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Omalizumab and long-term quality of life outcomes in patients with moderate-to-severe allergic asthma: a systematic review

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Giorgio Lorenzo Colombo, Sergio Di Matteo, Chiara Martinotti, Martina Oselin, Maria Chiara Valentino, Giacomo Matteo Bruno, Claudia Pitotti and Francesco Menzella

Abstract

Background: Asthma is a highly prevalent chronic inflammatory airways disease, with a considerable impact on quality of life (QoL). To express the effects of asthma on patients' subjective experience, patient-reported outcomes (PROs) represent an important instrument. The asthma QoL questionnaire (AQLQ) is one of the main PROs among these.

Materials and methods: To identify long-term asthma-related QoL outcomes associated with omalizumab therapy in patients with moderate-to-severe asthma, we developed a systematic review according to the PRISMA guidelines. Published real-world effectiveness studies of adults or adolescents (12 years or older) with moderate-to-severe allergic asthma treated with omalizumab for at least 48 weeks were reviewed. Sources used were *Medline* (*PubMed*), the *Cochrane Library* and *Google Scholar* up to February 2018. In addition, a cross-referencing search was conducted to complete the revision.

Results: A total of 255 potential papers were identified in the first search through the database. After full-text viewing, eight articles were finally included in the review. We summarized the results according to the study design, patient baseline characteristics and effectiveness outcomes assessed by AQLQ score results: variation from baseline to the end of study. Results confirmed the long-term benefits of omalizumab as an add-on therapy in patients with uncontrolled moderate-to-severe allergic asthma. Since there is a lot of evidence on omalizumab effectiveness, we aimed to focus on how a therapy can change patient's QoL in a long time period. Data showed long-term effects of omalizumab treatment on subjective (PROs) and objective (lung function, corticosteroid use, hospitalizations, asthma exacerbation) effectiveness measures.

Conclusion: Studies included in our review were observational trials that, due to their design, present a potential risk of selection bias in the patients included. Beyond this limit, the evaluation of QoL using the AQLQ showed a clear increase over time, following both 48 weeks and 9 years of observation, where QoL improvements still were significant over baseline values.

Keywords: Ashtma, quality of life, review, omalizumab

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Correspondence to:
Giorgio Lorenzo Colombo
Department of Drug Sciences, University of Pavia, Via G. Previati 74 20149 Milano c/o S.A.V.E., Pavia, Italy
giorgio.colombo@savestudi.it; giorgio.colombo@unipv.it

Sergio Di Matteo
Chiara Martinotti
Martina Oselin
Maria Chiara Valentino
Giacomo Matteo Bruno
S.A.V.E. Studi Analisi Valutazioni Economiche S.r.l., Health Economics & Outcomes Research, Milan, Italy

Claudia Pitotti
Novartis Farma, Origgio, VA, Italy

Francesco Menzella
Department of Medical Specialties, Pneumology Unit, Arcispedale Santa Maria Nuova- IRCCS, Azienda USL di Reggio Emilia, Reggio Emilia, Italy

Introduction

Asthma is a highly prevalent chronic inflammatory airways disease, with a considerable impact on quality of life (QoL) and a substantive burden in terms of morbidity, mortality and economic costs. Worldwide, more than 350 million people suffer from asthma.[1] Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness or cough, and by variable expiratory airflow limitation. Both symptoms and airflow

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limitation characteristics vary over time and in intensity.[2] Allergic mechanisms have been implicated for asthma in 50–80% of patients and these percentages are also applicable to patients with severe asthma.[3–7] The prevalence of severe asthma is estimated at about 5–10% but accounts for 50% of the global costs of the disease, being a clinical as well as social problem.[8–11] There is no cure for asthma, therefore the goal of the treatment is the achievement and the maintenance of the disease control and to minimize future risk following a stepwise approach.[2] Despite guidelines for the evaluation, classification and management of asthma, most patients, and particularly those with severe asthma, experience suboptimal asthma control in many countries.[12–15] The failure of pharmacotherapy to completely control asthma symptoms impairs QoL and functioning.[16] In addition, inadequately controlled asthma is associated with hospitalizations, emergency department visits, and productivity loss.[17,18] As such, asthma has a significant influence on daily QoL, not only in terms of symptoms and risk of serious exacerbations, but also in limitation of activities, sleep impairment, and emotional functioning.[19] The magnitude of such impairment hardly is identified by conventional clinical indices. Therefore, over time clinicians and researchers have adopted a more comprehensive view of the effects of asthma and its treatment on QoL, as seen by the increasing use of QoL measurement instruments in asthma clinical studies. In order to express effects of asthma and its treatment on patient's subjective experience, patient-reported outcomes (PROs) are important tools. Among these, one of the main is the asthma quality of life questionnaire (AQLQ), a disease-specific questionnaire designed to evaluate asthma-related QoL and control outcomes in clinical trials, which has good reliability and responsiveness with excellent cross-sectional and longitudinal validity.[20]

In these terms, omalizumab demonstrated good results in long-term clinical and observational studies conducted up to about 10 years. Omalizumab is a recombinant humanized monoclonal antibody that selectively binds to free human immunoglobulin (Ig)E, preventing it from binding to inflammatory cells, thereby inhibiting allergen-induced activation and subsequent asthma symptoms. It was approved by the European Medicines Agency in 2005 and its inclusion in asthma management guidelines has provided recommendation for its use in patients with severe allergic asthma with refractory response to high doses of inhaled steroids and long acting β2-agonists (LABAs) and those suffering from systemic steroid dependence.[21] The effectiveness and safety profile of omalizumab for the treatment of severe allergic asthma has been demonstrated in several randomized trials[22,23] and confirmed in real-world studies. Although several clinical studies have demonstrated benefits on asthma control, exacerbations, hospitalizations, corticosteroid use and QoL, there are few data about long-term omalizumab therapy, particularly about the effects on QoL. Given its high value, it is important to confirm omalizumab positive outcomes over time to optimize its position and use. Practitioners and decision-makers are encouraged to make use of the latest research and information about best practice, and to ensure that decisions are demonstrably rooted in this knowledge. Systematic reviews aim to identify, evaluate and summarize the findings of all relevant individual studies, thereby making the available evidence more accessible to decision-makers.[24]

To identify, evaluate and summarize long-term asthma-related QoL outcomes associated with omalizumab therapy in patients with moderate-to severe asthma, we developed a systematic review of data from published real-life effectiveness studies. The AQLQ was adopted as an asthma-related QoL measure.

Methods

The review was conducted following the general principles published in the Centre for Reviews and Dissemination (CRD)'s guidance for conducting systematic reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (supplementary material 1), inclusion and evaluation of studies in this review was based on PICOS (Population, Intervention, Comparators, Outcome and Study) design issues.[24,25]

Eligibility

This systematic review included published real-world effectiveness studies of adults or adolescents (⩾12 years) with moderate-to-severe allergic asthma treated with omalizumab meeting the following PRISMA-defined PICOS criteria: (1) Participants: Male/female adults or adolescents (12 years or older) diagnosed with moderate-to-severe allergic asthma; (2) Intervention: omalizumab treatment for moderate-severe allergic asthma for at least 48

weeks; (3) Comparators: pre-omalizumab standard treatment (permissible but not required); (4) Outcomes: the primary outcome was QoL impact measured with AQLQ; other outcomes included at least one measure of asthma control or change in pulmonary function (when available, healthcare resource use and exacerbations were considered); and (5) Studies: observational method studies including registry, retrospective and prospective observational studies.

Search strategy, screening, and data extraction

An electronic literature search on all available articles meeting the inclusion criteria was carried out using *Medline* (*PubMed*) (supplementary material 2), the *Cochrane Library* and *Google Scholar* up to February 2018. In addition, cross-referencing from the articles found was used to complete the search.

The keywords used to search titles and abstracts were 'omalizumab', 'asthma', 'allergic asthma', 'long-term outcomes', 'quality of life', and 'asthma quality of life questionnaire' or 'AQLQ', combined using the AND, OR Boolean operators. In order to assess long-term real-life effectiveness, only observational studies were included with the aim to confirm and extend findings of randomized clinical trials. According to the inclusion criteria, we only included studies with a duration ⩾48 week, examining the omalizumab effects on QoL measured by AQLQ. In included studies, omalizumab end-of-study outcomes were compared with baseline clinical data (pre-omalizumab treatment). Case reports and purely descriptive studies were excluded. Only original studies with human patients were considered, and only full texts were included among those that were potentially relevant. Abstract-only publications were not included due to lack of sufficiently detailed data. The reference lists of sources were reviewed for studies not previously identified. No language limits were imposed. Methodological quality and internal validity of observational studies were evaluated using quality assessment tool for before–after (pre–post) studies.[26] Heterogeneity was not analyzed and no quantitative pooling of data from these studies was undertaken. From all articles that met the review criteria, basic information was extracted by independent researchers and reported in summary tables created with Microsoft Excel®. From each publication the following data were extracted: authors, study design, trial participants general information (inclusion and exclusion criteria, method and place of recruitment, baseline characteristics). Then, we extracted outcome measures, focusing on changes in disease control and QoL over time, and we assessed the importance of the variations and reported the results in summary tables. During the data search and extraction phase we did not contact trial authors to obtain additional information.

Because of methodological and clinical heterogeneity between studies, a narrative synthesis was applied. The number of studies screened, assessed for eligibility, and included in the review, has is reported with a flow diagram in the results (Figure 1).

The following study-level data were extracted: authors, year of publication, country, evaluable sample size, sample baseline characteristics (demographics, relevant clinical data), prior asthma treatments, omalizumab treatment patterns, and outcomes. In all studies that reported safety data, we only focused on exacerbations. Among studies, there was variation in the timing of response measurements, pre-omalizumab start period and observation period. For each study, we considered the point of assessment prior to and post the start of omalizumab. QoL and asthma control outcomes were reported as changes in standard AQLQ scores, ACQ (asthma control questionnaire), ACT (asthma control test) or GETE (global evaluation of treatment effectiveness) scale. If included in study outcomes, the change in the average number of exacerbations and healthcare resource utilization were analyzed. The assessment of risk of bias in included studies was conducted at the outcome and study level, the internal and external validity were tested. For each study we considered the clarity and completeness in reporting information on the study design and methods (description of design, setting, locations, relevant dates, including periods of recruitment, exposure, follow up, and data collection). The sample size, patient's inclusion criteria and level of precision in presenting results were the main aspects considered in the assessment of risk of bias potentially able to influence the cumulative estimate of the result.

Study results were shown in summary tables reporting: study design, demographic and clinical baseline data, outcomes and QoL results.

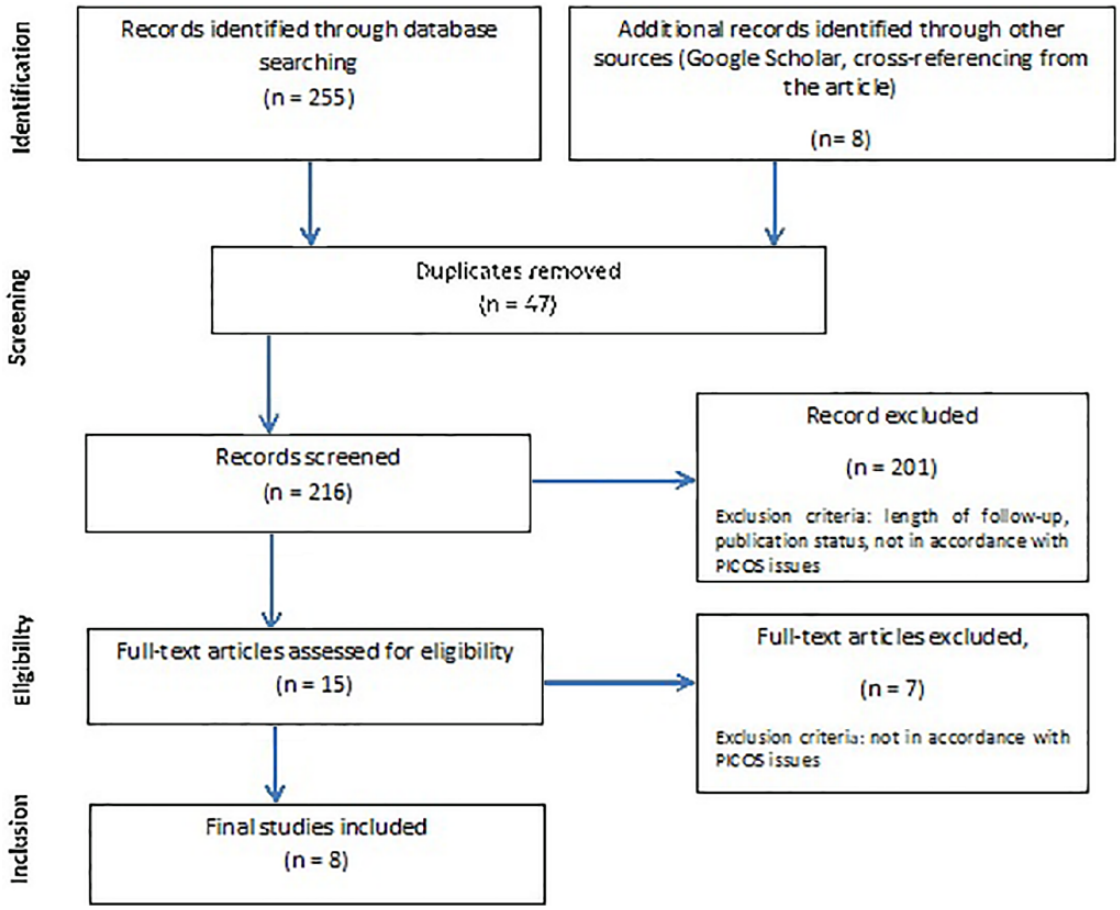

Figure 1. Flow diagram of included studies selection process: data identification, screening, eligibility and inclusion.

Summary of descriptive statistics were presented as mean ± standard deviation (SD) and *n* (%).

Assessment of quality of life

In all studies QoL was evaluated by using the AQLQ during omalizumab treatment period as compared with the baseline. The AQLQ is a health-related QoL questionnaire consisting of 32 items. The items are in four domains: symptoms (12), activity limitations (11), environmental stimuli (4), and emotional function (5). Patients record their experiences during the previous 2 weeks and score each item on a 7-point scale, where a higher score corresponds to a better QoL. Changes in the score, when assessed at two different time points, should be at least 0.5 in order that the change may be considered 'minimally important'. Improvements in the QoL scores higher than 1 are considered moderate and changes higher than 1.5 are considered excellent.[27,28]

Results

A total of eight observational studies were included in our systematic review; the study selection process is detailed in Figure 1.

As shown in flow diagram of the selection process below (Figure 1), 255 potential papers were identified in the first searching through database. After the inclusion of additional records identified through other sources (*Google Scholar* and cross-referencing from the articles) and duplicates removed, 216 records were screened, 201 of these were considered not eligible, due to the length of follow up, publication status or were not in accordance with PICOS issues. Only 15 were assessed for eligibility and, after full-text viewing, 8 articles were finally included in the review.

The primary characteristics of the included studies are summarized in Table 1 (study design and patient baseline characteristics) and Table 2

Table 1. Study design and patients' baseline characteristics.

Study	Country	Design	Study duration	Patients *n*	Age (y) mean (SD)	Female *n* (%)	IgE (IU/ml) (SD or range)	Severity/FEV_1 % (SD or range)
Brusselle and colleagues[29]	Belgium	Prospective: multicenter, open-label, observational study	1 year	158	48.17 (17.18)	85 (53.8%)	613.89 (860.19)	56.54 (14.72)
Menzella and colleagues[31]	Italy	Retrospective: observational study	4 years	11	47.5 (9.64)	4 (36.4%)	256 (31–687.6)	58.6% (42–75)
Barnes and colleagues[33]	UK	Retrospective: observational study	1 year	136	41.26 (14.5)	93 (68.4%)	/	62.94
Özgür and colleagues[34]	Denmark	Retrospective: observational study	3 years	26	47.6 (13.9)	21 (84%)	322 (178.1)	48.4 (10.4)
Tajiri and colleagues[30]	Japan	Prospective: single-arm, observational study	48 weeks	31	55 (16)	21 (67.7%)	102 (5–660)	93.5 (23.6)
Niven and colleagues[35]	UK	Prospective and retrospective: noninterventional, mixed methodology study	1 year	258	44.7 (14.2)	168 (65.1%)	/	66.8
Bhutani and colleagues[36]	Canada	Prospective and retrospective: multicentric, open-label, observational study	1 year	99	47.8 (13.8)	68 (68.7%)	668.1 (937.0)	72.9 (20.1)
Menzella and colleagues[32]	Italy	Retrospective: observational study	9 years	8	43 (9)	3 (37.5%)	201.58 (104.19)	58.5

FEV_1, forced expiratory volume in 1 second; IG, immunoglobulin; SD, standard deviation; UK, United Kingdom.

(outcomes assessed). Overall, two of the eight studies adopted a prospective design,[29,30] four adopted a retrospective design,[31–34] and the other two used a prospective and retrospective mixed design.[35,36] All studies included retrospective data, up to 12 months before the initiation of omalizumab therapy. The follow-up time varied among the studies: one study had a duration of 48 weeks,[30] four of 1 year,[29,33,35,36] while the remaining studies followed patients up to 3,[34] 4[31] and 9 years[32] after starting omalizumab administration. The sample sizes ranged from 8 to 258 omalizumab asthmatic patients.[32,35] A total of 727 patients with allergic asthma were included in these studies. A total of seven studies recruited patients with severe asthma, and only one[36] recruited moderate-to-severe allergic asthma patients. The mean age of the population was 45.8 years, and there were proportionately more women in six of the eight studies, with a proportion of female participants ranging 36.4–84%. Mean baseline forced expiratory volume in 1 second (FEV_1) values suggested a markedly impaired patient population, except for those reported by Tajiri and colleagues with a predicted FEV_1 of 93.5%.[30]

Table 2 shows a summary of effectiveness outcomes assessed in the studies. Asthma control was assessed by using the GETE scales in three studies, ACQ in two studies and ACT in the remaining three. Regardless of the scale adopted, all studies showed an improvement of asthma control after the treatment with omalizumab. Moreover, omalizumab treatment was associated with significant changes in lung function: FEV_1 improved by 12.4% after 1 year of omalizumab therapy,[33] by 23%, 29% and 48% after 3, 4 and 9 years respectively.[31,32,34] Asthma QoL was assessed in all included studies by adopting the AQLQ, two studies also evaluated general QoL through the EuroQol instrument (EQ-5D index/utility, EQ-5D visual analog scale).[29,35] The treatment with omalizumab resulted in marked improvements in patient-reported asthma-related QoL: the follow-up AQLQ measure compared with the baseline increased from 32% and 54% at 48 weeks and 1 year respectively[29,30,33,35,36] up to more than double at 3, 4 and 9 years.[31,32,34] AQLQ scores at baseline and at the latest assessment time are reported in Table 3. In all studies the score at the last follow up compared with baseline exceeded the 0.5 point, that represents the minimum important difference to achieve a benefit.[27] In five studies the score variation exceeded the 1.5 points, necessary to achieve a large important different;[29,31–34] in two studies changes resulted in a moderate important difference (exceeding 1 point)[29,34] and only one study reported a minimally important difference in AQLQ score.[36]

Figure 2 shows the variation in mean absolute AQLQ scores during treatment with omalizumab compared with baseline. The end of trial AQLQ scores varied from 4.39 to 5.9, with a difference from baseline in the range 0.9–3.4. Studies conducted over a period longer than 1 year were the minority, but showed larger improvements. Özgür and colleagues and Menzella and colleagues[31,32] reported the higher scores showing the omalizumab-related AQLQ score improvement over time. The higher absolute AQLQ values at the latest assessment time was reported in the 9-year observational study of Menzella and colleagues.[32] This study also showed the greater improvement in patient-reported asthma-related QoL compared with baseline.[34]

In addition to the improvement on asthma control, pulmonary function and QoL, a reduction of exacerbation and healthcare resources was also observed after the initiation of omalizumab. In all included studies, compared with baseline, asthma exacerbations were considerably reduced, up to more than 90% over 3 years of treatment.[29–36] Moreover, asthma-related hospitalizations, emergency room visits, and corticosteroid use showed a significant decline concurrent with omalizumab therapy.[29–36] The corticosteroid-sparing effect of omalizumab, reported in the included studies, is noteworthy (Table 4).

In fact, all studies, except Tajiri and colleagues,[30] assessed corticosteroid-sparing outcomes and significant reductions were shown. In particular, the Bhutani and colleagues[36] study showed that after 1 year of observation, 70.8% of patients either stopped corticosteroids or were able to reduce the dose of Oral corticosteroid (OCS) by 40% or more; Barnes and colleagues[33] reported a 34% reduction in mean total annual quantity of OCS prescribed between the 12 months pre and post-omalizumab initiation, 87 patients (64%) stopped/reduced OCS use by 20% or more and 66 (49%) stopped OCS completely, while Menzella and colleagues reported that all patient stopped OCS after 4 and 9 years.[31,32] These

Table 2. Summary of effectiveness outcomes assessed.

Study	Outcomes reported							
	Asthma control	Pulmonary function	QoL	Exacerbation	Healthcare care resource utilization			
					Physician visits	Emergency visits	Hospitalization	Concomitant corticosteroids
Brusselle and colleagues[29]	GETE scale	FEV	AQLQ	x				
			EQ-5D index/utility		x	x	x	x
			EQ-5D (VAS)					
Menzella and colleagues[31]	GETE scale	FEV	AQLQ	x	x	x	x	x
Barnes and colleagues[33]	ACT	FEV	AQLQ	x	x	x	x	x
Özgür and colleagues[34]	ACT	FEV	AQLQ	x		x	x	x
Taijiri and colleagues[30]	ACQ	FEV	AQLQ	x	x	x	x	
Niven and colleagues[35]	ACT	FEV	AQLQ	x	x			
			EQ-5D index/utility			x	x	x
			EQ-5D (VAS)					
Bhutani and colleagues[36]	ACQ	FeNO	AQLQ	x	x	x	x	x
Menzella and colleagues[32]	GETE scale	FEV	AQLQ	x	x	x	x	x

ACQ, asthma control questionnaire; ACT, asthma control test; AQLQ, asthma quality of life questionnaire; FEV, forced expiratory volume; GETE, global evaluation of treatment effectiveness; QoL, quality of life; VAS, visual analog scale.

Table 3. AQLQ score results.

Study	Baseline	Follow up	Follow-up time	Difference from baseline	Difference importance*
Brusselle and colleagues[29]	3.24 (1.21)	5.03	1 year	1.79 (1.13)	excellent
Menzella and colleagues[31]	2.8 (1.21–3.60)	5.6 (2.25–6.7)	4 years	2.8	excellent
Barnes and colleagues[33]	2.8	5.7	1 year	2.9	excellent
Özgür and colleagues[34]	1.98 (1.62–2.88)	5.34 (2.08–5.46)	3 years	3.36	excellent
Taijiri and colleagues[30]	4.2 (1.4)	5.56	48 weeks	1.36	moderate
Niven and colleagues[35]	3.20 (1.27)	4.39 (1.48)	1 year	1.20	moderate
Bhutani and colleagues[36]	3.9 (0.1)	4.8 (0.2)	1 year	0.9	minimal
Menzella and colleagues[32]	2.5	5.9	9 years	3.4	excellent

*Juniper and colleagues.[27]; Juniper is the source for difference importance.
Change in AQLQ score ⩾0.5: minimal important difference.
Change in AQLQ score >1: moderate important difference.
Change in AQLQ score >1.5 excellent important difference.
AQLQ, asthma quality of life questionnaire.

findings are in line with other published studies investigating oral corticosteroid use in patients treated with omalizumab.[37,38] Lastly, safety of omalizumab in long-term use was confirmed. Even after 9 years of treatment there were no safety concerns for continued omalizumab treatment.[32] Methodological quality and internal validity of observational studies were evaluated positively, allowing a good level of evidence for the results (supplementary material 3).

Discussion and conclusion

Results of our systematic review confirm the long-term benefits of omalizumab as an add-on therapy in patients with uncontrolled moderate-to-severe allergic asthma. Since there is a lot of evidence on omalizumab effectiveness, we aimed to focus on how a therapy can change a patient's QoL over a long time period.

Based on these assumptions, we conducted a systematic review in order to evaluate and summarize asthma-related QoL outcomes after the initiation of omalizumab therapy, focusing on a period of treatment ⩾48 weeks. A total of eight observational studies were included, according to PICOS issues defined for our study on the basis of specific guidelines.[24,25] The follow up was variable among studies, ranging from 48 weeks to 9 years: only three studies exceeded 1 year of observation.

The included studies first of all aimed to evaluate the long-term effectiveness of the drug and shared most of the overall outcomes measures reported in our analysis to assess this aspect, although some focused more on the consumption of corticosteroids (standard of treatment),[33–36] while others focused on asthma control measures.[29–32] Tajiri and colleagues[30] reported more specific clinical tests on pulmonary function, compared with other studies, which suggests omalizumab may have anti-inflammatory effects on small airways and alveolar regions in addition to the large airways, with benefits on the management of

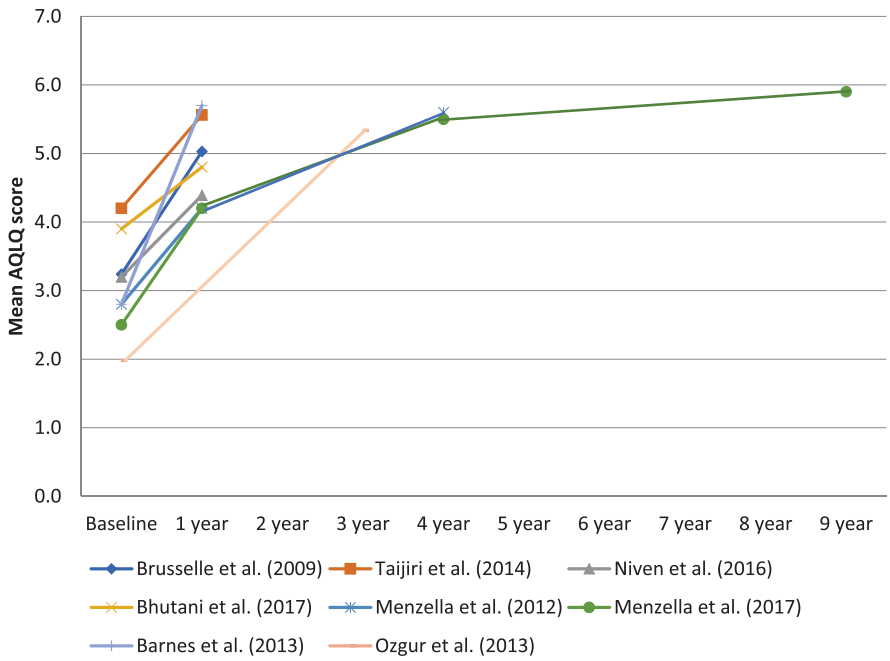

Figure 2. Mean AQLQ score change during treatment with omalizumab compared with baseline.
AQLQ, asthma quality of life questionnaire.

severe asthma and QoL. All studies evaluated PROs on QoL and among the secondary endpoints, all the studies considered the effects on healthcare resource utilization. Some studies paid more attention to the topic of resource saving considering a greater number of items.[29,35,36] In addition, Niven and colleagues[35] collected data related to days off sick from work/education due to its novelty and potential importance to the overall societal benefit of optimally treating severe asthma. Study designs were different between the included observational studies, adopting a prospective design,[29,30] a retrospective design,[32–34] or a prospective and retrospective mixed design.[35,36] The effects of omalizumab were therefore considered compared with retrospective data related to a population that did not take the drug, or in a single arm without a control. All studies indicated that a small sample size represents a limit to the robustness of study outcomes, as well as the absence of a control arm and the extraction of retrospective data.

The effects of omalizumab on QoL and asthma control were assessed by PROs, using specific questionnaires. Only studies adopting AQLQ to measure asthma QoL were considered for inclusion. Asthma control was evaluated in all studies and it was measured by different PRO instruments: ACT, ACQ, GETE. Included studies provided strong evidence that add-on omalizumab treatment significantly improves health-related QoL and asthma control outcomes in real-life settings. The greatest AQLQ score difference from baseline was reported in Menzella's study[32] although this presented patients with lower AQLQ scores at baseline. Higher absolute AQLQ values at the last follow up were reported for the 9-year [32] and 3-year[34] follow up respectively, underlining a correlation between QoL improvement and longer omalizumab treatment. Moreover, asthma control significantly increased in all studies after the treatment with omalizumab and it was maintained for longer follow-up periods, providing a cogent proof that omalizumab treatment leads to a clear asthma control improvement resulting in a clinically significant improvement in asthma-related QoL.

Although there is still no definitive cure for asthma, current treatments and those that will be available in the near future aim to achieve a better control of symptoms, a reduction in the rate of severe exacerbations and in the use of OCS. In particular, the reduction of inhaled and systemic corticosteroids use represents a better control of potential side effects of long-term therapy with

Table 4. Outcomes compared with baseline.

Study	Asthma control/ pulmonary function	Exacerbation frequency reduction (%)	Oral corticosteroids use	Healthcare care resource utilization
Brusselle and colleagues[29]	>72% of patients good/excellent GETE	65%	18.45% discontinued methylprednisolone average daily dose of methylprednisolone reduced by 39.4% average daily dose the average daily dose of budesonide	Total healthcare utilization reduction was of 18.68% in the ITT population and of 22.9% in the PP population
Menzella and colleagues[31]	81.8% of patients good/excellent GETE	94.7%	All patients stopped oral corticosteroids	A reduction in cost was observed for hospital admissions (97.3%), visits to emergency department (97.5%) and mild-moderate exacerbations (84%)
Barnes and colleagues[33]	ΔACT: +9 ΔFEV_1 (%): + 9 (from 66% to 75.2%)	53%	64% stopped/reduced OCS use by 20% or more, 49% stopped OCS	Accident and emergency visits reduced by 70% and hospitalizations by 61%
Özgür and colleagues[34]	ΔACT: + 11.6 ΔFEV_1 (%): + 23 (from 48.4% to 71.4%)	90%		>90% decrease in the number of emergency room visits and hospitalizations
Taijiri and colleagues[30]	ΔACQ: −1.11	50%		50% decrease in rate of hospitalization
Niven and colleagues[35]	ΔACT: 4.57 ΔFEV_1 (%): +4.5 (from 66.8 % to 71.3%)	58%	Daily dose of OCS decreased by 1.61 (−2.41 to −0.80) mg/patient/day	Mean number of accident and emergency visits, inpatient hospitalizations, outpatient, visits (excluding for omalizumab) and number of bed days/ patient decreased significantly ($p < 0.001$)
Bhutani and colleagues[36]	ΔACQ: −0.8 (from 2.7 to 1.9)	71%	70.8% of patients either stopped or were able to reduce the dose of OCS by 40% or more	Mean number of emergency department visits, hospitalizations and unscheduled healthcare professional visits were all significantly reduced during the treatment follow-up period

Table 4. (Continued)

Study	Asthma control/ pulmonary function	Exacerbation frequency reduction (%)	Oral corticosteroids use	Healthcare care resource utilization
Menzella and colleagues[32]	ΔFEV_1 (%): +27 (from 58.5% to 85.5%)	87%	86% of patients stopped OCS	No asthma-related hospitalizations or emergency department visits were documented

ACQ, asthma control questionnaire; ACT, asthma control test; FEV_1, forced expiratory volume in 1 second; GETE, global evaluation of treatment effectiveness; ITT, intent to treat; OCS, oral corticosteroid; PP, per protocol population.

high doses over time.[37–39] In addition high-dose inhaled corticosteroids plus a second controller or systemic corticosteroid treatment do not guarantee good disease control in many severe asthma patients, with a negative impact on patients' QoL and increasing utilization of health resources due to poor control and side-effect management.[40–42] In all included studies, omalizumab achieved better control of symptoms, a reduction in the rate of severe exacerbations and in OCS consumption. Definitely, the OCS withdrawal in the long term has important consequences on the prevention and reduction of steroid-related side effects, further improving QoL and reducing related costs. In addition, all studies assessed healthcare resource utilization, showing a significant reduction in hospitalizations and emergency room visits during omalizumab treatment that were closely related to a reduction in reported exacerbation events and, in general, to the maintenance of omalizumab effectiveness over time. Also, these findings are in line with those from previous studies evaluating the long-term effectiveness of omalizumab.[43–45]

Ultimately, data reviewed in our analysis showed the long-term effects of omalizumab treatment on subjective (PROs) and objective (lung function, corticosteroid use, hospitalizations, asthma exacerbation) effectiveness measures.

To confirm and extend the findings of clinical efficacy and safety of randomized controlled trials, we selected long-term effectiveness studies to better understand how efficacy data translate in real-life clinical practice. We focused on PROs to characterize the impact of omalizumab on a patient's subjective experience given the important humanistic burden of asthma. Compared with the systematic reviews already published on omalizumab effectiveness,[15,46] the strength of our analysis consists of the collection of long-term studies that consider QoL outcomes, updating and completing previous review.[16] The use of AQLQ to measure long-term QoL was an inclusion criterion that limited studies number, excluding trials adopting only EQ-5D. AQLQ offers an asthma-specific measurement tool, although, compared with EQ-5D, it is less suitable for pharmacoeconomic evaluation, where utilities are usually measured with EQ-5D. Indeed, in literature there are many cost-effectiveness analyses of omalizumab developed adopting EQ-5D measures[47–49] and in view of data reported on long-term effectiveness (up to 9 years) further studies could be conducted to demonstrate the significant value associated with omalizumab therapy. In fact, direct costs related to drug acquisition could be offset by long-term savings in terms of healthcare services and a patient's QoL improvement.

As in all studies, there are some limitations. The studies included in our review were observational trials that, due to their design, presented a potential risk of selection bias in the patients included. Pre and post-omalizumab time point assessment varied in studies as well as some baseline characteristics, such as study population ranging from 8 to 258 patients, and AQLQ scores. The small simple size of longer studies is definitely a limitation. Moreover, being a systematic review based on predefined inclusion criteria, any errors in the definition of the criteria could have led to the exclusion of some important studies and a poor number of included studies can represent a limitation. As regards the safety profile of omalizumab, overall it is good, no safety concerns were raised from severe adverse events reported in

studies; however, the analysis of the safety profile was carried out differently between the studies, making the judgment nonhomogeneous.

Beyond these limits, according to the methodological assessment of the included studies, results were considered to be valid, the assessment of the risk of bias in the included studies was conducted at the outcome and study level, and internal and external validity were tested. Despite the limits of our analysis, data collected and reported, can be of relevance to clinicians, payers and healthcare commissioners, bringing to the knowledge the growing body of evidence, derived from different countries and differing study designs, supporting the beneficial effects of omalizumab on asthma-related outcomes, QoL and resource utilization in unselected patients with asthma treated in normal clinical practice.

QoL, evaluated using the AQLQ, was reported to have considerably increased over time, both in 48 weeks and 9 years of observation, where the patients still presented a significant increase over baseline values. Although it was not systematically reviewed, it is important to note that improvement in a patient's QoL may be associated with better adherence to medication and lifestyle changes, providing incremental improvements in effectiveness outcomes. Accordingly, long-term omalizumab treatment may be recommended for responders and, in particular, for patients with daytime and night-time symptoms or important impaired lung function compromising QoL, and for patients at risk of exacerbations that potentially require systemic corticosteroid treatment or hospitalizations.

The efficacy and safety of omalizumab, as well as its effectiveness in the short and long term, have been shown in several randomized controlled trials and observational trials; however, data on the long-term QoL impact of omalizumab are still limited. Our systematic review looked to cover this gap providing, to the best of our knowledge, an updated synthesis of evidence that omalizumab treatment improves QoL and asthma control in the long-term in real-life settings. Compared with previous reviews, the most recent evidence on the long-term effects of omalizumab on QoL were included, showing that the effectiveness of the drug in the management of severe allergic asthma may extend up to 9 years, maintaining a good safety profile.

In conclusion, the results of our systematic review confirm, complement and extend evidence from randomized trials and short-term observational studies, highlighting the relevant role of the monoclonal anti-IgE antibody as an add-on treatment in patients with severe uncontrolled asthma. In long-term treatment, omalizumab provides a benefit for patients, continuing to reduce symptoms, exacerbations, and the medication burden, while improving QoL and asthma control.

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Conflict of interest statement

GLC, GMB, SDM, CM, MO and MCV are employees of S.A.V.E. S.r.l and consultants for Novartis. CP is an employee of Novartis Pharma, Origgio, Italy. GLC has received research and educational grants from Amgen, Takeda, Merck Sharp and Dompé, and LEO Pharma. FM participated in contracted research and clinical trials for Novartis and Sanofi and has received lecture fees and advisory board fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, and Novartis. The authors report no other conflicts of interest in this work.

Supplemental material

Supplemental material for this article is available online.

ORCID iD

Giorgio Lorenzo Colombo https://orcid.org/0000-0002-5790-8891

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Quality assessment tool for before-after (pre-post) studies with no control group: scale items (criteria for assessment)

Criteria
1. Was the study question or objective clearly stated?
2. Were eligibility/selection criteria for the study population pre-specified and clearly described?
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?
4. Were all eligible participants that met the pre-specified entry criteria enrolled?
5. Was the sample size sufficiently large to provide confidence in the findings?
6. Was the test/service/intervention clearly described and delivered consistently across the study population?
7. Were the outcome measures pre-specified, clearly defined, valid, reliable, and assessed consistently across all study participants?
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Quality assessment tool for before-after (pre-post) studies with no control group: scores of included studies

Scale Items*	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
						Score (Y, N, CD,NR,NA)**						
Studies												
Brusselle et al. (2009)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	NR	NA
Menzella et al. (2012)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NA
Barnes et al. (2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
Ozgur et al. (2013)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NA
Taijiri et al. (2014)	Y	Y	Y	Y	Y	Y	Y	NT	Y	Y	Y	NA
Niven et al. (2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
Bhutani et al. (2017)	Y	Y	Y	Y	Y	Y	Y	NT	Y	Y	Y	NA
Menzella et al. (2017)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NA

*Refer to table above for criteria

** Y =yes; N = no; CD = cannot determinate; NR = not reported; NA = not applicable

This tool was adapted from the original tool found at: National Heart Lung and Blood Institute. Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group [National Heart Lung and Blood Institute web site]. 2018. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed October 03, 2018.

Search strategy – PubMed electronic database

Search strategy for population

Asthma

Allergic asthma patients

Search strategy for interventions

Omalizumab

Search strategy for studies

Observational studies

Long-term real-life effectiveness studies

Search strategy for outcomes

Quality of Life

Asthma Quality of Life Questionnaire

AQLQ

long-term outcomes

Search strategy details

- **Main search**

("omalizumab"[MeSH Terms] OR "omalizumab"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields])

- **Limits**

No specific search limits have been selected for the first research, to avoid losing some useful texts. No language limits were imposed. Publication status or publication date were not selected.
Results shown, following the query with keywords, were then screened.
Only original studies with human subjects were considered and only full texts were included among those potentially relevant. Abstract-only publications were not included due to lack of sufficiently detailed data.