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 β2-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-
acting muscarinic antagonists. 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.

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. 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. Omalizumab is now widely used for various indications and has recently reached >1.75 million patient-years of exposure. 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 (FEV₁), asthma control measured by Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ), QoL assessed using different questionnaires including Asthma Quality of Life Questionnaire (AQOL), and Asthma Life Questionnaire (ALQ). In some studies, early clinical response to omalizumab treatment was evaluated using the validated “global evaluation of treatment effectiveness (GETE)” tool. HCRU in terms of steroidal use and number of hospitalizations, medical visits and ER visits was also assessed.

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. The proportion of patients experiencing exacerbations decreased over time, and notably, fewer or no episodes of exacerbations requiring ER visits or hospitalizations were observed. Furthermore, these improvements were observed and maintained over a long time period (>5 years).
| Publication                        | Study name                                      | Treatment duration or follow-up period | Number of patients enrolled (Male: Female) | Mean Age (mean ± SD), years |
|-----------------------------------|------------------------------------------------|----------------------------------------|-------------------------------------------|----------------------------|
| Schreiber J et al., 2020          | NA                                             | 3 years                                | 153 (M: 60; F: 93)                        | 49 ± 12.16                 |
| Cavaliere et al., 2020            | NA                                             | 36 Months                              | 10 (M: 06; F: 04)                         | 47 (26-70)                 |
| Kirchnerová OR et al., 2019       | eXpeRience registry (Czech Republic subgroup)   | 2 years                                | 112 (M: 44; F: 68)                        | 44.0 ± 13.0                |
| Pelaia C et al., 2018             | NA                                             | 5 years                                | 15 (M: 05; F: 10)                         | 46.60 ± 13.21             |
| Ke et al., 2018                   | NA                                             | 12 and 24 Months                       | 1564 (M: 598; F: 966)                     | 44.9 ± 15.67               |
| Al-Ahmad M et al., 2018           | NA                                             | 4 years                                | 65 (M: 22; F: 43)                         | 46.69 ± 11.55              |
| Iribarren C et al., 2017          | EXCELS study (data on cardiovascular and cerebrovascular events) | 5 years                                | 5007 (omalizumab cohort)                 |                           |
|                                   |                                                |                                        | 2829 (non-omalizumab cohort)              |                           |
|                                   |                                                |                                        | (M: 7857; F: 5079)                       |                           |
| Sposato B et al., 2017            | 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) |
|                                   |                                                |                                        |                                            | 12-24 M: 51 (40-61) |
|                                   |                                                |                                        |                                            | 24-60 M: 54 (46-62) |
|                                   |                                                |                                        |                                            | >60 M: 53 (44-63) |
| Sposato B et al., 2016            | NA                                             | 35.1 ± 21.7 months                     | 105 (M: 33; F: 72)                        | 29 ± 6 (18-39), 54 ± 7 (40-64), 69 ± 4 (≥65) |
| Tat TS et al., 2016               | NA                                             | 35.6 ± 17.8 months                     | 19 (M: 05; F: 14)                         | 69.3 ± 5.8                |
| Zazzali JL et al., 2015           | EXCELS study                                   | 5 years                                | 4930 (omalizumab cohort)                 |                           |
|                                   |                                                |                                        | 2779 (non-omalizumab cohort)              |                           |
|                                   |                                                |                                        | (M: 2714; F: 4993)                       |                           |
| Novelli F et al., 2015            | NA                                             | 32 (4-120) months                     | 306 (M: 36.9%; F: 63.1%)                 | 52.0 ± 13.7               |
| Lopez Tiro JJ et al., 2015        | NA                                             | 3 years                                | 52 (M: 10; F: 42)                         | 43.5 (15-67)               |
| Pereira Barbosa M et al., 2015    | eXpeRience study (Portuguese subgroup)          | 2 years                                | 62 (M: 19; F: 43)                         | 49.2 ± 15.0               |
| Caminati M et al., 2014           | NA                                             | 22.97 ± 16.55 months                   | 59 (M: 29; F: 30)                         | 45.59 ± 11.51             |
| Vieira T et al., 2014             | 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 | eXpeRience study (data on HCRU) | 2 years | 925 (M: 325; F: 600) | 45 ± 15.0 |
| Long A et al., 2014 | EXCELS study (safety data) | 5 years | 7857 (M: 2778; F: 5079) Omalizumab: 44 ± 17 Non-omalizumab: 46 ± 17 |
| Braunstahl GJ et al., 2013 | eXpeRience study | 2 years | 925 (M: 325; F: 600) | 45 ± 15.0 |
| Braunstahl GJ et al., 2013 | eXpeRience study (data on corticosteroid use) | 2 years | 263 (M: 94; F: 169) | 46 ± 13.13 |
| Lafeuille MH et al., 2013 | NA | 2 years | 3044 (M: 1146; F: 1898) | 48.5 ± 15.7 |
| Chen H et al., 2013 | 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 | NA | 40.81 ± 8.2 months | 26 (M: 05; F: 21) | 47.6 ± 13.9 |
| Vennera Mdel C et al., 2012 | NA | 2 years | 266 (M: 83; F: 183) | 51.0 ± 13.7 |
| Dal Negro RW et al., 2012 | NA | 3 years | 16 (M: 08; F: 08) | 45.4 (31-64) |
| Menzella F et al., 2012 | NA | 4 years | 11 (M: 07; F: 04) | 47.5 ± 9.64 |
| Tzortzaki EG et al., 2012 | NA | 4 years | 60 (M: 24; F: 36) | 54 ± 14 |

**Studies with pediatric patients (≥6 years to <18 years)**

| Publication | Study name | Treatment duration or follow-up period | Number of patients enrolled (Male: Female) | Mean Age (mean ± SD), years |
|-------------|------------|----------------------------------------|-------------------------------------------|-----------------------------|
| Sztafińska A et al., 2017 | NA | ~2 years | 19 (M: 15; F: 4) | 11.36 (6-15) |
| Odajima H et al., 2017 | NA | 116.6 (46.9-151.1) weeks | 38 (M: 23; F: 15) | 11.5 ± 2.52 |
| Deschildre A et al., 2015 | NA | 2 years | 104 (M: 60; F: 44) | 11.9 (11.3-12.5) |

**Omalizumab treatment for >5 years**

| Publication | Study name | Treatment duration or follow-up period | Number of patients enrolled (Male: Female) | Mean Age (mean ± SD), years |
|-------------|------------|----------------------------------------|-------------------------------------------|-----------------------------|
| Papaioannou AI et al., 2021 | NA | 10.6 ± 1.2 years | 45 (M: 15; F: 30) | 55.3 ± 12.2 |
| Mansur AH et al., 2017 | NA | 60.7 ± 30.9 months | 45 (M: 08; F: 37) | 44.9 (19-69) |
| Menzella F et al., 2017 | NA | 9 years | 8 (M: 05; F: 03) | 43 ± 9 |
| Di Bona et al., 2017 | NA | 3.8 ± 2.6 years | 91 (M: 24; F: 67) | 49.9 ± 14.9 |
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. In the XPORT study (Xolair Persistency Of Response After Long-Term Therapy), patients who continued omalizumab treatment 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]).

For treatment duration of 2–5 years, studies consistently showed sustained reduction in rate of exacerbations compared to baseline (rates range from 54.4% to 95% in omalizumab-treated patients, indicating sustained effectiveness [12,35,37,38]).

| Study | Duration | Follow-up | Patients | Mean/SD | Exacerbation Rate % |
|-------|----------|-----------|----------|---------|---------------------|
| Ledford D et al., 2017<sup>13</sup> | 6 years | 5.5–7 years | 176 (M: 53; F: 123) | 51.5 ± 12.5 |
| Gemícioğlu B et al., 2016<sup>45</sup> | NA | 5.5–7 years | 17 (M: 04; F: 13) | 48.3 ± 16.4 |
| Storms W et al., 2012<sup>46</sup> | NA | 6 years | 167 (M: 54; F: 113) | 52.0 (14-82)<sup>†</sup> |
| Pace E et al., 2011<sup>47</sup> | NA | 7 years | 7 (M: 04; F: 03) | 50 ± 8 |

**Studies with pediatric patients (≥ 6 years to <18 years)**

| Study | Duration | Follow-up | Patients | Mean/SD | Exacerbation Rate % |
|-------|----------|-----------|----------|---------|---------------------|
| Deschildre et al., 2019<sup>48</sup> | NA | 46.2 (31.5–90.3) months | 60 (M: 30; F: 30) | 11.25 (6-16.2)<sup>†</sup> |
| Folqué MM et al., 2019<sup>49</sup> | NA | Up to 6 years | 48 (M: 27; F: 21) | 11.5 (5-17)<sup>†</sup> |
| Namazova-Baranova L et al., 2015<sup>50</sup> | NA | 1-72 months | 101 | 13.4 (6-17)<sup>†</sup> |
| Nieto García A et al., 2021<sup>51</sup> | ANCHORS | Up to 6 years | 484 | 11.1 (1.9-17.9)<sup>†</sup> |

Table 1. (Continued) Publications that evaluated omalizumab use in asthma patients receiving the drug for >2 years. HCRU, healthcare resource utilization; NA, not applicable. *Treatment duration represented as median (range). †Treatment duration represented as mean ± SD. cAge represented as mean (range).
**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. 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. 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. 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, 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). Omalizumab treatment for ~2 years improved mean ACT scores by 6.0–7.0 points. 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). 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](http://doi.org/10.1016/j.waojou.2022.100695)
compared with 40-64 years (by ~7 points) and ≥65 years (by ~5 points). 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. 

Omalizumab treatment for 2 years increased the proportion of patients with controlled or partly controlled asthma by ~63% from baseline. 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. 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. 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).

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 and from 72.7% at 8 months to 81.8% after 4 years of treatment. 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.

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 and a 1.7-point decrease in mean ACQ7 score over 5 years, a 96.4% increase in ACT scores during a 6-year treatment, and a 2.2-point decrease in the mean symptom score after 7 years of omalizumab treatment (Fig. 2). 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. The XPORT study showed benefits of continuation of omalizumab treatment after long-term treatment results, supported by improved symptom control and reduced exacerbation risk.

Omalizumab use in pediatric patients with asthma

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

Quality of life

Omalizumab use for 2–5 years in adults with asthma

Omalizumab treatment for \(\sim 2\) years increased mean AQLQ score by 0.94 points and mean QoL score by 9 points. 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 and by 2.8 points after 4 years of treatment; a decrease in mean St. George’s Respiratory Questionnaire score of 21.4 points was observed after 3 years of treatment.

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.

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.

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. In addition, mean daily dose of prednisolone-equivalent OCS decreased from baseline to 2 years. Additionally, patients consistent (patient with \(\geq 1\) dispensing of omalizumab, \(\geq 6\) months of continuous eligibility before their first omalizumab dispensing [washout period], and had \(\geq 1\) 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. A similar profile was observed when omalizumab was continued for 3–4 years.

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. Approximately half of the patients receiving maintenance OCS at baseline discontinued OCS therapy during omalizumab treatment. 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. 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. 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).
**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 FEV₁ relative to baseline and by 17% of predicted. A further increase in FEV₁% predicted by 18% was observed after 7 years, and ~12% after 12 years of omalizumab treatment. A 13% improvement in mean FEV₁/FVC % predicted was observed from baseline to 7 years.

Omalizumab use in pediatric patients with asthma

Sztafińska et al reported no significant improvement in FEV₁ in children and adolescents with severe persistent allergic asthma after 2 years of omalizumab treatment. In children aged 6–18 years, compared with baseline (FEV₁ 88% [% predicted value] [95% CI: 83.8; 92.2]), mean FEV₁% predicted increased by 4.9% during 1 year of follow-up with no significant modification during the second year. Indeed, FEV₁ was maintained at a high level, 89.9% predicted (95% CI: 86.7%–93.0%) at the end of 2-year treatment. The increase, although small, did provide a positive outcome, close to the expected value in controlled children, as a decline in lung function has been described in severe asthmatic children followed up for many years. These results were confirmed by Deschildre et al showing an pre-β₂ agonist FEV₁ (% predictive value) of 97 (50–119) after 31.5–90.3 months of omalizumab treatment. In the ANCHORS study, FEV₁% 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%).

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%). 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). Other studies also reported improvement in HCRU in terms of decreased hospitalizations and ER/intensive care unit visits with omalizumab for 2–4 years. 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. In elderly asthmatics, the rate of hospitalization during omalizumab treatment decreased in ~90% of patients.

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.

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. 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. 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. 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. 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. 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. In a 2-year post-marketing observational study, 11.4% of patients experienced ≥1 AE; most commonly reported AEs were arthralgia and cephalgia. Furthermore, only 7 of 266 enrolled patients discontinued treatment because of AEs. 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. 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. 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.

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

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.

**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.

Although individual cases of bronchial cancer and malignant breast neoplasm 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). The rate (per 1000 person-years) of cardiovascular/cerebrovascular SAEs was higher in omalizumab versus non-omalizumab-treated patients (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.

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<sup>20</sup> **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<sup>21</sup> **Treatment duration:** 36 Months | - | Improvement in % FEV<sub>1</sub>, 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<sup>22</sup> **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<sub>1</sub> (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 |
| Study | Treatment duration | Proportion of patients with no severe exacerbations: | Increase in mean FEV₁ vs baseline: | Increase in ACT scores vs baseline: | Mean reduction in corticosteroids use (mg/day) vs baseline: | Overall reduction in OCS use: | Reduction in OCS use: Proportion of patients who did not use OCS | Baseline of the core study vs end of treatment period of the extension study: | Rate per patient-year at baseline of the core study vs overall treatment period of the extension study: |
|---|---|---|---|---|---|---|---|---|---|
| Pelaia C et al., 2018 | 5 years | Month 12: 89.9% Month 24: 95.1% | 1929 ± 564.8 mL vs 1636 ± 628.4 mL after 5 years; P < 0.05 | 21.67 ± 2.38 vs 14.60 ± 2.97 at 5 years; P < 0.0001 | 1.26 ± 3.61 vs 22.50 ± 5.17 at 5 years; P < 0.0001 | 20.3% (83.3% pre-index to 66.4% post-index, P < 0.001) | Proportion of patients who did not use OCS 1 year: 78.0% 4 years: 83.1 | Mean change in JPAC score from start of the extension study to end of the treatment period: 23.7% vs 76.3% | Mean change in JPAC score from start of the extension study to end of the treatment period: 23.7% vs 76.3% |
| Ke et al., 2018 | 1-2 years | Pre-index and Post-index periods: 66.6% and 44.2%; relative difference, 33.6%; P < 0.001 | – | – | – | – | 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 | Baseline of the core study vs end of treatment period of the extension study: | | | |
| Al-Ahmad M et al., 2018 | 4 years | 1.5% vs 47.7% patients after 4 years; P < 0.001 | 76.6% vs 55.6% at 4 years; P = 0.003 | 23 ± 3 vs 15 ± 3 at 4 years; P < 0.001 | 90.8% after 4 years (P < 0.001) | 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 | 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 |逆袭 13.2% from baseline of the core study to end of treatment period |
| Odajima H et al., 2017 | Median exposure: 116.6 weeks | – | – | – | – | – | Reduction in corticosteroids use: 20.3% (83.3% pre-index to 66.4% post-index, P < 0.001) | Mean change in JPAC score from start of the extension study to end of the treatment period: 3.0 (P < 0.001) | Mean change in JPAC score from start of the extension study to end of the treatment period: 3.0 (P < 0.001) |

(continued)
| Author; Treatment duration | Exacerbations | Lung function | Asthma control/QoL | Healthcare utilization | Corticosteroid use |
|----------------------------|---------------|---------------|--------------------|-----------------------|-------------------|
| Sposato B et al., 2016<sup>27</sup> **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 (<i>P = 0.049</i>) | **Median FEV<sub>1</sub>% predicted vs baseline**: Younger: 82.1% vs 70% Middle-aged: 82% vs 68% Elderly: 80% vs 67% <i>P < 0.001</i> in all groups | **Median ACT scores before vs after treatment**: Younger: 24 vs 15 Middle-aged: 21 vs 14 Elderly: 20 vs 15 <i>P < 0.001</i> in all groups | - | - |
| Tat TS et al., 2016<sup>28</sup> **Mean treatment duration**: 35.6 ± 17.8 months | **Mean number of exacerbations vs baseline**: 0.53 vs 4.12 (<i>P < 0.001</i>) | **Mean FEV<sub>1</sub>% predicted vs baseline**: 67.01 vs 54.84 (<i>P = 0.11</i>) | Well controlled symptoms in 47.4% of patients and partly-controlled in 42.1% of patients | **Mean number of hospitalizations vs baseline**: 0.23 vs 1.12 (<i>P = 0.004</i>) | - |
| Zazzali JL et al., 2015 (EXCELS study)<sup>15</sup> **Treatment duration**: 5 years | - | - | - | - | - |
| Deschildre A et al., 2015<sup>41</sup> **Treatment duration**: 2 years | **Mean rate of severe exacerbations per patient vs baseline**: 0.22 vs 4.4 (<i>P = 0.0001</i>) | **Mean FEV<sub>1</sub>% 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<sup>29</sup> **Median treatment duration**: 32 months (range: 4–120 months) | Significant reduction in exacerbation rate during treatment (<i>P < 0.001</i>) | - | **% 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% | - |
| Study                                    | Treatment period | Intensive care treatment: | Mean FEV₁% predicted vs baseline: | Mean ACT score vs baseline: | % of patients with HCRU vs baseline with: | Mean ICS dose vs baseline: |
|------------------------------------------|------------------|---------------------------|----------------------------------|-----------------------------|------------------------------------------|---------------------------|
| Lopez Tiro JJ et al., 2015              | 3 years          | 0.3% vs 3.6%              | 88.4% vs 66.3%                   | 20.5 vs 12.4                | ≥1 hospitalization: 2.1% vs 38.2% (P < 0.0001) | 765 µg/day (n = 42) vs 1750 µg/day (n = 47) |
| Pereira Barbosa M et al., 2015          | 2 years          | 2.1% vs 38.2% (P < 0.0001) | 19.1% vs 95.7% (P < 0.0001)      | 0% vs 4.2%                  | After 3 years: 5 patients discontinued ICS |
| Caminati M et al., 2014                  | 22.97 ± 16.55 months |                                 |                                  |                             |                                         |                           |
| Vieira T et al., 2014                    | 2 years          | 60% vs 6.5%               |                                  |                             |                                         |                           |
| Braunstahl et al., 2013/2014             | 2 years          | 70.1% vs 51.7% (P = 0.002) |                                  |                             |                                         |                           |
| 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% | 8.7% mean PEF: 34.0 L/min | ACQ score: −0.80 | 0.5 vs 6.2 | therapy: 14.2% vs 28.6% |
|                            |               |               | AQLQ score: 0.75 | % of patients vs baseline with: | Mean total daily OCS dose (prednisolone equivalent): 5.8 mg vs 15.5 mg |
|                            |               |               | Mini-AQLQ: 1.62 | No annualized asthma-related medical healthcare use: | Mean total daily ICS dose (beclomethasone equivalent): 1381 µg vs 1675 µg |
|                            |               |               | 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 | No hospitalization: 93.8% vs 62.3% | No ER visit: 91.9% vs 49.3% |
|                            |               |               |                    | No unscheduled doctor visit: 78.4% vs 19.3% | 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 |
| Lafeuille MH et al., 2013 | – | – | % 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 | % 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% |
| Treatment duration: 2 years | – | – | – | – | ICS monotherapy dose: 67.8%, 67.9%, and 60.1% |
| Chen H et al., 2012 | – | – | – | – | - |
| (EXCELS Study) Treatment duration: 2 years | – | – | – | – | - |
| Ozgur ES et al., 2013 | 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 FEV₁% 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) | 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 | Number of patients with systemic steroid use vs baseline: 0 vs 6 | 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 |
| Study                          | Treatment duration | Changes in Asthma Outcomes                                                                 | Discontinuation of OCS use: |
|-------------------------------|--------------------|------------------------------------------------------------------------------------------|----------------------------|
| Vennera Mdel C et al., 2012   | 2 years            | **Mean exacerbation rate vs baseline:** 1.04 vs 3.6  
**Mean FEV1% predicted vs baseline:** 71.3% vs 63.8%  
**Mean ACT score vs baseline:** 20.3 vs 14.3  
**Mean annualized hospitalizations rate vs baseline:** 0.2 vs 0.6  
**Mean annualized hospitalization rate vs baseline:** 0.2 vs 0.6  
**Corticosteroid use vs baseline:**  
**ICS dose (budesonide equivalent):** 1147.4 µg vs 1676.6 µg  
**No. of patients vs baseline with OCS use:** 5 vs 16  
Parenteral corticosteroids: 0 vs 6 | - |
| Dal Negro RW et al., 2012     | 3 years            | **Mean exacerbation rate vs baseline:** 0.94 vs 2.06;  
**Mean FEV1% predicted vs baseline:** 76% vs 57%;  
**Mean ACT score vs baseline:** 19.91 vs 11.56;  
**Mean annualized hospitalization rate vs baseline:** 0 vs 0.94;  
**Mean annualized ER visit rate vs baseline:** 0.25 vs 0.69;  
**No. of patients vs baseline with OCS use:** 5 vs 16  
Parenteral corticosteroids: 0 vs 6 | - |
| Menzella F et al., 2012       | 4 years            | **Rate of severe exacerbations and mild-to-moderate exacerbations decreased by 94.7% and 41.8%, respectively, from baseline**  
**Median FEV1% predicted vs baseline:** 75.4% vs 58.6%  
**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     | 4 years            | **Mean number of exacerbations vs baseline:** 0.66 vs 2.27  
(P < 0.0001)  
**Mean FEV1% 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) |
| Papaioannou AI et al., 2021   | 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 FEV1% predicted vs baseline:** 73.6% vs 61.5% after 12 years of treatment (P < 0.001)  
**Improvement in FEV1 (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 use: | (continued) |
| Author; Treatment duration | Exacerbations | Lung function | Asthma control/QoL | Healthcare utilization | Corticosteroid use |
|---------------------------|---------------|---------------|-------------------|-----------------------|-------------------|
| Mansur AH et al., 2017<sup>43</sup> | - | **Mean FEV₁% 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) | % 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<sup>14</sup> | **Mean annualized severe exacerbation rate vs baseline:** 0.63 vs 5 | **Median FEV₁% 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<sup>13</sup> (XPORT study) | 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<sup>16</sup> | **Mean exacerbation rates vs baseline:** 0.59 vs 2.57; P < 0.001 | **Mean FEV₁ 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% |
cerebrovascular SAEs were substantially reduced. 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). 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 malignancy 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 (omalizumab-discontinuation group) 7 months after withdrawal from the study. No patient from the omalizumab-continuation group reported an AE leading to study withdrawal. In the ANCHORS study, 21 of 484 (4.3%) patients experienced ≥1 AE; headache was the most frequently reported AE (1.7%).

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; FEV1, 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 β2 agonist; OCS, oral corticosteroids; PEF, peak expiratory flow; QoL, quality of life

In the study conducted in 38 children, 1 SAE was reported in 10 patients treated with omalizumab for ~2 years; 7 patients treated with omalizumab for 6 years and remained low during all the 6th year of treatment (P < 0.001) Mean symptom score vs baseline: 0.3 vs 2.5 (P < 0.02)

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). 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 malignancy 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 (omalizumab-discontinuation group) 7 months after withdrawal from the study. No patient from the omalizumab-continuation group reported an AE leading to study withdrawal. In the ANCHORS study, 21 of 484 (4.3%) patients experienced ≥1 AE; headache was the most frequently reported AE (1.7%).
| Study acronym or Author                  | Disease condition                          | Follow-up period | Adverse events                                                                                   | Serious adverse events/deaths                      |
|-----------------------------------------|--------------------------------------------|------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Papaioannou AI et al., 2021**           | 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**              | 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**           | Uncontrolled persistent allergic (n = 114)  | 2 years          | NA                                                                                              | 11 SAEs reported from 112 patients                |
| Al-Ahmad M et al., 2018**               | 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*                | Severe persistent allergic asthma (n = 8)   | 9 years          | No events                                                                                       | NA                                                |
| Di Bona et al., 2017**                  | 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**              | 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**                | 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 | 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**                | 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) |
| Study | Condition (n) | Treatment Duration | Median Exposure | AEs | SAEs |
|-------|--------------|--------------------|----------------|-----|------|
| Odajima H et al., 2017<sup>30</sup> | Uncontrolled severe asthma (n = 38) | 116.6 weeks (range: 46.9-151.1 weeks) | At least 1 AE: 100% patients (n = 38) | At least 1 SAE: 26.3% patients (n = 10) | Uncontrolled severe asthma (n = 38) |
| Tat TS et al., 2016<sup>28</sup> | 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) | Local adverse reaction (n = 1), myalgia (n = 1; drug-related) |
| Barbosa MP et al., 2015<sup>18</sup> (ExpeRience - Portugal subgroup) | Uncontrolled persistent allergic asthma (n = 62) | 2 years | | | Deaths (n = 1 due to bronchial cancer) |
| Lopez Tiro JJ et al., 2015<sup>30</sup> | Difficult-to-treat asthma (n = 49) | 3 years | 4 AEs: osteo-articular pain (n = 1), mild headache (n = 2) and vasovagal syncope (n = 1) | | Deaths (n = 1 due to bronchial cancer) |
| Namazova-Baranova L et al., 2015<sup>50</sup> | Severe persistent uncontrolled asthma (n = 65) | 1-72 months | Frequency of local AEs: 1/100-1/200 | | |
| Long A et al., 2014<sup>31</sup> (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-naive 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-naive group | |
| Vieira T et al., 2014<sup>17</sup> | 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) | | |
| Caminati M et al., 2014<sup>10</sup> | Allergic asthma (n = 59) | Mean omalizumab treatment: 22.97 ± 16.55 months | Large local reaction at injection site: 13.4% patients (n = 8) | | |
| Braunstahl GJ et al., 2013<sup>3</sup> (ExpeRience) | Uncontrolled persistent allergic asthma (n = 943) | 2 years | | 150 SAEs | No of patients who reported SAEs: 64 patients (6.9%) Most common SAEs: asthma, dyspnea, and pneumonia | |
| Study acronym or Author | Disease condition | Follow-up period | Adverse events | Serious adverse events/deaths |
|-------------------------|-------------------|-----------------|----------------|-------------------------------|
| 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 | **Drug-related SAEs:** 25  **Deaths:** 9 (not related to omalizumab)  **Discontinued omalizumab due to SAEs:** 38 |
| Menzella F et al., 2012\(^{27}\) | Severe persistent allergic asthma (n = 11) | 4 years | No events | NA |
| Tzortzaki EG et al., 2012\(^{28}\) | 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, cephalgia | 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 Garcia 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
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. Improvement in lung function was independent of baseline airflow limitation or gender. These improvements in lung function may have been driven by prevention of exacerbations, as previous studies have shown a strong relationship between exacerbation rates and decline in lung function.

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. Lung function (FEV₁) in children was well maintained, in contrast to the increasing bronchial obstruction usually observed in severe asthma. 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.

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. 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.

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. 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. 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.

| 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. SAEs, severe adverse events
Our findings that demonstrate a sustained clinical benefit of omalizumab over long treatment periods suggest a potential disease-modifying effect of omalizumab,\textsuperscript{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.\textsuperscript{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),\textsuperscript{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.\textsuperscript{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.

\textbf{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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\textbf{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
boards for Boston Scientific, Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, ALK, Novartis, Teva, Chiesi, Saonfi-Aventis, received lecture fees from Boston Scientific, Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, ALK, Novartis, Teva, Chiesi, Saonfi-Aventis, and received industry-sponsored grants from Boston Scientific, Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, ALK, Novartis, Teva, Chiesi, Saonfi-Aventis. AD declares fees for consulting and speaker fees from Novartis, ALK, GSK, Sanofi, Regeneron, Aimmune Therapeutics, DBV Technologies, Nestlé Health Science, Stallergènes-Greer and speaker fees only from Boehringer Ingelheim outside of the submitted work. AD also reports sponsorship to attend international conferences from ALK, Sanofi, Boehringer Ingelheim, Stallergènes Greer, Novartis, AstraZeneca, Meda, DBV Technologies, Aimmune, Nutricia. AD participated in the Data Safety Monitoring Board (DSMB) for BOOM study. PP is an ex-employee of Novartis. LGC and XJ are employees of Novartis.

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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