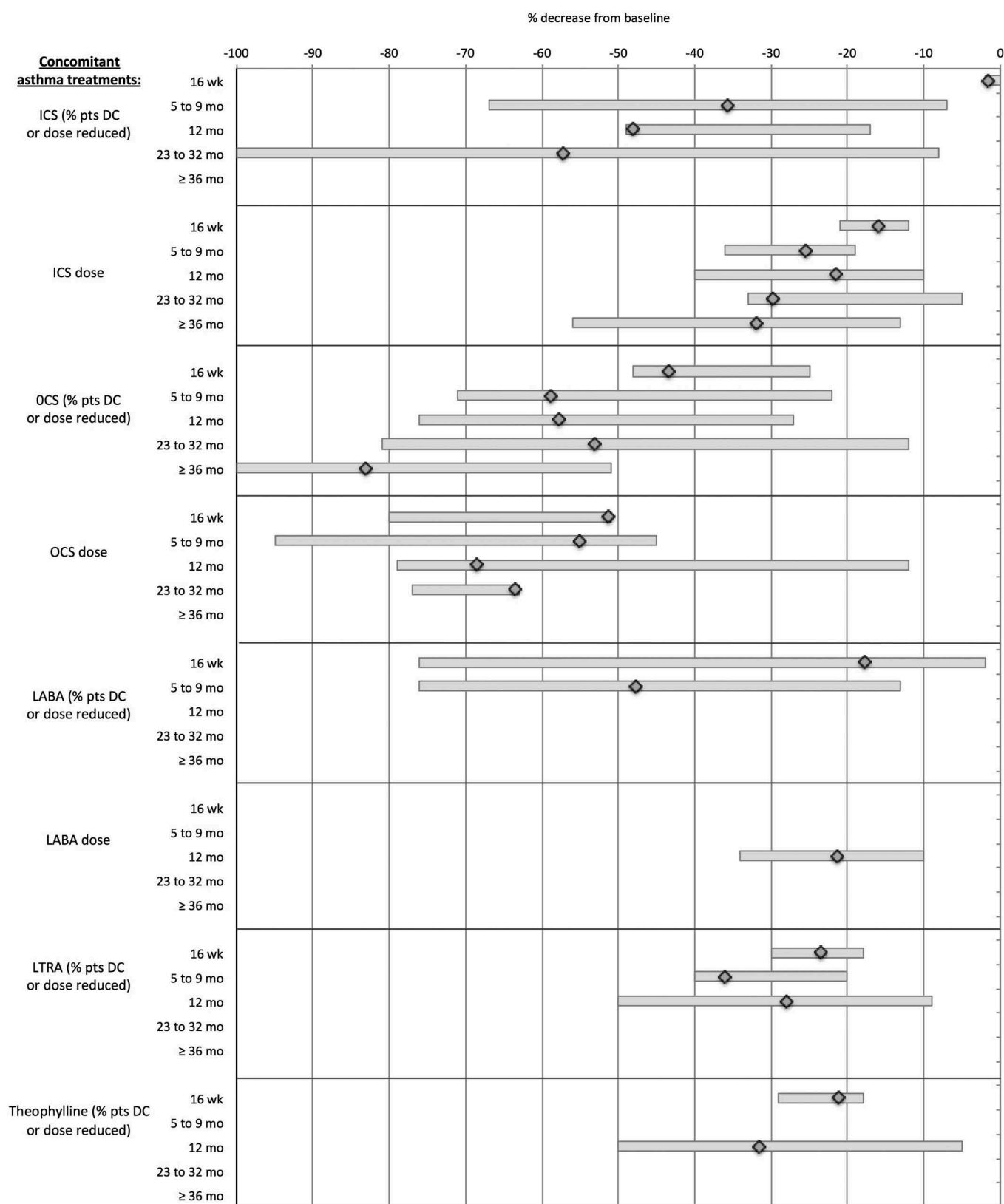


Figure 4. Effectiveness outcomes: % decrease from baseline for concomitant asthma treatments.

studies reported declines as high as 83%. In contrast, nighttime symptoms declined initially by 75.9% (5--9 months) over baseline. At 12 months, the decline in

nighttime symptoms was 59.6% but improved to 68.6% in the 23--32 month time window. Improvements in nighttime symptoms by as much as 84% (5--9 months) and 90%

(23–32 months) were reported in singular analyses.

As to asthma control, ACT scores improved by about 45% over baseline between 5 and 32 months, with an improvement by 55.6% noted at 36 months and beyond. Individual studies related changes as high as 77% at 12 months, 90% at 23–32 months, and 109% at ≥ 36 months. ACQ scores showed consistent average improvements by about one-third over baseline from the short-term (5–9 months) to the relatively long-term (23–32 months). Average improvements in GINA classification varied between 35.7% (12 months) and 75.4% (5–9 months); with the dual caveat that the GINA classification is limited to 4 levels and therefore yields relatively little variation in general, and that only 1 or 2 studies reported useable data further limiting variability.

On average, about two-thirds of patients were classified as good or excellent on the GETE scale at 16 weeks, 5–9 months, and 1 year after the start of omalizumab treatment. This increased to an average of 80.8% by 23–32 months.

3.3.2. Quality of life

AQLQ scores increased significantly to an average 46.1% over baseline over the first 9 months, to settle at average increases of 28.4% at 12 months and, based however on only two studies, 20.2% at 36 months and beyond. Improvements in quality of life, as measured by the AQLQ, reached as high as 55% between 16 weeks and 1 year. Though included in Table 3, EQ5D data should be considered with reservation because of the limited number of patients in the 1–2 studies using this method of measuring quality of life.

3.3.3. Healthcare resource utilization

Compared with the year before initiation of omalizumab therapy, emergency room visit events declined by an average of 80.6% in the first year of treatment and 90.6% in the 23–32 month time window. Singular studies reported decline rates of 93% and 94% at these respective times. The mean percentage of patients requiring one or more emergency room visits declined by an average annualized rate of 64.1% in the 5–9 month time window, 55% in the first year of omalizumab treatment, and 86.1% by 23–32 months since start of treatment; yet these results require reservation considering only 1 or 2 studies reported this metric.

In parallel, hospitalization events decreased by an average annualized rate 74.7% by the 5–9 month time window, 76.1% in the first year of treatment, and about 81% beyond 23 months. Most studies reported hospitalization rate decreases of 67% and higher at all time points and in all time windows, with top rates of decline ranging from 86% to 100%. The mean percentage of patients admitted once or more to the hospital declined by an average annualized rate of 74.5% in the 5–9 month time window, 61.4% in the first year of omalizumab treatment, and 87.2% by 23–32 months since start of treatment; with top decline rates ranging from 90% to 96% reported in singular studies.

3.3.4. Concomitant medication sparing

The average percentage of patients who were discontinued on ICSs or whose ICS dose was reduced, varied between 35.7% in the 5–9 month time window and declining further to 48.1% at

12 months and further to 57.2% in the 23–32 month window; with reported singular decline rates across these time points of 49% to 100%. Mean ICS dose reductions ranged from 21.5% at 12 months to 31.9% in the ≥ 36 months period.

As to OCSs, the average percentage of patients discontinued or with dose reductions over baseline declined by about 58% in the 5–9 month window and at 12 months, by 53.1% in the 23–32 month time window, and by 83.1% in the ≥ 36 months period. Mean OCS dose reductions varied from 55.1% at 5–9 months to 68.6% at 12 months and 63.6% at 23–32 months.

Data on LABA use are limited. The reduction in the average percentage of patients prescribed LABAs and the average LABA dose are, at best, indicative of a trend of lower concomitant LABA treatment. Similarly, the reductions in patients discontinued from LTRAs or theophylline, or with dose adjustments on these agents, should be considered as indicative as well.

3.4. Safety

The estimated adverse event rate at any level of seriousness and severity and irrespective of follow-up duration was 26.8% (range 0% to 55.6% reported in $n = 20$ studies, $n = 5877$ patients). The estimate for serious adverse event rate irrespective of follow-up duration was 12.6% (range 0% to 23.9% from $n = 17$ studies, $n = 6289$ patients).

4. Expert commentary

The benefit of real-world effectiveness studies is the insight such studies provide about the effect of drugs, shown in clinical trials to be efficacious and safe, across variations in patients, clinicians, clinical settings, and treatment regimens. In the case of omalizumab in severe asthma, such studies complement and extend the findings of efficacy trials, which are focused on the *pharmacological* effect of omalizumab. The real-world studies reviewed here enable a better understanding of the *pharmacotherapeutic* effect of omalizumab as part of treatment regimens in broad cross-sections of the general population of patients with severe asthma.

The present systematic review of 42 real-world omalizumab studies covering 9377 patients from 35 countries worldwide confirms and extends the conclusions of our systematic review published in 2016 [48], which covered studies published up to 2015 (and likely concluded in 2014 at the latest). Our prior review provided strong evidence for the short-term (16 weeks to 1 year) effectiveness of omalizumab, and emergent yet still tentative evidence that the effectiveness may extend up to 2 to 4 years. This present review firmly establishes the short-term effectiveness of omalizumab at 16 weeks and 1 year, and provides strong evidence of its long-term effectiveness: seven studies reported outcomes at 2 years [37,39,43,45,60,70,76], seven studies at 3 years or more [36,47,58,63,64,66,70,73], one study at 4 years [36], and one study with a mean follow-up of 60.7 months followed patients for as long as 121 months [66]. Thus, our review provides strong evidence on the major outcomes of interest for up to 2 to 4 years; and emergent evidence reaching well beyond 4 years. Note in this regard that Menzella et al. [79,80]

report on a subsample of patients from the Bousquet et al. [30] study already included in this review who had been on omalizumab for, respectively, four ($n = 11$) and nine ($n = 9$) years. Significant improvements over baseline in AQLQ and FEV₁ found at four years were maintained after nine years of treatment; reduction in serious exacerbations, emergency department visits and hospitalizations were also observed with no safety concerns in this small cohort of patients on long-term therapy.

Focusing on the studies that reported outcomes in either the 23–32 month time window or at 36 months and beyond (and taking the latest of the two; Table 3), there is convincing evidence to infer the long-term effectiveness of omalizumab in the management of severe allergic asthma.

In terms of lung function,

- FEV₁, the only objective marker of lung function included in the studies, improved by 26%.

As to exacerbations and symptoms,

- the rate of patients experiencing exacerbations declined by 60%, and the average number of events per patient per year by 71%; and
- the proportion of patients reporting daytime symptoms decreased by 41%, while the proportion relating nighttime symptoms declined by 69%.

Regarding asthma control,

- ACT scores increased by 56%; and
- ACQ scores decreased by 32%.

In terms of overall assessment,

- the GINA classification score improved for 69% of patients; and
- 81% of patients were classified at good or excellent on the GETE scale.

As to quality of life,

- AQLQ quality of life scores rose by 20%.

In terms of healthcare resource utilization,

- emergency department visits (per patient per year) declined on average by 91%, and the proportion of patients with one or more emergency department visits annually by 86%; and
- in parallel, hospitalizations (per patient per year) dropped an average of 81%, and the proportion of patients with one or more hospitalizations annually by 87%.

As to medication use,

- for 57% of patients on ICS, this treatment was discontinued or the ICS dose was reduced, with an average dose reduction of 32%;

- for 83% of patients on OCS, this treatment was discontinued or the OCS dose was reduced, with average dose reduction of 64%;
- for 66% of patients treated with LTRAs and for 69% of patients prescribed theophylline, therapy was discontinued or dose was reduced; but
- the percentage of patients who were discontinued on LABAs or whose dose was reduced varied over time with no discernible pattern.

Safety data tended to be reported rather inconsistently across the studies detailing AEs and SAEs. Over-reporting of some and under-reporting of other AEs and SAEs are likely given the lack of harmonization in how safety data were collected across studies.

Although outside of the scope of the current review on severe allergic asthma, a number of real-world studies have been published on cohorts of patients with moderate-to-severe allergic asthma. Findings on this body of evidence of over 6,000 patients, with treatment durations ranging from six months to five years, are qualitatively similar to our findings on patients with severe asthma. Significant improvements in these moderate-to-severe allergic asthma patients were found for: FEV₁ [81], exacerbations [81–83], asthma symptom scores [84], ACT scores [50,81,83], ACT classification of well-controlled (ACT >20) [85], ACQ scores [82], AQLQ scores [82], emergency department visits [81,82,86], hospitalizations [81–83,86], ICS use [86] and dose [87], OCS use [81,82,85,86] and dose [82], SABA puffs/day [87], use of high-dose ICS [85], symptoms of coughing, shortness of breath, and wheezing [85], and asthma-affected work, school and regular daily activities [50]. Improvements were also found in a subgroup of moderate-to-severe allergic asthma patients with IgE levels above 700 IU/mL for ACT, emergency department visits, and OCS use [88]. Likewise, our findings are in line with real-world practice in children with severe allergic asthma [51,52].

The published body of evidence of real-world omalizumab use in severe allergic asthma demonstrates: 1) the short-term treatment effectiveness, mirroring the efficacy found in clinical trials, and 2) long-term on-treatment effectiveness up to and beyond 4 years. However, data on any sustained effect following treatment discontinuation are still needed.

In conclusion, there is strong long-term evidence that omalizumab improves lung function and asthma control, enhances quality of life, decreases emergency department visits and hospitalizations, and lowers the need for corticosteroid treatment and other therapies. This translates into marked reductions in suffering and significant health care savings. In both the short- and long-term, omalizumab is highly effective in managing severe allergic asthma in adults as well as adolescents in routine clinical practice and heterogeneity in patients, clinicians, and settings.

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Declaration of interest

K MacDonald, I Abraham and CS Lee are associated with and K MacDonald and I Abraham hold equity in Matrix45. By company policy Matrix45 associates are prohibited from owning equity in sponsor organizations (except

through mutual funds or other independently administered investment instruments) or contracting independently with sponsor organizations. Matrix45 provides similar services to those described in this paper to other biopharmaceutical companies on a non-exclusivity basis. A Kavati and B Ortiz are both an employee and shareholder of Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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