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Long-term effectiveness and safety of omalizumab in pediatric and adult patients with moderate-to-severe inadequately controlled allergic asthma

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ABSTRACT

Omalizumab is recommended as an add-on therapy in patients aged ≥6 years with inadequately controlled, moderate-to-severe persistent allergic asthma. The efficacy and safety of omalizumab treatment in allergic asthma clinical trials and its effectiveness in the real world have been reported in numerous studies. In this review, we examine clinical evidence in pediatric and adult patients with allergic asthma who received omalizumab treatment for at least 2 years, to assess its effectiveness, durability, and trajectory of response over time as well as safety. We performed a literature search from inception until March 2022 in PubMed using the keywords "omalizumab" and "allergic asthma" to retrieve articles examining the effects of omalizumab in patients with allergic asthma, aged ≥6 years. Only articles that evaluated the effectiveness of omalizumab for at least 2 years were included. Data from case reports were excluded. Our review confirmed the long-term effectiveness and safety of omalizumab, demonstrating reduced rate of exacerbations, improved lung function, asthma control, and quality of life, decreased health care resource utilization, and use of corticosteroids (oral/inhaled) with a favorable safety and tolerability profile for up to 9 years in adult patients with moderate-to-severe allergic asthma. Similar results were also observed in the pediatric population with up to 7.5 years of omalizumab treatment. This review highlights and confirms the sustained clinical benefits of omalizumab over long periods of treatment in pediatric and adult populations with allergic asthma.

Keywords: Allergic asthma, Efficacy, Long-term, Omalizumab, Safety, Pediatric

INTRODUCTION

Patients with moderate or severe asthma require treatment with medium-to high-dose inhaled corticosteroids (ICS) ± long-acting β_2-agonists (LABAs) or other add-on controllers. However, some patients with severe asthma remain uncontrolled despite treatment with high-dose ICS/LABA ± other add-on agents such as leukotriene receptor antagonists and/or long-

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acting muscarinic antagonists.[1] While assessing severe asthma, attention to possible comorbidities, differential diagnoses, and accurate phenotyping are needed prior to consideration of complex therapies, such as biologics. Failure to do so may result in non-response to all biologics.[2]

Omalizumab, an anti-IgE monoclonal antibody, was the first biologic approved for patients aged ≥6 years with moderate-to-severe persistent asthma (USA) or severe persistent allergic asthma (Europe), uncontrolled despite appropriate high-dose ICS treatment.[3,4] Randomized clinical studies and real-world evidence have demonstrated the efficacy and effectiveness of omalizumab in reducing asthma exacerbations and hospitalization rates, improving quality of life (QoL) and asthma daily symptoms. In addition, omalizumab has a very satisfactory short- and long-term safety profile in children aged 6–12 years, teenagers, and adults.[5–15] Omalizumab is now widely used for various indications and has recently reached >1.75 million patient-years of exposure.[16] In this review, we comprehensively examine the existing clinical evidence from real-world studies, including pediatric and adult patients with allergic asthma who have received omalizumab treatment for ≥2 years, to evaluate its effectiveness and safety and help clinicians assess the durability and trajectory of its response over time.

METHODOLOGY

We performed a literature search in PubMed published from inception until March 2022, using the keywords "omalizumab" and "allergic asthma" to retrieve articles evaluating the effects of omalizumab in allergic asthma in patients aged ≥6 years. Studies that evaluated the effectiveness of omalizumab for ≥2 years, with real-life experiences, registry-based or observational designs, and published in the English language, were deemed eligible for inclusion. Case reports were excluded. The included articles were further categorized into 2 sections based on treatment duration: omalizumab use for 2–5 years and >5 years (Table 1).

Data on exacerbation rate, lung function, asthma control, QoL, systemic corticosteroid (SCS) or ICS use, and healthcare resource utilization (HCRU) were reported as measures of effectiveness of omalizumab. Although the criterion set for defining exacerbations differed for each study, making between-study comparisons difficult, certain criteria such as exacerbations requiring oral corticosteroids (EROCS), worsening of asthma, increased need for ICS or SCS, hospitalizations, and emergency room (ER) visits are common in many of the studies for definitions of exacerbations (Supplementary Table 1).

Other parameters assessed were lung function in terms of forced expiratory volume in 1 second (FEV_1), asthma control measured by Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ), QoL assessed using different questionnaires including Asthma Quality of Life Questionnaire (AQLQ), and Asthma Life Questionnaire (ALQ).[9,11,17,18] In some studies, early clinical response to omalizumab treatment was evaluated using the validated "global evaluation of treatment effectiveness (GETE)" tool.[9] HCRU in terms of steroidal use and number of hospitalizations, medical visits and ER visits was also assessed.[19]

RESULTS

We identified 42 publications meeting the inclusion criteria, 30 of which included a treatment duration/follow-up of 2–5 years and 12 were of >5 years. The eligible literature data with demographic details of the patients are shown in Table 1.

Long-term effectiveness

Asthma exacerbations

Omalizumab treatment showed ≥72% reduction in exacerbation rates in patients with moderate-to-severe allergic asthma.[17,36,41] The proportion of patients experiencing exacerbations decreased over time, and notably, fewer or no episodes of exacerbations requiring ER visits or hospitalizations were observed.[23–25,29] Furthermore, these improvements were observed and maintained over a long time period (>5 years).[42]

Publication	Study name	Treatment duration or follow-up period	Number of patients enrolled (Male: Female)	Mean Age (mean ± SD), years
Omalizumab treatment for 2–5 years				
Studies with adult patients (>18 years)				
Schreiber J et al., 2020[20]	NA	3 years	153 (M: 60; F: 93)	49 ± 12.16
Cavaliere et al., 2020[21]	NA	36 Months	10 (M: 06; F: 04)	47 (26–70)[c]
Kirchnerová OR et al., 2019[22]	eXpeRience registry (Czech Republic subgroup)	2 years	112 (M: 44; F: 68)	44.0 ± 13.0
Pelaia C et al., 2018[23]	NA	5 years	15 (M: 05; F: 10)	46.60 ± 13.21
Ke et al., 2018[24]	NA	12 and 24 Months	1564 (M: 598; F: 966)	44.9 ± 15.67
Al-Ahmad M et al., 2018[25]	NA	4 years	65 (M: 22; F: 43)	46.69 ± 11.55
Iribarren C et al., 2017[26]	EXCELS study (data on cardiovascular and cerebrovascular events)	5 years	5007 (omalizumab cohort) 2829 (non-omalizumab cohort) (M: 7857; F:5079)	Omalizumab: 44 ± 17 Non-omalizumab: 46 ± 17
Sposato B et al., 2017[52]	NA	Patients divided into different subgroups based on treatment duration: <12, 12–24, 24–60, and >60 months	340 (M: 121; F: 219)	≤12 M: 51 (42–64)[c] 12–24 M: 51 (40–61)[c] 24–60 M: 54 (46–62)[c] >60 M: 53 (44–63)[c]
Sposato B et al., 2016[27]	NA	35.1 ± 21.7 months[b]	105 (M: 33; F: 72)	29 ± 6 (18–39), 54 ± 7 (40–64), 69 ± 4 (≥65)
Tat TS et al., 2016[28]	NA	35.6 ± 17.8 months[b]	19 (M: 05; F: 14)	69.3 ± 5.8
Zazzali JL et al., 2015[15]	EXCELS study	5 years	4930 (omalizumab cohort) 2779 (non-omalizumab cohort) (M: 2714; F: 4993)	Omalizumab: 44.4 ± 16.6 Non-omalizumab: 46.2 ± 17.1
Novelli F et al., 2015[29]	NA	32 (4–120) months[a]	306 (M: 36.9%; F: 63.1%)	52.0 ± 13.7
Lopez Tiro JJ et al., 2015[30]	NA	3 years	52 (M: 10; F: 42)	43.5 (15–67)[c]
Pereira Barbosa M et al., 2015[18]	eXpeRience study (Portuguese subgroup)	2 years	62 (M: 19; F: 43)	49.2 ± 15.0
Caminati M et al., 2014[10]	NA	22.97 ± 16.55 months[b]	59 (M: 29; F: 30)	45.59 ± 11.51
Vieira T et al., 2014[17]	NA	2 years	15 (M: 02; F: 13)	46.5 ± 10.8

(continued)

Publication	Study name	Treatment duration or follow-up period	Number of patients enrolled (Male: Female)	Mean Age (mean ± SD), years
Braunstahl GJ et al., 2014[19]	eXpeRience study (data on HCRU)	2 years	925 (M: 325; F: 600)	45 ± 15.0
Long A et al., 2014[31]	EXCELS study (safety data)	5 years	7857 (M: 2778; F: 5079)	Omalizumab: 44 ± 17 Non-omalizumab: 46 ± 17
Braunstahl GJ et al., 2013[9]	eXpeRience study	2 years	925 (M: 325; F: 600)	45 ± 15.0
Braunstahl GJ et al., 2013[32]	eXpeRience study (data on corticosteroid use)	2 years	263 (M: 94; F: 169)	46 ± 13.13
Lafeuille MH et al., 2013[33]	NA	2 years	3044 (M: 1146; F: 1898)	48.5 ± 15.7
Chen H et al., 2013[34]	EXCELS study (interim analysis)	2 years	~5000 (omalizumab-treated) >2800 (non-omalizumab treated) (M: 2753; F: 5082)	New starts: 44.3 ± 16.0 Established user: 44.5 ± 16.6 Non-omalizumab: 46.2 ± 17.1
Ozgur ES et al., 2013[35]	NA	40.81 ± 8.2 months[b]	26 (M: 05; F: 21)	47.6 ± 13.9
Vennera Mdel C et al., 2012[36]	NA	2 years	266 (M: 83; F: 183)	51.0 ± 13.7
Dal Negro RW et al., 2012[11]	NA	3 years	16 (M: 08; F: 08)	45.4 (31–64)[c]
Menzella F et al., 2012[37]	NA	4 years	11 (M: 07; F: 04)	47.5 ± 9.64
Tzortzaki EG et al., 2012[38]	NA	4 years	60 (M: 24; F: 36)	54 ± 14
Studies with pediatric patients (≥ 6 years to <18 years)				
Sztafińska A et al., 2017[39]	NA	~2 years	19 (M: 15; F: 4)	11.36 (6–15)
Odajima H et al., 2017[40]	NA	116.6 (46.9–151.1) weeks[a]	38 (M: 23; F: 15)	11.5 ± 2.52
Deschildre A et al., 2015[41]	NA	2 years	104 (M: 60; F: 44)	11.9 (11.3–12.5)[c]
Omalizumab treatment for >5 years				
Studies with adult patients (>18 years)				
Papaioannou AI et al., 2021[42]	NA	10.6 ± 1.2 years	45 (M: 15; F: 30)	55.3 ± 12.2
Mansur AH et al., 2017[43]	NA	60.7 ± 30.9 months[b]	45 (M: 08; F: 37)	44.9 (19–69)[c]
Menzella F et al., 2017[14]	NA	9 years	8 (M: 05; F: 03)	43 ± 9
Di Bona et al., 2017[44]	NA	3.8 ± 2.6 years[b] (range 0.2–9 years)	91 (M: 24; F: 67)	49.9 ± 14.9

Ledford D et al., 2017[13]	XPORT	6 years (5 years during EXCELS study and 1-year follow-up)	176 (M: 53; F: 123)	51.5 ± 12.5
Gemicioğlu B et al., 2016[45]	NA	5.5–7 years	17 (M: 04; F: 13)	48.3 ± 16.4
Storms W et al., 2012[46]	NA	6 years	167 (M: 54; F: 113)	52.0 (14–82)[c]
Pace E et al., 2011[47]	NA	7 years	7 (M: 04; F: 03)	50 ± 8
Studies with pediatric patients (≥ 6 years to <18 years)				
Deschildre et al., 2019[48]	NA	46.2 (31.5–90.3) months	60 (M: 30; F: 30)	11.25 (6–16.2)[c]
Folqué MM et al., 2019[49]	NA	Up to 6 years	48 (M: 27; F: 21)	11.5 (5–17)[c]
Namazova-Baranova L et al., 2015[50]	NA	1–72 months	101	13.4 (6–17)[c]
Nieto García A et al., 2021[51]	ANCHORS	Up to 6 years	484	11.1 (1.9–17.9)[c]

Table 1. (Continued) Publications that evaluated omalizumab use in asthma patients receiving the drug for >2 years. *HCRU, healthcare resource utilization, NA, not applicable.* [a]*Treatment duration represented as median (range).* [b]*Treatment duration represented as mean ± SD.* [c]*Age represented as mean (range)*

Omalizumab use for 2–5 years in adults with asthma

All the studies included in this review showed that omalizumab treatment resulted in decreased asthma exacerbation rates (Fig. 1).[9–11,17,23,27,28,35–38,41,52] Patients treated with omalizumab for 2 years showed a marked decrease in mean annualized exacerbation rate ranging from 71.1% to 95.1% across studies.[9,17,24,36,41,42] In addition, a higher proportion of patients who were free from exacerbations requiring emergency visits or hospital admissions were observed with ~2 years of omalizumab treatment compared with the pretreatment period (88.6% vs 41.9%).[10] Similar results were observed for exacerbations requiring oral steroids with 79% patients reported to be exacerbation free after ~2 years of omalizumab treatment compared with 16.3% patients during the pretreatment period.[10] The effect of omalizumab on exacerbations was observed, irrespective of patients' baseline lung function, steroid use, or smoking history.[10] Evaluation of data from studies with a longer treatment duration of ~3–4 years also demonstrated reductions in the rate of exacerbations by 54.4%–95% in omalizumab-treated patients, indicating sustained effectiveness.[11,28,35,37,38]

Omalizumab use for >5 years in adults with asthma

From pretreatment to the end of the 5-year omalizumab treatment period (follow-up: 5.5–7.0 years) the mean annualized exacerbation rate significantly decreased by 77.1% in 17 allergic patients.[45] Sustained reduction in rate of exacerbations was observed with omalizumab treatment in a 7-year study in 7 patients (~78% decrease),[47] 9-year study in 8 patients (~87% decrease), and ~10-year study in 45 patients (75% decrease; Fig. 1).[14,42] In the XPORT study (Xolair Persistency Of Response After Long-Term Therapy), patients who continued omalizumab beyond 5 years were significantly less likely to experience a protocol-defined exacerbation compared with those who withdrew from treatment (odds ratio: 0.45 [95% CI: 0.24–0.83]). In addition, treatment continuation (1 year) prolonged the time-to-first exacerbation (hazard ratio [HR], 0.49 [95% CI: 0.28–0.86]).[13]

Omalizumab use in pediatric patients with asthma

In a cohort of 78 severe allergic asthmatic children aged 6–18 years, Deschildre et al observed a continuous decrease in severe exacerbation rates after 2 years of omalizumab treatment, with a trend to zero exacerbations at the end of 2 years, since the rate reached a mean (95% CI) of 0.22 (0.03–0.41) per year in the second year. A significant decrease of –72% and –83% in rate of exacerbation requiring emergency visits or hospitalization was observed during the first and second year ($P = 0.0001$) with no hospitalization for exacerbation during the second year.[41] Folqué et al in a 6-year follow-up study showed a significant decrease in the rate of hospital admissions and visits to the ER for asthma exacerbations during the third and fourth years of follow-up, respectively.[49] In another 6-year follow-up study of 426 patients (ANCHORS), the mean number of moderate-to-severe exacerbations decreased significantly from 7.9 at baseline to 1.1 during the first year [−80.2%, $P < 0.001$]), and these improvements were sustained during the 6 year follow-up period with exacerbation numbers trending to zero after 2 years of omalizumab treatment.[51] It is important to highlight the improvements observed in terms of rate of exacerbations requiring systemic corticosteroids, reaching nearly zero in pediatric patients after 2 years of omalizumab treatment,[41,51] which indeed is an important treatment goal in asthma management.

Asthma control and GETE score

Overall, omalizumab improved ACT scores in patients across all age groups, with greater improvements in the younger patients compared with the older patients. Patients who continued omalizumab treatment were more likely to have controlled asthma compared with those who discontinued and never reinitiated. The proportion of patients with good or excellent omalizumab response on global evaluation of treatment effectiveness (GETE) scale increased over years of treatment.

Omalizumab use for 2–5 years in adult with asthma

In a retrospective study, 44% of patients who received consistent omalizumab treatment for 24 months had uncontrolled asthma during the follow-up period (13–24 months) compared with 55% of patients who discontinued omalizumab at 12 months (and never reinitiated).[33]

Omalizumab treatment for ~2 years improved mean ACT scores by 6.0–7.0 points.[9,17,18,25,36] A longer duration of treatment (3–4 years) demonstrated a further increase in mean ACT scores (from 4.2 to 11.6 points; Fig. 2).[11,23,25,30,35,38] Sposato et al showed that although ACT scores increased in all age groups of patients treated with omalizumab for ~3 years, the level of improvement was greater in patients aged 18–39 years (by ~9 points)

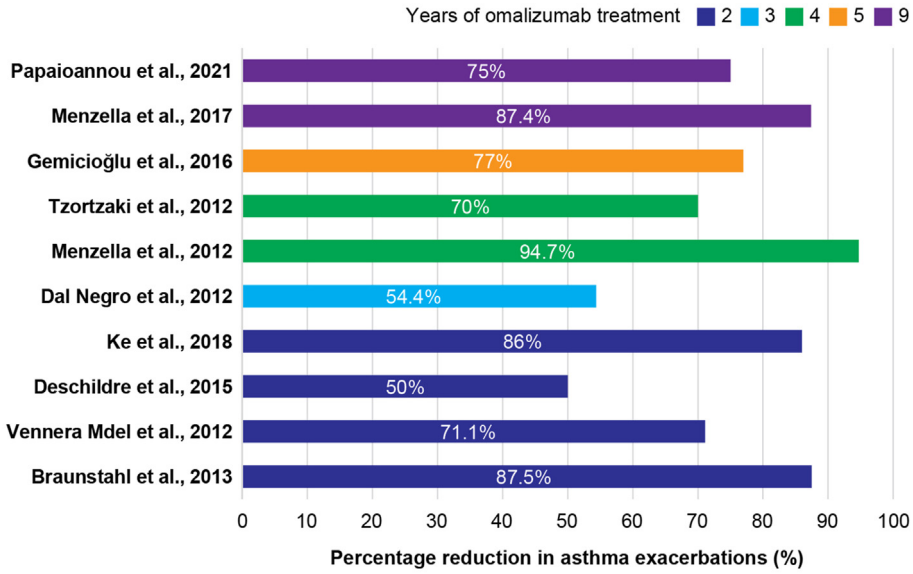

Fig. 1 Effect of omalizumab on exacerbation rate in allergic asthma

compared with 40–64 years (by ~7 points) and ≥65 years (by ~5 points).[27] In contrast, Tat et al reported significant improvements in ACT scores by 11.4 points from baseline in elderly patients for the same treatment duration.[28]

Omalizumab treatment for 2 years increased the proportion of patients with controlled or partly controlled asthma by ~63% from baseline.[9] In another real-world study, as compared to 24.1% of patients at baseline, 92.1% and 87.1% patients reported controlled/partially controlled asthma with omalizumab after 12 and 24 months of treatment, respectively.[22] Omalizumab treatment for a median duration of 32 months resulted in good asthma control in 25.2%, partial control in 47.1%, and poor control in 24.5% of patients, according to GINA.[29] Additionally, in the EXCELS study (Epidemiologic Study of Xolair [Omalizumab]: Evaluating Clinical Effectiveness and Long-term Safety in Patients With Moderate to Severe Asthma), more patients were well-controlled (ACT score of >20) after 5 years of omalizumab treatment compared with prior to treatment (66.7% vs 48.6% for omalizumab-naïve cohort, 60.3% vs 25% for new starters, and 61.3% vs 47.8% for established users).[15]

Studies that evaluated response to omalizumab treatment on the GETE scale showed that the proportion of patients with good or excellent response increased from 74.6% at 4 months to 81.6% after 2 years of treatment[36] and from 72.7% at 8 months to 81.8% after 4 years of treatment.[37] In a real-life, observational surveillance study, Al-Ahmad et al evaluated treatment response of omalizumab using modified physician GETE (mGETE) scale, which demonstrated an excellent response in 53.8% of patients at 16 weeks that increased to 73.8% after 4 years of treatment.[25]

Omalizumab use for >5 years in adults with asthma

Significant improvements in asthma control from baseline have been reported in most studies that assessed omalizumab treatment for >5 years. This was demonstrated by a 5.1-point increase in mean ACT score[45] and a 1.7-point decrease in mean ACQ7 score over 5 years,[43] a 96.4% increase in ACT scores during a 6-year treatment,[46] and a 2.2-point decrease in the mean symptom score after 7 years of omalizumab treatment (Fig. 2).[47] A recent study with ~10 years of omalizumab treatment demonstrated nearly 6-point increase in ACT score at 3 years which remained high up to 8 years of treatment.[42] The XPORT study showed benefits of continuation of omalizumab treatment after long-term treatment results, supported by improved symptom control and reduced exacerbation risk.[13]

Omalizumab use in pediatric patients with asthma

Omalizumab treatment for ~2 years improved Japanese pediatric asthma control program

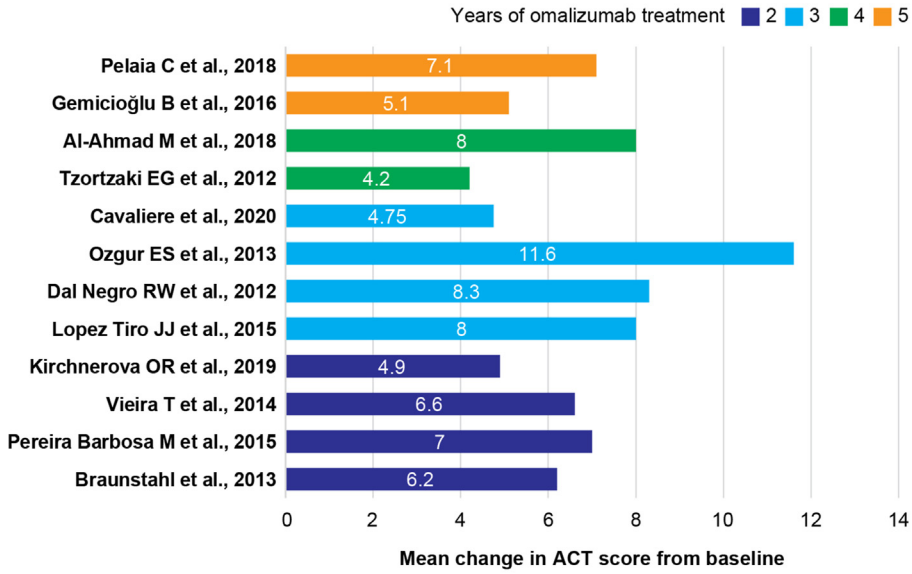

Fig. 2 Effect of omalizumab on asthma control, as demonstrated by Asthma Control Test (ACT) score, in allergic asthma. Bars indicate the ACT score changes in individual studies. ACT, Asthma Control Test

(JPAC) mean score by 3 points.[40] In a French cohort of uncontrolled severe allergic asthmatic children, 80% of 73 children were well-controlled (Global Initiative for Asthma – GINA criteria) after 2 years of omalizumab treatment.[41] In severe allergic asthmatic children who had received omalizumab for 24 months, 76.7% of 30 children were controlled who were still on omalizumab maintenance therapy after a mean treatment duration of 46.2 months.[48] In the ANCHORS study (Asthma iN CHildren: Omalizumab in Real-life in Spain), 8.4% of 334 patients were controlled at baseline which improved significantly to 45.0% (148/329; [$P < 0.001$]) during the first year of omalizumab treatment and increased to 89.3% (75/84) at year 6.[51]

Quality of life

Omalizumab use for 2–5 years in adults with asthma

Omalizumab treatment for ~2 years increased mean AQLQ score by 0.94 points[22] and mean QoL score by 9 points.[40] Sustained improvement in QoL was observed with omalizumab for 3–4 years, as reflected by an increase in median AQLQ scores by 3.4 points after 3 years[35] and by 2.8 points after 4 years[37] of treatment; a decrease in mean St. George's Respiratory Questionnaire score of 21.4 points was observed after 3 years of treatment.[11]

Omalizumab use for >5 years in adults with asthma

In the only study that evaluated the effect of omalizumab on QoL beyond 5 years, a significant increase in median AQLQ score by 3.4 points was observed over 9 years from baseline.[14]

Omalizumab use in pediatric patients with asthma

The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) scores improved after 16, 24, and 104 weeks of omalizumab treatment compared with baseline, although the difference between time points was not significant. Significant improvements in total PAQLQ scores >1.5 points were achieved by 41.5% and 39.6% of children after 52 and 104 weeks of treatment, respectively. Of the total population, only 5% of children did not respond (improvement of PAQLQ <0.5 points) to omalizumab therapy.[39]

Use of oral corticosteroids

Omalizumab use for 2–5 years in adults with asthma

Treatment with omalizumab for 2 years resulted in decrease in the rate of OCS use as well as proportion of patients receiving OCS compared with baseline.[12,20,25,26,28] In addition, mean daily dose of prednisolone-equivalent OCS decreased from baseline to 2 years.[12,25] Additionally, patients consistent (patient with ≥1 dispensing of omalizumab, ≥6 months of continuous eligibility before their first omalizumab dispensing [washout period], and had ≥1 diagnosis for asthma during the baseline period) with omalizumab treatment at 2 years showed a greater decrease in OCS use compared with those who were not consistent.[39] A similar profile was observed when omalizumab was continued for 3–4 years.[20,32,36,41–44,58]

Omalizumab use for >5 years in adults with asthma

During a mean follow-up of >5 years in patients receiving omalizumab, mean daily maintenance OCS dose significantly decreased by >75%, along with a decrease in mean annualized number of steroid courses per patient.[45] Approximately half of the patients receiving maintenance OCS at baseline discontinued OCS therapy during omalizumab treatment.[45,48] Omalizumab decreased the number of OCS cycles after 4 and 7 years of treatment. The improvements observed at 4 years were more evident after 7 years of treatment.[53] During a 9-year follow-up study, 7 of 8 patients were using OCS at baseline, whereas after omalizumab treatment, only 1 patient used OCS. The mean daily OCS dose was decreased to 1.6 mg/day after 8 years of omalizumab treatment as compared to 7.8 mg of prednisolone or the equivalent per day.[45] In pediatric patients with asthma, at the end of first year of omalizumab treatment, in a cohort of 92 severe allergic asthmatic children aged 6–18 years, no patient remained under daily OCS treatment (6 at baseline).[41]

Use of inhaled corticosteroids

Omalizumab use for 2–5 years in adults with asthma

Omalizumab treatment resulted in a decrease in the mean daily dose of beclomethasone-equivalent ICS and budesonide-equivalent ICS from baseline to 2 years.[38,42] In the EXCELS study, following 2 years of omalizumab therapy, the mean total ICS daily dose was reduced by 57.7%, 44.7%, and 42.4% in new starters, established users, and omalizumab-naïve patients, respectively. Similarly, ICS monotherapy dose was also reduced by 60%–68% in all groups.[40] A decrease in ICS dose with omalizumab treatment was observed across all age groups.[30,55]

Omalizumab use for >5 years in adult patients with asthma

Omalizumab treatment for 7 years decreased the need for nebulized corticosteroid/bronchodilator and reduced the dose of ICS/LABA in 4 of 7 patients, with 2 patients discontinuing ICS/LABA.[53] In addition, of all patients receiving high-dose ICS at baseline, only 1 patient remained on high dose after 9 years of treatment. Other patients reported a 65% decrease in ICS dose.[14,45]

Omalizumab use in pediatric patients with asthma

In a pediatric study, a decrease of 30% of mean ICS dose (703 µg at initiation and 488 µg fluticasone equivalent per day after 1 year) was noted during the first year. No further significant decrease was observed at 2 years (mean = 429 µg/day); however, 63% of patients benefited from ≥50% decrease in initial dose of ICS.[41] In a long-term study by Deschildre et al the median daily ICS dose (range, µg/d) decreased significantly from 1000 (250–1250) to 375 (0–1000) in a subgroup of 30 children still treated after a mean of 46.2 months (31.5–90.3).[48] Sztafińska et al showed that 63.33% of pediatric patients achieved a reduction in ICS dose (median reduction of 300 µg/day after 52-weeks of omalizumab treatment). No further reduction in ICS use was observed between 52 and 104 weeks of treatment.[39] A 6-year follow-up study in 48 children with allergic asthma reported a significant decrease in the use of maintenance therapy (fluticasone) in patients after six months (329.89 µg/day) of omalizumab therapy compared to baseline (452 µg/day). The difference was maintained throughout the follow-up period.[49] In the ANCHORS study, the mean daily ICS dose decreased significantly after 1 year (867.3 vs 663.4 µg budesonide equivalent) of omalizumab treatment that continued over 6 years (350.2 µg budesonide equivalent compared with baseline).[51]

Lung function

Patients with severe asthma experience an accelerated decline in lung function over time, which may further increase the risk of exacerbations.[18] Of the 19 studies evaluating the effect of omalizumab on lung function in patients with allergic asthma for ~2–5 years, omalizumab improved lung function in 16 studies.[9–11,18,21–23,25,27–30,35–38,52] In pediatric patients, Deschildre et al showed improvement in lung function (FEV_1) during the first year of omalizumab treatment with no significant additional improvement in the second year.[41]

Omalizumab use for 2–5 years in adults with asthma

Omalizumab treatment for 2 years significantly increased mean FEV_1 (% predicted) by 7.5%–16.75% and mean peak expiratory flow (PEF) by 21.8–45.4 L/min.[9,17,18,21,22,36] Further improvement in lung function was observed with longer periods of omalizumab treatment (~3–4 years), with an increase in mean FEV_1 (% predicted) ranging from 16.8% to 24.5%.[11,21,25,30,35,37,38] A study by Vennera et al showed that omalizumab treatment for 2 years significantly increased FEV_1 (% predicted) in patients aged <50 years (14.2%) compared with those aged ≥50 years (3.2%).[36] A non-significant increase in FEV_1 (% predicted) of 12.2% was observed in elderly patients aged ≥65 years who received omalizumab for a mean duration of ~3 years.[28] In contrast, omalizumab treatment for a mean of 35 months resulted in comparable improvements in lung function (overall increase in FEV_1 [% predicted] of 12%–14%) in 3 subgroups of patients categorized by age (18–39, 40–64, and ≥65 years).[52]

Omalizumab use for >5 years in patients with asthma

Patients who received omalizumab for ≥5 years reported an 11% increase in FEV_1 relative to baseline[45] and by 17% of predicted.[43] A further increase in FEV_1% predicted by 18% was observed after 7 years,[47] 27% after 9 years,[14] and ∼12% after 12 years of omalizumab treatment.[42] A 13% improvement in mean FEV_1/FVC % predicted was observed from baseline to 7 years.[47]

Omalizumab use in pediatric patients with asthma

Sztafińska et al reported no significant improvement in FEV_1 in children and adolescents with severe persistent allergic asthma after 2 years of omalizumab treatment.[39] In children aged 6–18 years, compared with baseline (FEV_1, 88% [% predicted value] [95% CI: 83.8; 92.2]), mean FEV_1% predicted increased by 4.9% during 1 year of follow-up with no significant modification during the second year. Indeed, FEV_1 was maintained at a high level, 89.9% predicted (95% CI: 86.7%–93.0%) at the end of 2-year treatment.[41] The increase, although small, did provide a positive outcome, close to the expected value in controlled children,[41] as a decline in lung function has been described in severe asthmatic children followed up for many years.[53] These results were confirmed by Deschildre et al showing an pre-β_2 agonist FEV_1 (% predictive value) of 97 (50–119) after 31.5–90.3 months of omalizumab treatment.[48] In the ANCHORS study, FEV_1% predicted increased significantly from 84.6% at baseline to 92.3% after one year of treatment ($P < 0.001$), and these improvements remained consistent during 6 years of follow-up (92.8%).[51]

Healthcare resource utilization

Omalizumab use for 2–5 years in adults with asthma

Omalizumab treatment for 2 years reduced the mean number of annualized healthcare visits per patient (6.4 vs 0.5) and increased the proportion of patients with no annualized healthcare visit (12.3% vs 75.4%).[9,19,22] Patients who received consistent omalizumab treatment for 24 months showed a 70% reduction in asthma-related ER visits and 39% reduction in hospitalizations compared with patients who discontinued omalizumab at 12 months and did not reinitiate. Furthermore, consistent omalizumab treatment for 2 years demonstrated ∼94% reduction in HCRU and significantly prolonged time-to-first asthma-related ER visit/hospitalization (HR: 0.70; 95% CI: 0.58–0.84; $P < 0.01$).[22,33] Other studies also reported improvement in HCRU in terms of decreased hospitalizations and ER/intensive care unit visits with omalizumab for 2–4 years.[11,17,18,30,35–37] Of note, in one study, omalizumab treatment for 4 years resulted in no hospitalizations during the treatment period compared with almost two-thirds of patients who reported ≥1 annualized hospitalization prior to treatment.[37] In elderly asthmatics, the rate of hospitalization during omalizumab treatment decreased in ∼90% of patients.[28]

Omalizumab use for >5 years in adults with asthma

Omalizumab treatment from the pre-treatment period to ≥5 years resulted in reduction in number of hospitalizations and ER visits by 80.7% and 48.5%, respectively. A reduction in mean annual per-patient hospitalization and ER visit was also observed.[43]

Omalizumab use in pediatric patients with asthma

Improvement in HCRU with omalizumab has also been reported in pediatric patients. In children, the rate of hospitalizations and ER visits/patient-year significantly decreased from baseline during omalizumab treatment.[40] In the French cohort, there was a huge improvement with 88.5% decrease in hospitalizations during the first year and no patients hospitalized for exacerbations in the second year of treatment, compared to 44% in the year preceding the initiation.[41] In the 6-year ANCHORS study, the number of healthcare visits decreased significantly after 1 year of omalizumab treatment ($P < 0.001$), with no ICU admissions from the second year onward.[51] Table 2 summarizes the efficacy findings from the studies included in this review.

Long-term safety

Data from studies that evaluated the short-term use of omalizumab (<2 years) in asthma patients have reported that omalizumab has a favorable

safety and tolerability profile.[12,54] Overall, the incidences of adverse events (AEs) and serious adverse events (SAEs) were similar between long- and short-term use, reassuring the safety profile of omalizumab after prolonged use. These results are supported by at ≥1.75 million patient-years of omalizumab exposure in the post-marketing setting.[16] Table 3 summarizes the safety findings from the studies included in this review.

Adverse events (AEs)

Omalizumab use in adults with asthma

Long-term omalizumab treatment for 2–5 years was well-tolerated in most studies. As anticipated with most subcutaneous biological agents, local injection-site reaction with omalizumab was reported in a few studies.[10,25,35,38,42] In a 2-year post-marketing observational study, 11.4% of patients experienced ≥1 AE; most commonly reported AEs were arthralgia and cephalgia.[36] Furthermore, only 7 of 266 enrolled patients discontinued treatment because of AEs.[36] In another study, headache and nausea (26.7%) and fatigue and paresthesia (13.3%) were the most frequent AEs reported during 2 years of omalizumab treatment; however, most of these events did not lead to treatment discontinuation.[17] Repeat acute asthma episodes, myalgia and paresthesia, and breast neoplasm (causal relationship with omalizumab not established) reported in 1 patient each led to treatment discontinuation.[17] In a 3-year real-life study, osteo-articular pain and vasovagal syncope were reported in 1 patient each, and mild headache was reported in 2 of 49 patients. Two cases, one of severe headache and another of mild anaphylaxis, were reported after initiating omalizumab; hence, treatment was discontinued in these patients.[30]

In elderly patients who received omalizumab for ~3 years, 2 of 19 patients reported a local adverse reaction and drug-related myalgia.[28] No systemic adverse reactions related to omalizumab use (such as anaphylaxis) were reported in these patients.[28]

Similar to the AE profile observed with 2–3 years of omalizumab treatment, 11.6% of patients treated with omalizumab for 4 years reported AEs (of mild to moderate severity), with headache, local injection-site reaction, and arthralgia being the most frequent; none of these events led to treatment discontinuation.[38]

Severe adverse events (SAEs)

Omalizumab use for 2–5 years in adults with asthma

In the 2-year eXpeRience study, 150 SAEs were reported in 64 (6.9%) patients; asthma (3.5%), dyspnea (0.8%), and pneumonia (0.8%) were the most common SAEs. Of 25 SAEs suspected of being drug-related, dyspnea, sudden chest tightness, and headache were the most common (3 events each); 14 SAEs led to treatment discontinuation. Nine deaths were reported during the study, none of which was omalizumab-related.[9]

Although individual cases of bronchial cancer[28] and malignant breast neoplasm[17] are reported in different studies after 3 and 3.5 years of omalizumab treatment, respectively, no association between tumor and omalizumab treatment is reported. Further evidence on the correlation of omalizumab treatment with malignancy was evaluated in the dedicated 5-year EXCELS study, which demonstrated that crude malignancy rates for all malignancies, and all malignancies excluding non-melanoma skin cancer were similar in omalizumab and non-omalizumab users, with a rate ratio of 0.84 (95% CI, 0.62–1.13) and 0.98 (95% CI, 0.71–1.36).[31]

The rate (per 1000 person-years) of cardiovascular/cerebrovascular SAEs was higher in omalizumab versus non-omalizumab–treated patients[49] (Table 4). After control for measured confounders, the estimated increase in risk was reduced considerably. In addition, rates of ischemic stroke (0.5 [95% CI: 0.2–1.0] vs 0.7 [95% CI: 0.3–1.4]) and cardiovascular death (2.4 [95% CI: 1.6–3.3] vs 2.0 [95% CI: 1.2–3.1]) were similar in both groups.[55]

As the primary endpoint in the EXCELS study was to assess malignancy risk, patients were not randomized or balanced based on their cardiovascular risk at baseline, and this constitutes one of the confounders for cardiovascular risk assessment. After considering confounding imbalances between the cohorts, crude associations between omalizumab and cardiovascular/

Author; Treatment duration	Exacerbations	Lung function	Asthma control/QoL	Healthcare utilization	Corticosteroid use
Schreiber J et al., 2020[20] **Treatment duration**: 3 years	**Proportion of patients experiencing ≥ 2 severe exacerbations remained low and stable:** First year: 12.42%, Second year: 7.87% Third year: 11.97%	-	**Reduction in mean ± SD ACQ-6 total score vs baseline:** 1.7 ± 1.23 vs 2.0 ± 1.22 at 3 years change from baseline: −0.18 ± 1.07 ($P = 0.340$) **Improvement in Mini-AQLQ total score vs baseline (4.5 ± 1.26):** Month 6: 5.0 ± 1.35; $P = 0.002$ 1 year: 4.9 ± 1.36; $P = 0.001$ 1.5 years: 4.8 ± 1.40; $P = 0.009$ 2 years: 4.9 ± 1.48; $P = 0.011$ 3 years: 4.7 ± 1.48; $P = 0.186$ **Increase in Mini AQLQ score at 3 years vs baseline:** 0.26 ± 1.35, $P = 0.186$	-	-
Cavaliere et al., 2020[21] **Treatment duration**: 36 Months	-	**Improvement in % FEV_1 predicted vs baseline (81.25 ± 11.57)**: Month 6: 88.37 ± 6.25; $P = 0.10$ Month 12: 94.25 ± 6.11 Month 24: 98 ± 11.33 Month 36: 99.37 ± 6.11 ($P < 0.001$)	**Improvement in mean ± SD asthma control (ACT) vs baseline (18.25 ± 1.58)**: Month 6: 21.62 ± 0.91 Month 12: 22 ± 0.92 Month 24: 21.62 ± 1.5 Month 36: 23 ± 1.69 ($P < 0.001$)	-	-
Kirchnerová OR et al., 2019[22] **Treatment duration**: 2 years	**Reduction in clinically significant exacerbations vs baseline**: 0.7 vs 5.7 at months 24 Proportion of patients with no clinically significant exacerbations: Month 12: 56.2% Month 24: 63.0% **Reduction in severe exacerbations vs**	**Improvement in mean FEV_1 (mL): Change from baseline:** Week 16:205 Month 8: 215 Month 12: 273 Month 18: 200 Month 24: 137 **Improvement in PEF (L/min); Mean change from baseline:**	**Improvement in ACT scores vs baseline**: 17.3 vs 12.4 at months 24 Proportion of patients with controlled/partly controlled asthma vs baseline: Month 12: 92.1% Month 24: 87.7% **Mean change in mini-AQLQ vs baseline**:	**Reduction in mean number of asthma-related hospitalizations vs pre-treatment period:** 0.0 ± 0.2 vs 0.5 ± 1.2 at month 24 **Reduction in mean ± SD number of days stayed in hospital vs pre-treatment period:** 0.2 ± 2.2 vs 3.3 ± 9.8 at month 12	**Reduction in OCS use vs baseline**: Month 12: 50% vs 33.9% Month 24: 52.6% vs 33.9% **Reduction in mean total daily dose (in prednisolone equivalent mg) of OCS vs baseline**: 6.4 vs 11.6 at months 24

	baseline: 2.2 vs 0.1 at months 24 Proportion of patients with no severe exacerbations: Month 12: 89.9% Month 24: 95.1%	Week 16: 11.01 Month 8: 18.38 Month 12: 32.82 Month 18: 25.18 Month 24: 21.85	Month 12: 0.8 points Month 24: 0.94 points	**Patients free from asthma-related hospitalizations at months 12 and 24**: 100% and 98.8%	
Pelaia C et al., 2018[23] **Treatment duration**: 5 years	**Reduction in mean annualized exacerbation rates vs baseline:** 0.63 ± 0.99 vs 3.66 ± 2.01 after 5 years; $P < 0.0001$	**Increase in mean FEV_1 vs baseline:** 1929 ± 564.8 mL vs 1636 ± 628.4 mL after 5 years; $P < 0.05$	**Increase in ACT scores vs baseline:** 21.67 ± 2.38 vs 14.60 ± 2.97 at 5 years; $P < 0.0001$	-	**Mean reduction in corticosteroids use (mg/day) vs baseline:** 1.66 ± 3.61 vs 22.50 ± 5.17 at 5 years; $P < 0.0001$
Ke et al., 2018[24] **Treatment duration**: 1-2 years	**Proportion of patients with any asthma exacerbation**: Pre-index and Post-index periods: 66.6% and 44.2%; relative difference, 33.6%; $P < 0.001$)	-	-	-	**Overall reduction in OCS use**: 20.3% (83.3% pre-index to 66.4% post-index, $P < 0.001$)
Al-Ahmad M et al., 2018[25] **Treatment duration**: 4 years	**Reduction in severe asthma exacerbations vs pre-treatment**: 1.5% vs 47.7% patients after 4 years; $P < 0.001$	**Improvement in % FEV_1 predicted vs baseline**: 76.6% vs 55.6% at 4 years; $P = 0.003$	**Increase in ACT score vs baseline:** 23 ± 3 vs 15 ± 3 at 4 years; $P < 0.001$	**Decrease in HCRU:** No. of ER visits decreased by 90.8% after 4 years ($P < 0.001$) Patients with ≥1 hospitalizations due to severe asthma exacerbation decreased from 47.7% at baseline to by 1.5% after 4 years ($P < 0.001$)	**Reduction in OCS use:** **Proportion of patients who did not use OCS** Week 16: 55.4% 1 year: 78.0% 4 years: 83.1 **Proportion of patients with reduction in ICS/LABA use at different time points**: Week 16: 35.4% 1 year: 44.6%; $P < 0.014$ 4 years: 56.9%; $P < 0.001$
Odajima H et al., 2017[40] **Median exposure:** 116.6 weeks	-	**Baseline of the core study vs end of treatment period of the extension study:** **Mean FEV_1% predicted:** 90.3% vs 89.2% **Mean $FEF_{25\%-75\%}$ predicted:** 76.3% vs 75.1%	**Mean change in JPAC score from start of the extension study to end of the treatment period**: 3.0 ($P < 0.001$) **% of patients with well controlled asthma at start of extension study vs end of treatment period:** 23.7% vs 76.3% **Median QoL scores at baseline of the core**	**Rate per patient-year at baseline of the core study vs overall treatment period of the extension study:** **Hospitalizations**: 1.33 vs 0.16 ($P < 0.001$) **ER visits**: 0.68 vs 0.15 ($P = 0.002$)	ICS dose decreased by **13.2%** from baseline of the core study to end of treatment period

(continued)

Author; Treatment duration	Exacerbations	Lung function	Asthma control/QoL	Healthcare utilization	Corticosteroid use
			study vs end of treatment period: 39 vs 48 ($P < 0.001$)		
Sposato B et al., 2016[27] **Mean treatment duration**: 35.1 ± 21.7 months	After omalizumab treatment, 76.9%, 49.2% and 29% of younger, middle-aged, and elderly subjects were exacerbation-free ($P = 0.049$)	**Median FEV_1% predicted vs baseline:** Younger: 82.1% vs 70% Middle-aged: 82% vs 68% Elderly: 80% vs 67% $P < 0.001$ in all groups	**Median ACT scores before vs after treatment:** Younger: 24 vs 15 Middle-aged: 21 vs 14 Elderly: 20 vs 15 $P < 0.001$ in all groups	-	-
Tat TS et al., 2016[28] **Mean treatment duration**: 35.6 ± 17.8 months	**Mean number of exacerbations vs baseline:** 0.53 vs 4.12 ($P < 0.001$)	**Mean FEV_1% predicted vs baseline:** 67.01 vs 54.84 ($P = 0.11$)	Well controlled symptoms in 47.4% of patients and partly-controlled in 42.1% of patients **Mean ACT score vs baseline:** 21.8 vs 10.44 ($P < 0.001$)	**Mean number of hospitalizations vs baseline:** 0.23 vs 1.12 ($P = 0.004$)	-
Zazzali JL et al., 2015 (EXCELS study)[15] **Treatment duration**: 5 years	-	-	**% of patients with asthma control vs baseline:** **Omalizumab-naïve cohort:** Well-controlled asthma: 66.7% vs 48.6% Poorly controlled asthma: 14.8% vs 26.6% **Omalizumab cohort:** Well-controlled asthma: 61.2% vs 45.2% Poorly controlled asthma: 19.0% vs 31.6%	-	-
Deschildre A et al., 2015[41] **Treatment duration:** 2 years	**Mean rate of severe exacerbations per patient vs baseline:** 0.22 vs 4.4 ($P = 0.0001$)	**Mean FEV_1% predicted vs baseline:** 88% vs 89.9%	-	-	**Mean ICS daily dose (fluticasone equivalent) vs baseline:** 429 µg vs 703 µg
Novelli F et al., 2015[29] **Median treatment duration**: 32 months (range: 4–120 months)	Significant reduction in exacerbation rate during treatment ($P < 0.001$)	-	**% of patients with good, partial, and poor asthma control after treatment:** 25.2%, 47.1% and 24.5%	**Percentage of patients with HCRU vs baseline:** ER visits: 7.5% vs 57.2% Hospitalizations: 6.5% vs 45.7%	-

				Intensive care treatment: 0.3% vs 3.6%	
Lopez Tiro JJ et al., 2015[30] **Treatment period**: 3 years	-	**Mean FEV_1% predicted vs baseline:** 88.4% vs 66.3%	**Mean ACT score vs baseline:** 20.5 vs 12.4	**% of patients with HCRU vs baseline with:** **≥1 hospitalization:** 2.1% vs 38.2% ($P < 0.0001$) **≥1 ER visits:** 19.1% vs 95.7% ($P < 0.0001$) **≥1 intensive care admission:** 0% vs 4.2%	**Mean ICS dose vs baseline:** 765 µg/day (n = 42) vs 1750 µg/day (n = 47) **After 3 years:** 5 patients discontinued ICS
Pereira Barbosa M et al., 2015[18] (eXpeRience study -Portuguese subgroup) **Treatment duration:** 2 years	**% of patients free from clinically significant exacerbations vs baseline:** 60% vs 6.5%	**Increase from baseline in Mean FEV_1% predicted:** 9.6% **Mean PEF:** 45.4 L/min	**Increase from baseline in mean ACT score:** 7.0 **mean mini-AQLQ score:** 2.7 Increase in ACT score by ≥ 2 points and mini-AQLQ scores by ≥ 0.5 points is considered minimal clinically important difference	-	**Corticosteroids use vs baseline:** **Patients on OCS**: 8.2% vs 17.7% **Patients on ICS**: 88.9% vs 96.8% **Mean total daily OCS dose (prednisolone equivalent):** 13.1 mg vs 16.7 mg **Mean total daily ICS dose (beclomethasone equivalent):** 1351.1 µg vs 1497.5 µg
Caminati M et al., 2014[10] **Mean treatment duration**: 22.97 ± 16.55 months	**% of patients free from exacerbations vs baseline:** **Major exacerbations:** 88.6% vs 41.9%; $P < 0.001$ **Minor exacerbations:** 79.6% vs 16.3%; $P < 0.001$	Significant improvement in **FEV_1 and FVC** from baseline to the end of treatment period ($P < 0.001$)	-	-	-
Vieira T et al., 2014[17] **Treatment duration:** 2 years	Exacerbation rate decreased from baseline to 1st year by 70.1% ($P = 0.002$) and from 1st year to 2nd year by 75.9% ($P = 0.05$)	**Mean FEV_1% predicted vs baseline:** 65% vs 51.7% $P = 0.007$	**Mean ACT score vs baseline:** 18.9 vs 12.3 $P = 0.008$ **Mean ALQ score vs baseline:** 11.8 vs 15.3 $P = 0.024$	Unscheduled health care visits decreased from baseline to 1st year by 86.1% ($P = 0.002$) and from 1st year to 2nd year by 69% ($P = 0.12$)	**Corticosteroid use vs baseline:** **Mean daily ICS dose (budesonide equivalent):** 1111.1 µg vs 1653.3 µg $P = 0.028$ **Percentage of patients with daily OCS use:** 10% vs 53%
Braunstahl et al., 2013/2014[9,19,32] (eXpeRience)	**At 2 years vs baseline, % of patients free from clinically**	**Increase from baseline in mean FEV_1% predicted:**	**Mean change from baseline in ACT score:** +6.2	**Mean annualized no. of health-care visits/ patient vs baseline:**	**Corticosteroids use vs baseline:** **Maintenance OCS**

(continued)

Author; Treatment duration	Exacerbations	Lung function	Asthma control/QoL	Healthcare utilization	Corticosteroid use
Treatment duration: 2 years	**significant exacerbations:** 67.3% vs 6.8% **severe clinically significant exacerbations:** 89.9% vs 30.2% Mean annualized no. of clinically significant and severe clinically significant exacerbations vs baseline: 0.6 and 0.1 vs 4.9 and 2.2 respectively	8.7% **mean PEF:** 34.0 L/min	**ACQ score:** −0.80 **AQLQ score:** 0.75 **Mini-AQLQ:** 1.62 Increase in ACT score by ≥ 3 points, AQLQ/ mini-AQLQ scores by ≥ 0.5 points and decrease in ACQ score by ≥ 0.5 points is considered minimal clinically important difference	0.5 vs 6.2 **% of patients vs baseline with: No annualized asthma-related medical healthcare use:** 75.4% vs 12.3% **No hospitalization:** 93.8% vs 62.3% **No ER visit:** 91.9% vs 49.3% **No unscheduled doctor visit:** 78.4% vs 19.3%	**therapy:** 14.2% vs 28.6% **Mean total daily OCS dose (prednisolone equivalent):** 5.8 mg vs 15.5 mg **Mean total daily ICS dose (beclomethasone equivalent):** 1381 μg vs 1675 μg
Lafeuille MH et al., 2013[33] **Treatment duration:** 2 years	-	-	% of patients with uncontrolled asthma who were consistent with omalizumab at 24 months vs non-consistent at 12 months and never re-initiated omalizumab: 44% vs 55%	Mean number of asthma-related ER visits and hospitalizations in patients consistent with omalizumab at 24 months vs non-consistent at 12 months and never re-initiated omalizumab: 0.038 vs 0.126 and 0.106 vs 0.173, respectively	Mean number of OCS claims in patients consistent with omalizumab at 24 months vs non-consistent at 12 months and never re-initiated omalizumab: 1.648 vs 2.446
Chen H et al., 2012[34] (EXCELS Study) **Treatment duration:** 2 years	-	-	-	-	**% reduction in dose from baseline in new starters, established users, and omalizumab-naïve patients respectively, by: total ICS dose:** 57.7%, 44.7%, and 42.4% **ICS monotherapy dose:** 67.8%, 67.9%, and 60.1%
Ozgur ES et al., 2013[35] **Mean treatment duration**: 40.81 ± 8.2 months	Number of exacerbations decreased by 90% from baseline to 12 months and improvement sustained until end of treatment ($P < 0.05$)	**Increase in FEV_1% predicted from baseline:** Month 24: 21.5 Month 36: 23 End of visit: 20.4 (All $P < 0.05$)	**Increase in mean ACT score from baseline:** Month 24: 10.3 Month 36: 11.6 End of visit: 11 ($P = 0.001$, all) **Mean AQLQ total score vs baseline:** 5.34 vs 1.98 Increase in AQLQ	**Decrease in HCRU vs baseline:** No. of exacerbations by 90% No. of ER visits by 93.3% No. of hospitalizations by 71.3% Improvement was	**Number of patients with systemic steroid use vs baseline:** 0 vs 6

			scores by ≥ 0.5 points is considered minimal clinically important difference	maintained until end of treatment ($P < 0.05$)	
Vennera Mdel C et al., 2012[36] **Treatment duration:** 2 years	**Mean exacerbation rate vs baseline:** 1.04 vs 3.6 $P < 0.05$	**Mean FEV_1% predicted vs baseline:** 71.3% vs 63.8% $P < 0.05$	**Mean ACT score vs baseline:** 20.3 vs 14.3 $P < 0.05$	**Mean annualized hospitalizations rate vs baseline:** 0.2 vs 0.6 $P < 0.05$	**Corticosteroid use vs baseline:** **Mean ICS dose (budesonide equivalent):** 1147.4 µg vs 1676.6 µg $P < 0.05$ **No. of patients:** 19 vs 89 $P < 0.05$
Dal Negro RW et al., 2012[11] **Treatment duration**: 3 years	**Mean exacerbation rate vs baseline:** 0.94 vs 2.06; $P < 0.01$	**Mean FEV_1% predicted vs baseline:** 76% vs 57%; $P < 0.01$	**Mean ACT score vs baseline:** 19.91 vs 11.56; $P < 0.01$	**Mean annualized hospitalization rate vs baseline:** 0 vs 0.94; $P < 0.01$ **Mean annualized ER visit rate vs baseline:** 0.25 vs 0.69; $P < 0.05$	**No. of patients vs baseline with** OCS use: 5 vs 16 Parenteral corticosteroids: 0 vs 6
Menzella F et al., 2012[37] **Treatment duration**: 4 years	Rate of severe exacerbations and mild-to-moderate exacerbations decreased by 94.7% and 41.8%, respectively, from baseline	**Median FEV_1% predicted vs baseline:** 75.4% vs 58.6% ($P = 0.009$)	**Median AQLQ score vs baseline:** 5.6 vs 2.8 Increase in AQLQ scores by ≥ 0.5 points is considered minimal clinically important difference	-	-
Tzortzaki EG et al., 2012[38] **Treatment duration**: 4 years	**Mean number of exacerbations vs baseline:** 0.66 vs 2.27 ($P < 0.0001$)	**Mean FEV_1% predicted vs baseline:** 71.76% vs 60.13% ($P < 0.0001$) **Mean FVC% predicted vs baseline:** 82.29% vs 71% ($P = 0.0002$)	Mean ACT score vs baseline: 21.50 vs 17.28 ($P < 0.0001$) **% of patients with controlled asthma vs baseline:** 87% vs 39%	-	ICS dose vs baseline: 893.24 µg vs 1021.62 µg ($P = 0.014$)
Omalizumab treatment for >5 years					
Papaioannou AI et al., 2021[42] **Treatment duration**: 10.6 ± 1.2 years	**Reduction in exacerbations vs pretreatment:** 1.1 vs 4.1 per year after 1 year of treatment and remained low during all the years up to the 8th year of treatment ($P < 0.001$)	**Improvement in FEV_1% predicted vs baseline:** 73.6% vs 61.5% after 12 years of treatment ($P < 0.001$) **Improvement in FEV_1 (ml) vs baseline:** 239.8 vs. 160.8 after 12	**Improvement in asthma control expressed as ACT vs pre-treatment:** 22.1 vs 16.2 after 3 years and remained as high up to the 8th year of treatment ($P < 0.001$)	-	**Discontinuation of OCS use:** 21.1% patients discontinue at 6 months; 47.4% and 31.6% of patients were on OCS after 4 years and 8 years, respectively **Proportion of patients with ≥50% OCS**

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Author; Treatment duration	Exacerbations	Lung function	Asthma control/QoL	Healthcare utilization	Corticosteroid use
		years of treatment ($P < 0.001$)			**reduction:** Month 6: 36.8% 2 years: 68.4%
Mansur AH et al., 2017[43] **Mean treatment duration:** 60.7 ± 30.9 months	-	**Mean FEV_1% predicted vs baseline:** 75.7% vs 59.2% ($P = 0.0013$)	**Mean ACQ7 score vs baseline:** 2.3 vs 4.0 ($P < 0.0001$)	**Treatment vs baseline:** Number of hospitalizations: 40 vs 207 Mean annual per patient hospitalizations: 0.89 vs 4.8 ($P < 0.00001$) Number of emergency visits: 42 vs 80 Mean annual per patient emergency attendance: 3.0 vs 4.4 ($P = 0.17$) Mean annual per patient ICU admissions: 0.19 vs 0.48 ($P = 0.13$)	**Treatment vs baseline:** % of patients with maintenance OCS use: 44.2% vs 82% Mean daily maintenance OCS dose (prednisolone equivalent): 6.0 mg vs 25.8 mg ($P < 0.0001$) Mean annual number of steroid courses per patient: 3.1 vs 6.1 ($P < 0.001$)
Menzella F et al., 2017[14] **Treatment duration**: 9 years	**Mean annualized severe exacerbation rate vs baseline:** 0.63 vs 5	**Median FEV_1% predicted vs baseline:** 85.5% vs 58.5%	**Median AQLQ score vs baseline:** 5.9 vs 2.5 ($P < 0.001$)	-	**Number of patients with steroids vs baseline:** High-dose ICS: 1 vs 8 Medium-dose ICS: 2 vs 0 Low-dose ICS: 5 vs 0 OCS: 1 vs 7
Ledford et al., 2017[13] (XPORT study) **Treatment duration**: 6 years	Time-to-first exacerbation was longer in the omalizumab-continuation group versus the omalizumab-discontinuation group **(HR, 0.49 [95% CI: 0.28, 0.86])**	-	**Mean change in score from baseline to Week 52 in omalizumab-continuation group vs omalizumab-discontinuation group:** **ACT score**: −1.16 vs −2.88; $P = 0.0188$ **ACQ score**: 0.22 vs 0.63; $P = 0.0039$	-	-
Gemicioğlu B et al., 2016[45] **Treatment duration**: 5.5–7 years	**Mean exacerbation rates vs baseline:** 0.59 vs 2.57; $P < 0.001$	**Mean FEV_1 vs baseline** 1.50 L vs 1.34 L	**Mean ACT score vs baseline:** 22.8 vs 17.7; $P < 0.01$	-	**Baseline vs 5 years:** Drop in the inhaled steroid dosage by 65%

Storms W et al., 2012[46] **Treatment duration:** 6 years	-	**Mean FEV_1% predicted at 3 years vs baseline:** 69.8% vs 66.8%	Mean ACT score increased by **96.4%** at 6 years	-	-
Pace E et al., 2011[47] **Treatment duration:** 7 years	-	**Mean FEV_1% predicted vs baseline:** 71% vs 53% ($P < 0.05$) **Mean FEV_1/FVC % predicted vs baseline:** 65% vs 52% ($P < 0.05$)	**Mean symptom score vs baseline:** 0.3 vs 2.5 ($P < 0.02$)	-	**Corticosteroid use vs baseline:** No. of nebulized corticosteroids and bronchodilator cycles: 1 vs 9 No. of OCS cycles: 0.25 vs 3.5
Nieto García A et al., 2021[51] **Treatment duration:** 6 years	**Mean number of exacerbations vs baseline:** 1.1 vs 7.9 per year, after 1 year of treatment and remained low during all the years up to the 6th year of treatment ($P < 0.001$)	**Mean FEV_1% predicted vs baseline:** 92.8% vs 84.6% ($P < 0.001$)	**% of patients with controlled asthma vs baseline:** 89.3% vs 8.4%	**Mean annualized hospitalizations rate vs baseline:** 0.1 vs 1.0 ($P < 0.001$) **Mean annualized pediatric ICU admissions rate:** 0.0 vs 0.1 ($P < 0.001$)	**ICS dose vs baseline (budesonide equivalent):** 350.2 µg vs 867.3 µg ($P < 0.001$)

Table 2. An overview of clinical experience with omalizumab from studies included in this review. *ACQ, asthma control questionnaire; ACT, asthma control test; ALQ, asthma life quality; AQLQ, asthma quality of life questionnaire; ER, emergency room; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCRU, healthcare resource utilization; HR, hazards ratio; ICS, inhaled corticosteroids; JPAC, Japanese pediatric asthma control; LABA, long-acting β_2 agonist; OCS, oral corticosteroids; PEF, peak expiratory flow; QoL, quality of life*

cerebrovascular SAEs were substantially reduced.[55]

Omalizumab use for >5 years in adults with asthma

In the XPORT study, the rate (per 100 patient-years) of SAEs was similar in omalizumab-continuation and omalizumab-discontinuation groups (8.3 vs 9.1).[13] Asthma exacerbation was the most common SAE (5.9 vs 6.8 per 100 patient-years) reported in omalizumab continuation versus discontinuation groups. Among 176 patients, 2 patients reported malignant SAEs: (i) adenocarcinoma of the colon (omalizumab-continuation group) and (ii) a mixed Müllerian tumor (omalizumab-discontinuation group); one death due to an SAE of a mixed Müllerian tumor was reported (placebo group) 7 months after withdrawal from the study.[13] No patient from the omalizumab-continuation group reported an AE leading to study withdrawal.[13]

Omalizumab use in pediatric patients in asthma

In a study conducted in 38 children, ≥1 SAE was reported in 10 patients treated with omalizumab for ~2 years; 7 patients reported asthma exacerbations. Peri-tonsillar abscess reported in one patient was suspected of being drug-related.[40] In the ANCHORS study, 21 of 484 (4.3%) patients experienced ≥1 AE; headache was the most frequently reported AE (1.7%).[51]

DISCUSSION

Despite treatment with standard-of-care medications, patients with moderate-to-severe allergic asthma may remain uncontrolled.[36,57] In such patients, once asthma has been confirmed as the cause despite adherence to therapy, omalizumab treatment is recommended to achieve daily symptom control and decrease exacerbation rates.[58] Even though substantial evidence exists regarding the efficacy and effectiveness of omalizumab, understanding its effectiveness and safety in long-term/chronic use is of utmost importance.

In this review, we examined data from various studies to evaluate the long-term effectiveness of omalizumab in different patient populations. Overall, omalizumab demonstrated up to 9 years of continuous treatment effectiveness in reducing

Study acronym or Author	Disease condition	Follow-up period	Adverse events	Serious adverse events/deaths
Papaioannou AI et al., 2021[45]	Severe uncontrolled allergic asthma (n = 45)	10.6 ± 12 years	Local reactions and/or erythema at injection sites: 11 patients; upper respiratory tract infection: 8 patients; ankle swelling: 1 patient	No SAEs
Schreiber J et al., 2020[20]	Seasonal allergic asthma (n = 161)	3 years	79.5% of patients reported at least one AE; Infections and infestations: 28.5% Respiratory, thoracic, or mediastinal disorders: 24.8%	13.0% of patients reported SAEs (related to omalizumab)
Kirchnerová OR et al., 2019[25]	Uncontrolled persistent allergic (n = 114)	2 years	NA	11 SAEs reported from 112 patients
Al-Ahmad M et al., 2018[28]	Poorly controlled allergic asthma patients (n = 80)	4 years	12 patients reported mild adverse reactions: headache 5 (6.3%); tiredness/fatigue 2 (2.5%); hair loss 1 (1.3%); local reactions (mild pain and swelling at the site of injection) 4 (6.1%)	2 patients developed serious comorbidities: Malignancy and Liver cirrhosis
Menzella F et al., 2017[14]	Severe persistent allergic asthma (n = 8)	9 years	No events	NA
Di Bona et al., 2017[44]	Poorly controlled severe asthma (n = 91)	Mean treatment: 3.8 ± 2.6 years (range: 0.2–9 years)	Treatment-related AEs: n = 6 AEs causing discontinuation: Arthralgia/Myalgia (n = 3), urticaria, angioedema (n = 1), bleeding (n = 1), and relapsing herpes labialis (n = 1)	NA
Iribarren C et al., 2017[558] (EXCELS)	Moderate-to-severe asthma (n = 7836)	>5 years	NA	Rate (per 1000 person-years) of cardiovascular or cerebrovascular SAEs and arterial thromboembolic events in the omalizumab vs omalizumab-naïve group: 13.4 and 6.66 vs 8.1 and 4.64, respectively
Ledford D et al., 2017[13]	Moderate-to-severe persistent asthma (n = 176)	6 years	Rate of AEs/100 patient-year in omalizumab-continuation vs omalizumab-discontinuation groups: 413.2 vs 425.9 **Most common AEs**: asthma, sinusitis, upper respiratory tract infection, acute sinusitis	Rate of SAEs/100 patient-year in omalizumab-continuation vs omalizumab-discontinuation groups: 8.3 vs 9.1 **Most common SAE**: asthma **Malignancy SAEs:** adenocarcinoma of colon (omalizumab-continuation group) and Müllerian tumor (omalizumab-discontinuation group Deaths: 1 (omalizumab-discontinuation group)
Mansur AH et al., 2017[43]	Severe allergic asthma (n = 45)	Mean treatment: 60.7 ± 30.9 months	Generalized arthralgia and myalgia (n = 2), headache (n = 2), symptoms of fatigue and sleepiness (n = 1), isolated	Breast cancer (n = 1) and multiple basal cell carcinoma (n = 1)

			episodes of skin rashes (n = 2), mouth ulcers and boils (n = 1); shingles (n = 1), gout associated with severe weight loss (n = 1)	
Odajima H et al., 2017[40]	Uncontrolled severe asthma (n = 38)	Median exposure: 116.6 weeks (range: 46.9–151.1 weeks)	At least 1 AE: 100% patients (n = 38) Most common AEs: nasopharyngitis, influenza, upper respiratory tract infection, asthma exacerbations Drug-related: n = 11 (most common: injection-site swelling)	At least 1 SAE: 26.3% patients (n = 10) Most common SAE: asthma exacerbations Drug-related SAE: peri-tonsillar abscess (n = 1)
Tat TS et al., 2016[28]	Allergic asthma in elderly patients (n = 19)	Mean treatment duration: 35.6 ± 17.8 months	Local adverse reaction (n = 1), myalgia (n = 1; drug-related)	Deaths (n = 1 due to bronchial cancer)
Barbosa MP et al., 2015[18] (eXpeRience – Portugal subgroup)	Uncontrolled persistent allergic asthma (n = 62)	2 years	NA	2 SAEs: pulmonary embolism (suspected to be drug-related and led to study discontinuation) and tracheobronchitis
Lopez Tiro JJ et al., 2015[30]	Difficult-to-treat asthma (n = 49)	3 years	4 AEs: osteo-articular pain (n = 1), mild headache (n = 2) and vasovagal syncope (n = 1)	NA
Namazova-Baranova L et al., 2015[50]	Severe persistent uncontrolled asthma (n = 65)	1–72 months	Frequency of local AEs: 1/100–1/200 Local allergic reactions such as rashes: n = 2	NA
Long A et al., 2014[31] (EXCELS study)	Moderate-to-severe asthma (n = 7836)	>5 years	295 malignancy AEs in 220 patients in omalizumab group and 190 malignancy AEs in 126 patients in omalizumab-naïve group. Most common malignancy AEs: non-melanoma, breast cancer, prostate cancer, colorectal cancer, melanoma, lung cancer	At least 1 non-malignant SAE in 1263 patients (25.2%) in omalizumab group and 571 patients (20.2%) in the omalizumab-naïve group
Vieira T et al., 2014[17]	Uncontrolled severe persistent allergic asthma (n = 15)	2 years	**AEs:** Headache (n = 4), nausea (n = 4), myalgia (n = 2), exuberant injection site reaction (n = 2), repeated acute asthma episodes (n = 1), breast neoplasm (n = 1)	NA
Caminati M et al., 2014[10]	Allergic asthma (n = 59)	Mean omalizumab treatment: 22.97 ± 16.55 months	Large local reaction at injection site: 13.4% patients (n = 8)	NA
Braunstahl GJ et al., 2013[9] (eXpeRience)	Uncontrolled persistent allergic asthma (n = 943)	2 years	NA	**SAEs:** 150 SAEs **No of patients who reported SAEs:** 64 patients (6.9%) **Most common SAEs:** asthma, dyspnea, and pneumonia

(continued)

Study acronym or Author	Disease condition	Follow-up period	Adverse events	Serious adverse events/deaths
				Drug-related SAEs: 25 **Deaths**: 9 (not related to omalizumab) **Discontinued omalizumab due to SAEs:** 38
Ozgur ES et al., 2013[35]	Severe allergic asthma (n = 26)	Mean duration: 40.81 ± 8.2 months	1 patient reported moderate local injection-site reaction during 32nd month of treatment	NA
Menzella F et al., 2012[37]	Severe persistent allergic asthma (n = 11)	4 years	No events	NA
Tzortzaki EG et al., 2012[38]	Severe allergic asthma (n = 60)	4 years	At least 1 AE: 11.6% patients (n = 7) Most frequent: headache (n = 3), local injection-site reaction (n = 2), arthralgia (n = 2)	NA
Vennera M del C et al., 2012[36]	Uncontrolled severe asthma (n = 266)	2 years	AEs in 11.4% patients (n = 30) Most common AEs: arthralgia, cephalea	No severe adverse events
Dal Negro RW et al., 2012[11]	Difficult-to-treat allergic asthma (n = 16)	3 years	No events	NA
Domingo C et al., 2011[56]	OCS-dependent asthma (n = 31)	Mean follow-up 17.2 ± 8.5 months	Flu-like syndrome: n = 3	NA
Pace E et al., 2011[47]	Uncontrolled persistent severe asthma (n = 7)	7 years	NA	NA
Nieto García A et al., 2021[51]	Severe persistent allergic asthma (n = 484)	Up to 6 years	At least 1 AE: 4.3% patients (n = 21). Most frequent AEs: headache (n = 8); malaise, fatigue, asthenia, low-grade fever, myalgia, and/or flu-like syndrome (n = 5), injection-site pain/ reaction (n = 4), dizziness/loss of consciousness/vasovagal syncope (n = 4), transient urticaria (n = 2)	NA

Table 3. Clinical experience with omalizumab in asthma and other disease conditions – Summary of safety data. *AE, adverse event; OCS, oral corticosteroids; SAE, serious adverse event.NA: information not available*

SAEs	Omalizumab treated	Non-omalizumab-treated
Any cardiovascular/cerebrovascular event	13.4, 95% CI: 11.6–15.4	8.1, 95% CI: 6.5–10.1
Arterial thromboembolic	6.66, 95% CI: 5.43–8.10	4.64, 95% CI: 3.40–6.19
Transient ischemic attack	0.7, 95% CI: 0.4–1.3	0.1, 95% CI: 0.0–0.6
Myocardial infarction	2.1, 95% CI: 1.4–3.0	0.8, 95% CI: 0.3–1.6
Pulmonary hypertension	0.5, 95% CI: 0.2–1.0	0.0, 95% CI: 0.0–0.4
Pulmonary embolism/venous thrombosis	3.2, 95% CI: 2.4–4.3	1.5, 95% CI: 0.8–2.5
Unstable angina	2.2, 95% CI: 1.5–3.0	1.4, 95% CI: 0.8–2.4

Table 4. Rate (per 1000 person-years) of SAEs in omalizumab and non-omalizumab users.[26] *SAEs, severe adverse events*

the rate of (severe) exacerbations, improving lung function, asthma control, and QoL, and decreasing HCRU and use of corticosteroids (oral/inhaled) in patients with moderate-to-severe allergic asthma.[10,52] Improvement in lung function was independent of baseline airflow limitation or gender[10,27] These improvements in lung function may have been driven by prevention of exacerbations,[10,22,23,28,35,37] as previous studies have shown a strong relationship between exacerbation rates and decline in lung function.[59]

In the pediatric population (omalizumab treatment up to 7.5 years), an important and sustained improvement in asthma control has been reported, with a trend to zero exacerbations, almost no hospitalizations and no more ICU admissions, and a stabilization of lung function close to the normal range, associated with a large decrease in daily ICS use and use/need of OCS.[41,51] Lung function (FEV_1) in children was well maintained, in contrast to the increasing bronchial obstruction usually observed in severe asthma.[60] This effect may be a consequence of the decrease in severe exacerbations.

Furthermore, reductions in exacerbations with fewer or no episodes of severe exacerbations requiring hospitalization can reduce direct and indirect asthma-related healthcare costs. Costa et al demonstrated that omalizumab use reduces key drivers of asthma-related costs, including acute exacerbation episodes, ER visits, and the need for in-patient care, all of which account for the cost-effectiveness of this biologic treatment.[61]

ICS are suggested as the first-line therapy in the management of persistent asthma and are generally considered safe in both adults and children at recommended doses; however, long-term use of high-dose ICS or SCS may result in safety concerns. Our review demonstrates that long-term use of omalizumab can reduce the use/need for these treatments.[9,19] This, in turn, reduces comorbid diseases such as osteoporosis, hypertension, and obesity that are related to the use of ICS/SCS, which may further worsen asthma symptoms.[62]

The long-term safety profile was similar to that observed in short-term studies. Overall, omalizumab shows a favorable safety and tolerability profile, and majority of the studies reported no safety concerns even with 9 years of follow-up. However, a few cases of long-term omalizumab in adults reported higher rates of cardiovascular/cerebrovascular SAEs than in non-omalizumab users.[26] It should be noted that these episodes are not new and are consistent with the known and well-managed safety profile of omalizumab based on extensive clinical trial data and post-marketing experience.[4] Furthermore, these were open-label, single-arm studies and could not estimate the AEs due to placebo. In addition to this, omalizumab use during pregnancy in the EXPECT registry (Xolair Pregnancy Registry), did not appear to increase the prevalence of major congenital defects, and the risk of preterm birth or small for gestational age infants than those reported in the general population with asthma. It is important to weigh the safety profile of omalizumab treatment during pregnancy against the risks of uncontrolled asthma.[63]

Our findings that demonstrate a sustained clinical benefit of omalizumab over long treatment periods suggest a potential disease-modifying effect of omalizumab,[64–66] based on the European Medicine Agency (EMA) definition, where a drug is considered disease modifying if the progression of the disease is reduced or slowed and these results are linked to a significant effect on adequately qualified and validated biomarkers.[67]

However, asthma disease modification does not have one definition or one facet. A disease modification effect can be controlling or reversing the tissue remodeling (as shown in various studies),[68–73] clinical remission (no symptoms on treatment or after enough treatment), functional remission (pulmonary function including bronchial responsiveness evaluation normalized), therapeutic remission (no symptoms and standard-of-care medications, with or without omalizumab) or even cure of the disease after an accepted treatment duration.

With considerable and reassuring data on the long-term effectiveness and safety of omalizumab in patients with moderate-to-severe allergic asthma, continued or chronic long-term use of omalizumab seems to stabilize and control the disease. Patients may go through clinical remission on treatment (without exacerbations or with controlled asthma). This has been observed in patients who are resistant to high-dose treatment strategy, which highlights the mechanism of action by different pathways. Furthermore, in children, improvement of antiviral defenses has been suggested.[74] This review improves the rationale for the step-up personalized strategy with biologics by showing the long-term benefit of omalizumab in severe uncontrolled allergic asthma.

In conclusion, omalizumab seems to provide an anti-remodeling effect, which needs to be proven in additional large studies. The long term-use of omalizumab in adults and children (aged >6 years) is effective in controlling the disease, reducing exacerbations, OCS and ICS use, HCRU, and inducing clinical remission on treatment and is well-tolerated.

Abbreviations

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AE, adverse event; AQLQ, Asthma Quality of Life Questionnaire; EMA, European Medicine Agency; ER, emergency room; EROCS, exacerbations requiring oral corticosteroids; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GETE, global evaluation of treatment effectiveness; GINA, Global Initiative for Asthma; HCRU, healthcare resource utilization; ICS, inhaled corticosteroids; ICU, intensive care unit; IgE, immunoglobulin E; JPAC, Japanese pediatric asthma control; LABA, long-acting $beta_2$-agonists; OCS, oral corticosteroids; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; PEF, peak expiratory flow; QoL, quality of life; SAE, serious adverse event; SCS, systemic corticosteroids; USA, United States of America.

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Declaration of competing interest

NAH reports receiving consulting fees from GSK, AstraZeneca, Sanofi, Regeneron, Teva, Amgen, Roche/Genentech, Boehringer Ingelheim, and Novartis; and his institution has received research support from Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca, Sanofi, Teva, Genentech and Novartis. RN has received lecture fees from AstraZeneca and Novartis. P.C has undertaken consultancy services Boston Scientific, Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, ALK, Novartis, Teva, Chiesi, Saonfi-Aventis, and SNCF, served on advisory

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100695.

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