

Omalizumab lowers asthma exacerbations, oral corticosteroid intake and blood eosinophils: Results of a 5-YEAR single-centre observational study

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ABSTRACT

Omalizumab is a humanized monoclonal antibody which binds to human immunoglobulins E (IgE), thus preventing their interactions with both high affinity and low affinity IgE receptors. Therefore, omalizumab is currently recommended for add-on biological therapy of uncontrolled allergic asthma, mainly characterized by type 2 airway eosinophilic inflammation. Because omalizumab has been the first, and for a long time the only available monoclonal antibody for add-on treatment of type 2 asthma, some long-term studies have been published which provide a clear evidence of the therapeutic effectiveness of the anti-IgE pharmacological strategy.

Within this context, the present single-centre observational study refers to 15 patients with severe allergic asthma, treated with omalizumab for at least 5 years at the Respiratory Unit of “Magna Græcia” University Hospital located in Catanzaro, Italy. In these asthmatic subjects we observed significant increases in asthma control test (ACT) score, with respect to baseline (14.60 ± 2.97), after 1 year (19.20 ± 2.98 ; $p < 0.0001$) and 5 years (21.67 ± 2.38 ; $p < 0.0001$) of add-on treatment with omalizumab. More importantly, omalizumab significantly lowered the number of annual asthma exacerbations (baseline: 3.66 ± 2.01) after 1 year (0.83 ± 1.14 ; $p < 0.0001$) and 5 years (0.63 ± 0.99 ; $p < 0.0001$), respectively. This excellent therapeutic outcome made it possible to drastically decrease the daily oral intake of prednisone (baseline: 22.50 ± 5.17 mg) after 1 year (1.83 ± 4.06 mg; $p < 0.0001$), as well as after 5 years (1.66 ± 3.61 mg; $p < 0.0001$). With regard to lung function, omalizumab significantly and persistently enhanced FEV₁ (baseline: 1636 ± 628.4 mL) after 1 year (2000 ± 679.7 mL; $p < 0.05$) and 5 years (1929 ± 564.8 mL; $p < 0.05$), respectively. Such relevant clinical and functional improvements were associated with reductions of blood eosinophil counts (baseline: 646.0 ± 458.9 cells/ μ L), already detectable after 1 year (512.7 ± 327.8 cells/ μ L; not significant), which reached the threshold of statistical significance after 5 years (326.0 ± 171.8 cells/ μ L; $p < 0.05$).

Therefore, these real-life data referring to our single-centre observational investigation further corroborate the long-term therapeutic ability of omalizumab to improve several clinical, functional and haematological signatures of severe type 2 asthma.

1. Introduction

Asthma is a largely diffuse airway disease, featured by a variable bronchial obstruction sustained by chronic inflammation and structural remodelling [1,2]. Several pathobiologic mechanisms drive the different phenotypes and endotypes of asthma, which are the result of a complex interplay between genetic factors and environmental agents

[3–5]. Within this context, allergy plays a prominent pathogenic role, mediated by key functions exerted by immunoglobulins E (IgE) [6,7]. Indeed, IgE-dependent atopic asthma encompasses the whole spectrum of disease severity, thus being also involved in difficult-to-treat allergic phenotypes associated with a type 2 immunity pattern, mostly characterized by eosinophilic inflammation refractory to corticosteroids [8,9]. In particular, allergy is believed to be implicated in more than

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half of cases of severe asthma [10]. Therefore, T helper 2 (Th2)-cell driven IgE responses are also responsible for severe allergic asthma. In particular, IgE crucially contribute to bronchial inflammation and remodelling via a tight binding to both high affinity (FcεRI) and relatively low affinity (FcεRII/CD23) receptors, expressed by immune-inflammatory cells as well as by resident/structural airway cells [7,11–14]. As a consequence of these antibody-FcεRI/FcεRII interactions, IgE induce mast cell/basophil degranulation [15], mast cell and eosinophil survival [16,17], up-regulation of FcεRI basophil expression [18], IgE synthesis by B cells [19], and antigen presentation by myeloid dendritic cells to T lymphocytes [20]. Furthermore, at level of plasmacytoid dendritic cells IgE-dependent stimulation of FcεRI receptors leads to suppression of the production of anti-viral factors such as interferons [21]. In addition to driving allergic inflammation, IgE can also affect airway remodelling by acting on resident cells. In this regard, IgE have been shown to promote the production of transforming growth factor-β (TGF-β) by bronchial epithelial cells [22]. At level of airway smooth muscle cells, activation of FcεRI receptors by IgE leads to an increased synthesis of collagens I/III and fibronectin [23–25].

For all the above reasons, IgE constitute an excellent target for add-on biological therapies of uncontrolled, exacerbation-prone atopic asthma [26]. Such a therapeutic rationale explains the relevant benefits experienced by atopic severe asthmatics receiving omalizumab, a humanized anti-IgE monoclonal antibody [27]. Omalizumab effectively inhibits all IgE-triggered cellular events by interacting with the Cε3 domain of the constant region of human IgE, thus building-up IgE/anti-IgE immune complexes that block IgE and neutralize their bioactivities by impeding antibody binding to FcεRI and FcεRII [28,29]. In fact, IgE interact with both these receptors through their Cε3 domains, which of course are not available for receptor binding when they are occupied by omalizumab. Via this strategic mechanism of action, in severe allergic asthmatics omalizumab significantly improves symptom control and quality of life, and especially decreases asthma exacerbation rate [28,29]. Indeed, omalizumab not only prevents allergen-driven exacerbations, but also exerts a valid protective action against virus-induced exacerbations. This effect is largely mediated by omalizumab via reversal of the negative impact of IgE on the innate anti-viral properties of plasmacytoid dendritic cells; as a consequence, omalizumab effectively restores the protective function of these cells against viral infections, thereby reinstating the production of interferon-α [30]. In inadequately controlled patients with severe allergic asthma, all these very positive therapeutic effects have been clearly demonstrated by placebo-controlled trials [31], and especially by real-life studies performed worldwide since omalizumab was approved for use in clinical practice as anti-asthma add-on drug more than a decade ago [32–35].

Within this context, the present single-centre observational investigation has been carried out in severe allergic asthmatic patients, with the aim of evaluating the long-term impact of omalizumab on symptom control, asthma exacerbations, oral corticosteroid intake, lung function and blood eosinophils.

2. Patients and methods

This single-centre observational and retrospective study has been conducted in 15 outpatients with severe allergic asthma, referring to the Respiratory Unit of “Magna Græcia” University Hospital located in Catanzaro, Italy. Such patients experienced frequent asthma exacerbations and an inadequate symptom control, though they received high dosages of inhaled corticosteroids (ICS) plus long-acting β₂-adrenergic agonists (LABA), integrated by treatments with long-acting muscarinic antagonists (LAMA), leukotriene inhibitors and oral corticosteroids (OCS). All enrolled subjects exhibited positive skin prick tests versus perennial aeroallergens, and their total serum IgE levels were included within 30 and 1500 IU/mL. Moreover, forced expiratory volume in 1 s (FEV₁) was less than 80% of the predicted value, and increased of at least 12% and 200 mL within 30 min after inhalation of 400 μg of

Table 1
Baseline patient characteristics.

Age (years)	46.60 ± 13.21
Sex (M/F)	5/10
Weight (kg)	69.00 ± 11.90
Height (cm)	161.30 ± 7.37
FEV ₁ (% predicted)	61.47 ± 19.07
FEV ₁ /FVC (%)	56.55 ± 10.76
Total serum IgE (IU/mL)	359.3 ± 222.6
Monthly dose of Omalizumab (mg)	410.0 ± 165.0
Blood eosinophils (cells/μL)	646.0 ± 458.9

salbutamol. Baseline patient characteristics are summarized in Table 1.

Omalizumab was injected for at least 5 years via the subcutaneous route every 2 or 4 weeks, depending on serum IgE levels and body weight. Across the study period, all the following evaluations were recorded at baseline, as well as 1 and 5 years after the first administration of omalizumab: asthma control test (ACT), number of annual asthma exacerbations, daily consumption (mg) of prednisone, FEV₁, and blood eosinophil count. Furthermore, all recruited asthmatic subjects were accurately monitored with the aim of promptly detecting the eventual onset of adverse events.

This observational investigation was performed according to the standards of Good Clinical Practice (GCP) and to the principles of the Declaration of Helsinki. The study was approved by the local ethics committee, and all enrolled patients gave their written informed consent.

3. Statistical analysis

Study results are expressed as mean ± standard deviation (SD). Statistical analysis of the results was carried out by Dunnett's multiple comparison test (ACT, FEV₁, and eosinophil count) and by Student's *t*-test for paired data (asthma exacerbations and prednisone consumption) [36]. A *p* value lower than 0.05 was considered to be significant.

4. Results

All our 15 patients with severe allergic, exacerbation-prone, and OCS-dependent eosinophilic asthma were enrolled to start an add-on treatment with omalizumab at least 5 years ago. After 1 year and 5 years of add-on therapy with omalizumab, all subjects noticed a marked improvement in both nocturnal awakenings and daily symptoms caused by asthma. These clinical benefits resulted to be statistically significant, as shown by the increases in ACT scores recorded after 1 year (from baseline 14.60 ± 2.97 to 19.20 ± 2.98; *p* < 0.0001) and 5 years (21.67 ± 2.38; *p* < 0.0001), respectively (Fig. 1). Frequent disease exacerbations are probably the most important clinical manifestations of severe uncontrolled asthma. In this regard, omalizumab significantly lowered the annual exacerbation rates after 1 year (from baseline 3.66 ± 2.01 to 0.83 ± 1.14; *p* < 0.0001) and 5 years (0.63 ± 0.99; *p* < 0.0001) of add-on therapy, respectively (Fig. 2). Such a dramatic drop of asthma exacerbations made it possible for all patients to avoid, during the 5 years of observation, the need for either access to emergency room or hospitalization for asthma worsening. In addition, the noticeable decreases of yearly asthma exacerbation rates allowed to 11 patients a complete interruption, following a progressive tapering, of OCS intake. For the remaining 4 patients, it was possible to drastically reduce the daily OCS dosage. Hence, the overall consumption of prednisone sharply diminished, with respect to baseline, from 22.50 ± 5.17 mg/day to 1.83 ± 4.06 mg (*p* < 0.0001) after 1 year, and to 1.66 ± 3.61 mg/day (*p* < 0.0001) after 5 years (Fig. 3). This remarkable long-term decrease in the daily need for OCS intake was associated, especially in some female patients, with a relevant weight loss due to the marked reduction of the systemic side effects of OCS. With regard to lung function, add-on anti-IgE therapy with omalizumab

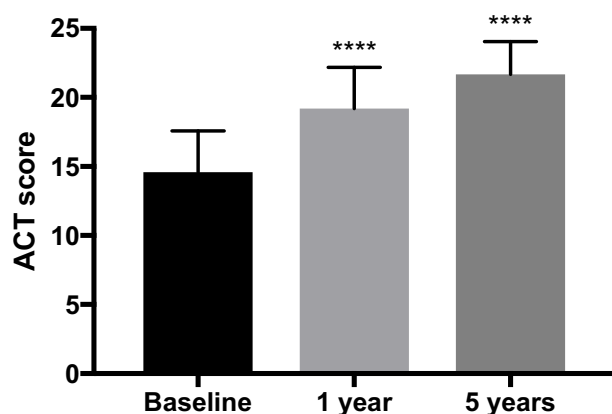


Fig. 1. Effect of omalizumab on ACT score. Mean ACT values, evaluated at baseline, as well as after 1 and 5 years of add-on treatment with omalizumab. **** $p < 0.0001$.

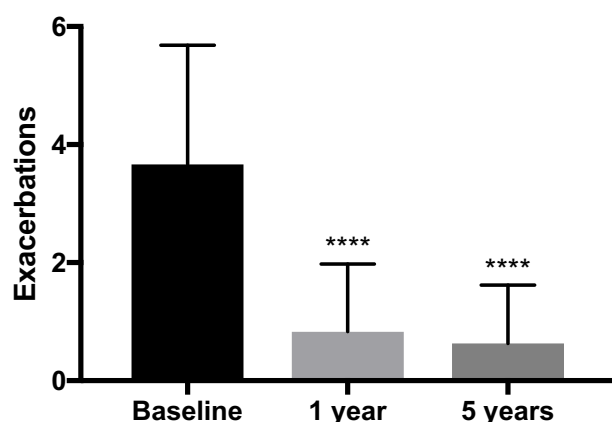


Fig. 2. Effect of omalizumab on annual asthma exacerbations. Mean exacerbation numbers, referring to the year before treatment (baseline), and also recorded after 1 and 5 years of add-on therapy with omalizumab. **** $p < 0.0001$.

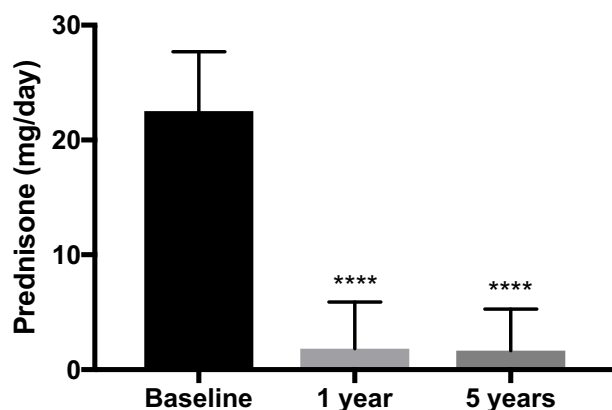


Fig. 3. Effect of omalizumab on daily intake of oral corticosteroids. Mean prednisone daily dosages, assessed at baseline, as well as after 1 and 5 years of add-on treatment with omalizumab. **** $p < 0.0001$.

significantly enhanced FEV_1 , when compared to baseline, from 1636 ± 628.4 mL to 2000 ± 679.7 mL ($p < 0.05$) after 1 year, and to 1929 ± 564.8 mL ($p < 0.05$) after 5 years, respectively (Fig. 4). Finally, after 1 year omalizumab elicited a trend towards a decrease in blood eosinophil count with respect to baseline, from 646.0 ± 458.9 cells/ μ L to 512.7 ± 327.8 cells/ μ L (not significant).

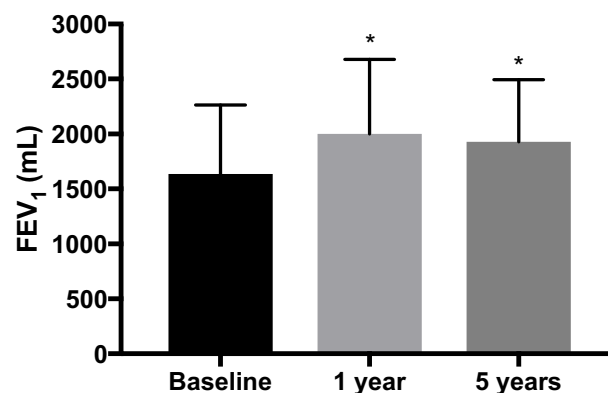


Fig. 4. Effect of omalizumab on FEV_1 . Mean FEV_1 values, measured at baseline, as well as after 1 and 5 years of add-on treatment with omalizumab. * $p < 0.05$.

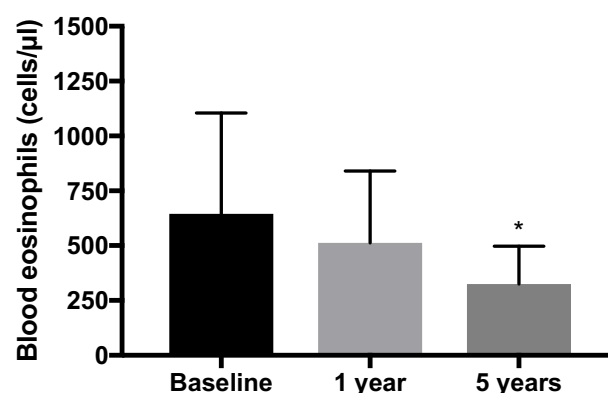


Fig. 5. Effect of omalizumab on blood eosinophil levels. Mean eosinophil numbers, counted at baseline, as well as after 1 and 5 years of add-on treatment with omalizumab. * $p < 0.05$.

This haematological effect of omalizumab reached the threshold of statistical significance after 5 years, when blood eosinophil level resulted to be 326.0 ± 171.8 cells/ μ L ($p < 0.05$) (Fig. 5). Globally, the overall amelioration of asthma control experienced by all our patients resulted in a better quality of life.

The comprehensive improvement of the global health status was expressed by an increased tolerance to exercise, as well as by an attenuation of depression and anxiety, and also by a sharp reduction of the loss of working days and hours (data not shown). In regard to the adverse events eventually linked by a very probable cause-effect relationship to omalizumab, only spontaneously resolving local skin reactions were detected at injection sites in 3 patients.

Therefore, taking into consideration all the results of our observational study, omalizumab was comprehensively characterized by a very satisfactory profile of efficacy, safety and tolerability.

5. Discussion

The results of this real-life observational investigation further confirm that omalizumab is capable of providing long-term effective benefits in patients with severe allergic asthma. In particular, add-on anti-IgE therapy induced a clinically important improvement in symptom control, significantly and persistently decreased asthma exacerbations, thus markedly reducing the need for OCS treatment, and also ameliorated lung function and lowered blood eosinophil count.

With regard to asthma symptoms, omalizumab elicited a remarkable increase of ACT score, whose mean value after 1 year of treatment approached the satisfactory control threshold of 20, which was even

exceeded after 5 years. Indeed, in real-life settings ACT is a reliable, easily understandable and simple to fill in clinical tool, probably more useful than other scores such as that one referring to the asthma control questionnaire (ACQ) [37]. This result is consistent with similar data reported by other studies. For example, Al-Ahmad et al. showed that ACT scores significantly and progressively increased throughout all the consecutive 4 years of their study, always exceeding the critical 20 threshold [38]. Moreover, our findings are in agreement with those previously published by Tzortzaki et al., Zazzali et al., and Vieira et al., who also performed real-life long-term evaluations [39–41]. Therefore, our present observations contribute to corroborate the validity of ACT as a reliable indicator of the clinical efficacy of omalizumab.

Anyway, the most important clinical finding of our observational study refers to the striking reduction of asthma exacerbations. Indeed, this very relevant outcome resulted to be well above the value of at least 50% decrease, stated by the British National Institute for Health and Care Excellence (NICE) as a crucial criterion in order to establish as adequate a therapeutic response to another anti-asthma biologic such as mepolizumab [42]. Our results are similar to those reported by Pace et al., who showed that the preventive action of omalizumab on severe asthma exacerbations, well evident after 4 years, further strengthened after 7 years [43]. All these findings are also consistent with the results obtained by Menzella et al., who monitored up to 9 years the long-lasting protective effect of omalizumab against severe asthma exacerbations [44].

Such a very strong ability of omalizumab to decrease asthma exacerbations, due to both anti-allergic and anti-viral properties [45], made it possible for our patients to progressively reduce, and in many cases to completely interrupt OCS consumption. This effect, previously observed by our group already after 40 weeks of add-on therapy with omalizumab [35], has been detected also after 7 years of treatment [43]. As a consequence of the abrogation of OCS systemic side effects, many of our patients benefited from weight loss, reversal of iatrogenic diabetes, and improvement of both arterial hypertension and depression. Moreover, the OCS-sparing effect of omalizumab allowed to satisfy another key NICE criterion referring to the therapeutic responses to anti-asthma drugs [42].

With regard to lung function, we noticed a significant and persistent effectiveness of omalizumab in increasing FEV₁, whose elevation after 1 year was about 300 mL, and such a positive result was confirmed also after 5 years. We had previously reported a similar effect on FEV₁ already after 40 weeks of add-on biological treatment with omalizumab [35]. Furthermore, such a relevant improvement in lung function has also been observed after 4, 7, and 9 years of anti-IgE therapy with omalizumab, respectively [38,43,44]. Al-Ahmad et al. documented that after starting treatment with omalizumab, patients with severe allergic asthma exhibited, throughout 4 years of observation, a good correlation between FEV₁ improvements and ACT score increases at all time points of their real-life study [38]. Of course, the main mechanism by which omalizumab improves lung function depends on its capability of remarkably dampening airway type 2 immune inflammation. However, attenuation of airway remodelling leading to a reduction of bronchial wall thickness, could also contribute to omalizumab-driven improvement of airflow limitation [46,47]. A better lung function might also be the result of the very effective decrease of asthma exacerbations induced by omalizumab. Indeed, it is well known that a close relationship exists between the recurrence of asthma exacerbations and the progressive decline of pulmonary function occurring in frequent exacerbators suffering from severe asthma [48]. On the other hand, patients with severe airflow limitation are more susceptible to asthma exacerbations [49]. Hence, it is very likely that the most common triggers of asthma exacerbations such as respiratory viruses and inhaled allergens activate cellular and molecular mechanisms responsible for airway inflammation and remodelling, which accelerate the progressive loss of lung function that characterizes severe asthma. The resulting worsening of airflow limitation in turn enhances the risk of future asthma

exacerbations. This dangerous vicious cycle can be effectively broken by omalizumab via its ability to exert anti-allergic and anti-viral effects, thus inhibiting bronchial inflammation and remodelling, as well as also preventing the development of asthma exacerbations.

In addition to the very relevant clinical and functional therapeutic actions of omalizumab observed in our patients, we also noticed that add-on anti-IgE treatment decreased the numbers of peripheral blood eosinophils, and this effect resulted to be statistically significant at the 5th year. Such an eosinophil-lowering property of omalizumab had been already reported by us and by other groups [35,50]. In particular, Massanari et al. found that in patients with moderate-to-severe allergic asthma there was a correlation between omalizumab-dependent reduction of blood eosinophils and several positive outcomes including a decreased requirement for OCS, an increased FEV₁, and a favourable judgment by study investigators with regard to global evaluation of treatment effectiveness [50]. Indeed, omalizumab neutralizes the strong survival signal for eosinophils provided by IgE, which exert an anti-apoptotic action on these cells [17]. Therefore, a pro-apoptotic effect on eosinophils can be induced by omalizumab, which has been shown by Noga et al. to significantly increase the staining of these cells with annexin V, a well-known cellular marker of apoptosis [51]. Omalizumab-mediated eosinophil apoptosis is mainly due to inhibition of T cell production of granulocyte macrophage-colony stimulating factor (GM-CSF), which is a powerful growth factor and survival mediator for eosinophils [51]. Moreover, omalizumab is able to decrease eosinophil numbers not only in peripheral blood, but also in induced sputum and bronchial biopsies taken from asthmatic patients, as reported by Djukanovich et al. [52]. It is thus very reasonable that the effects of omalizumab on eosinophils significantly contribute to its therapeutic effects in asthma, due to attenuation of type 2 airway eosinophilic inflammation, as well as to inhibition of bronchial remodelling. In fact, eosinophils are an abundant cellular source of TGF- β , a key growth factor involved in the development of airway structural changes, especially evident in severe asthma [53]. On the other hand, high blood eosinophil levels, together with increased concentrations of serum periostin and fractionated exhaled nitric oxide (FeNO), are currently believed to be reliable predictors of good therapeutic responses to omalizumab [54].

Overall, taken together our findings corroborate, throughout a long-term follow-up period, the results of some recent studies, referring to either placebo-controlled trials or real-life investigations. In particular, by performing a post-hoc analysis of pooled data from two seminal phase III registration trials, Casale et al. showed that the best therapeutic responses to omalizumab, expressed in terms of greater decreases in exacerbation rates, can be detected in patients very similar to ours, characterized by the most severe asthma phenotypes [55]. Indeed, in such patients a high disease intensity can be inferred by multiple clinical, functional, and biological indices including frequent emergency room accesses and hospitalizations due to asthma exacerbations, high ICS/LABA dosages, low FEV₁ values, and high blood eosinophil counts [55]. Moreover, in a real-world setting the 1-year PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) study demonstrated that, with respect to the 12 months prior to treatment, omalizumab significantly reduced asthma exacerbations and hospital admissions, and also increased ACT scores, thereby allowing to most enrolled subjects who were uncontrolled before starting to receive omalizumab, to become controlled at study end [56].

Finally, our observational investigation further confirms that in real-life omalizumab is featured by an excellent long-term profile of safety and tolerability. Indeed, we did not observe any serious adverse event, and only sporadically we detected some mild skin reactions at injection sites. In this regard, our results are in agreement with those of longer and even more reassuring studies [27]. In particular, Di Bona et al. have recently reported that omalizumab appeared to be remarkably safe and well tolerated by patients with severe uncontrolled

asthma undergoing treatment for 9 years [57]. These authors have shown that add-on therapy with omalizumab for many consecutive years did not enhance the risk of side effects, and no case of anaphylaxis developed during such a long period of real-life observation [57].

Similar to all real-life studies, an obvious limitation of our observational investigation is the absence of a placebo control. Another limitation refers to the relatively small number of enrolled subjects. Otherwise, a strength of this study is the substantial homogeneity of the clinical, functional and biological phenotypes/endotypes of our patients, that makes it possible to infer quite generalizable conclusions. With regard to the available scenario of biological treatments for severe type 2 asthma, our findings further corroborate the key position held by omalizumab which has been, is, and will be an excellent add-on therapeutic choice for treatment of difficult-to-control allergic asthma. Indeed, our results suggest that omalizumab is very effective as biological therapy for allergic patients with severe eosinophilic asthma. However, in order to better understand the therapeutic differences existing between omalizumab and other anti-eosinophilic biologics such as mepolizumab, reslizumab and benralizumab [58–62], targeting either IL-5 or IL-5 receptor, head-to-head comparative studies should be performed. Indeed, these comparisons might help to provide a valuable platform for a more personalized, patient-oriented strategy within the current context of add-on biological therapies for inadequately controlled asthma [63].

In conclusion, the present 5-year single-centre real-life study, carried out in 15 patients with severe allergic asthma, provides clear evidence that omalizumab can effectively improve symptom control and lung function, and especially decreases asthma exacerbations, thus significantly sparing OCS use; these very positive clinical and functional outcomes seem to be associated with a detectable reduction of peripheral blood eosinophils. The current interest for such long-term real-life studies arises from the importance of monitoring the patients with severe atopic asthma, with the aim of elucidating if an anti-IgE treatment could eventually impact on the natural history of uncontrolled exacerbation-prone disease, thus possibly slowing down the progressive decline in lung function which characterizes the most severe phenotypes/endotypes of this widespread chronic respiratory disorder. If further and longer clinical/functional real-life investigations will corroborate and consolidate the results reported by us and other authors, omalizumab could realistically be considered as a potential disease-modifying biological drug for patients suffering from severe allergic asthma.

Autorship contribution

All authors contributed to design and carry out the study protocol, as well as to write the text and draw the figures.

Conflicts of interest

Corrado Pelaia, Cecilia Calabrese, Sarah Barbuto, Maria Teresa Busceti, Mariaimmacolata Preianò, Luca Gallelli, and Rocco Savino have no conflict of interest.

Alessandro Vatrella has received lecture fees and consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti-Malesci, Menarini, Mundipharma, Novartis, Teva.

Girolamo Pelaia has received lecture fees and consultancy fees from AlfaSigma, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti-Malesci, Menarini, Mundipharma, Novartis, Sanofi, Teva, Zambon.

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