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Omalizumab decreases exacerbation frequency, oral intake of corticosteroids and peripheral blood eosinophils in atopic patients with uncontrolled asthma

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Key words
omalizumab – anti-IgE – exacerbation-prone asthma – oral steroid-dependent asthma – eosinophils

Abstract. Omalizumab is a humanized monoclonal anti-IgE antibody approved in 2005 by the European Medicine Agency (EMA) for the treatment of severe persistent allergic asthma, which remains inadequately controlled despite optimal therapy with high doses of inhaled corticosteroids and long-acting β_2-adrenergic agonists. Within this context, the present observational study refers to 16 patients currently treated with omalizumab at the Respiratory Unit of "Magna Græcia" University Hospital located in Catanzaro, Italy, whose anti-IgE therapy was started in the period included between March 2007 and February 2010, thus lasting at least 10 months. After 40 weeks of add-on treatment with omalizumab, very relevant decreases were detected, in comparison with pre-treatment mean (± standard deviation) values, in monthly exacerbation numbers (from 1.1 ± 0.6 to 0.2 ± 0.4; $p < 0.01$) and oral corticosteroid consumption (from 22.6 ± 5.0 to 1.2 ± 2.9 mg/day of prednisone; $p < 0.01$). These changes were associated with stable improvements in lung function, expressed as increases of both FEV_1 (from 53.6 ± 14.6% to 77.0 ± 14.9% of predicted values; $p < 0.01$) and FEV_1/FVC ratio (from 56.3 ± 9.5% to 65.8 ± 9.2%; $p < 0.01$). Moreover, in 5 patients who persistently had increased numbers of eosinophils (mean ± SD: 15.9 ± 8.0% of total WBC count; absolute number: 1,588.0 ± 956.9/μl) despite a long-lasting therapy with inhaled and systemic corticosteroids, the peripheral counts of these cells decreased down to near normal levels (mean ± SD: 6.3 ± 2.3% of total WBC count; absolute number: 462.0 ± 262.3/μl) after 16 weeks of treatment with omalizumab. Therefore, this descriptive evaluation confirms the efficacy of add-on omalizumab therapy in selected patients with exacerbation-prone, chronic allergic uncontrolled asthma, requiring a continuous intake of oral corticosteroids.

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Introduction

Asthma is a complex and heterogeneous disease characterized by various immunopathologic and clinical phenotypes, based on different patterns of airway inflammation involving immune/inflammatory cell types such as T and B lymphocytes, mast cells, eosinophils, basophils, neutrophils, monocytes/macrophages and dendritic cells, as well as structural cellular elements including both epithelial and mesenchymal cells [1, 2]. This widespread respiratory disease, which originates from multiple interactions between genetic factors and environmental agents such as allergens, respiratory viruses and airborne pollutants, is characterized by recurrent episodes of dyspnea, wheezing, chest tightness and cough, associated with a reversible airflow limitation and an exaggerated bronchoconstrictive response to several different stimuli (airway hyperresponsiveness). Asthma constitutes a heavy medical, social and economic burden, because its prevalence is continuously increasing worldwide [3]. Indeed, asthma affects over 300 million people around the world, and some epidemiologic projections estimate that this number will further increase during the next decades [4]. Although a good control of asthma symptoms can be achieved in many patients by current standard therapies mainly based on combinations of inhaled corticosteroids and β_2-adrenoceptor agonists [5, 6], a small percentage (about 5 – 10%) of asthma patients who are affected by the most severe forms of the disease, though receiving

the best available inhaled treatments, remain symptomatic and inadequately controlled thus having a poor quality of life. Patients included within the most severe sector of the overall phenotypic asthma spectrum are those characterized by the greatest unmet medical needs [7]. Therefore, though being a minority of the global asthmatic population, patients with severe asthma are those who use the largest share of economic resources and health care services, including emergency visits, hospitalizations and additional consumption of drugs utilized for recurrent exacerbations. With regard to this latter aspect, some asthmatic patients express the so-called "exacerbation-prone" sub-phenotype of severe asthma, in that they are predisposed to very frequent and sometimes severe exacerbations, which represent their main distinguishing clinical feature [8]. In addition to requiring high doses of inhaled corticosteroids, such patients are continuously or near continuously compelled to take these drugs also by the oral route, thus satisfying both major criteria conventionally adopted to define severe asthma [9].

According to various studies, IgE-mediated, positive reactions to skin prick tests for common aeroallergens are detectable in a percentage of severe asthmatics ranging from about 50% to 80% [7, 10, 11]. In these patients asthma symptoms can be further worsened by concomitant comorbidities including rhinitis, sinusitis, gastro-esophageal reflux, obesity and obstructive sleep apnea [12]. For all these reasons, anti-IgE therapy was included in 2006 within the Step 5 of GINA (Global Initiative for Asthma) guidelines [13], as add-on treatment to inhaled and eventually oral corticosteroids, long-acting β_2-adrenergic agonists and other controller medications such as leukotriene modifiers and theophylline. After being introduced in Australia (2002) and the United States (2003), utilization of the anti-IgE monoclonal antibody, omalizumab, was approved in 2005 also by the European Medicines Agency (EMA) as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma, who have an impaired lung function ($FEV_1 < 80\%$ predicted) and experience frequent daytime symptoms and/or nocturnal awakenings, associated with multiple severe exacerbations despite daily high doses of inhaled corticosteroids and long-acting β_2-adrenoceptor agonists. Recently, the use of omalizumab has also been approved for children being at least 6 years old [14].

In particular, omalizumab (molecular weight: 150 kD) is a recombinant humanized antibody comprising a human IgG framework which embeds the complementarity-determining region obtained from an anti-IgE antibody raised in mice [15]. Omalizumab selectively binds to the Cε3 domain of the constant Fc portion of free IgE immunoglobulins, thereby preventing their interactions with both high-affinity (FcεRI) and low-affinity (FcεRII/CD23) IgE receptors, expressed by several different immune/inflammatory cells [16, 17, 18]. Through this mechanism of action, omalizumab reduces serum levels of free IgE by 96 – 99%, and can thus inhibit allergen-induced degranulation of mast cells and basophils, FcεRI cellular expression and new IgE synthesis [18, 19, 20]. As a consequence of these pharmacological characteristics, when given in addition to standard therapy with inhaled corticosteroids and other anti-asthma drugs, omalizumab is very effective in asthmatic patients with severe disease not adequately controlled by standard treatments. Indeed, omalizumab efficacy has been documented by many Phase III trials, which have shown that this drug is able to improve asthmatic symptoms and quality of life, as well as to decrease asthma exacerbations, unscheduled outpatient visits, emergency room visits and hospitalizations, and also the requirement for both inhaled corticosteroids and rescue bronchodilators [21, 22, 23, 24, 25, 26, 27, 28]. Such a favorable pharmacodynamic pattern has also been recently corroborated by Phase IV, post-marketing surveillance trials referring to patients affected by severe persistent allergic asthma, treated with omalizumab in real-life practice in France, Germany, Belgium and Italy [29, 30, 31, 32, 33]. The efficacy and safety of omalizumab in adults, adolescents and children with moderate to severe asthma have been further confirmed by a recent meta-analysis referring to eight placebo-controlled studies, published between 2001 and 2009 and globally involving more than 3,000 patients [34].

Our present observational study involves 16 patients with severe allergic asthma, referring since March 2007 to the Respiratory Unit of "Magna Græcia" University Hospital located in Catanzaro, Italy. Omalizumab

was prescribed to these subjects because all of them were oral steroid-dependent, inadequately controlled by standard inhaled and systemic treatments, and expressed the clinical sub-phenotype defined as "exacerbation-prone" asthma.

Patients and methods

This observational study was carried out 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.

Between March 2007 and February 2010, 16 outpatients started a treatment with omalizumab at the Respiratory Unit of "Magna Græcia" University Hospital located in Catanzaro, Italy. These asthmatic subjects were selected for add-on therapy with omalizumab in accordance with GINA and EMA guidelines. In particular, all patients were non-smokers and affected by uncontrolled severe persistent asthma, characterized by frequent daily symptoms and/or nocturnal awakenings despite a regular treatment with high doses of inhaled corticosteroids and long-acting β_2-adrenergic agonists. All subjects had positive skin prick tests and/or in vitro reactivity against at least one perennial aeroallergen. Their total serum IgE levels were between 57.4 and 695 IU/ml, and body weight ranged from 50 to 96 kg. Forced expiratory volume in one second (FEV_1) was less than 80% of the predicted value, and improved of at least 12% and 200 ml within 30 minutes after inhalation of 400 µg of salbutamol. Furthermore, all patients experienced very frequent asthma exacerbations and, in addition to inhaled therapy, they were also treated continuously or near continuously with oral corticosteroids. Baseline patient characteristics are schematically illustrated in Table 1.

The dosage of omalizumab was individually determined by taking into consideration serum pre-treatment levels of total IgE and patient's body weight, according to dosing tables which approximately reflect the use of the following formula: 0.016 mg/kg per IU/ml of IgE per 4 weeks [35]. Depending on individual omalizumab doses, the drug was administered by subcutaneous injections every 2 or 4 weeks. The mean monthly dose of omalizumab was 440.6 (± 168.5) mg. All patients were clinically evaluated every time they came to receive omalizumab injections. In particular, at these time points patients provided detailed information about their monthly rate of asthma exacerbations, as well as about the consumption of short-acting β_2-adrenergic agonists (SABA) reported as number of inhalations/day, fixed combinations of inhaled corticosteroids (ICS) and long-acting β_2-adrenergic agonists (LABA) expressed as µg/day, and oral corticosteroids quantified as daily intake (mg) of prednisone. Moreover, lung function was recorded and eventual adverse events attributable to omalizumab were carefully checked.

Table 1. Baseline patient characteristics.

Age (y)	46.1 ± 11.5
Sex (males/females)	4/12
Weight (kg)	68.2 ± 13.9
Height (cm)	157.7 ± 9.1
Body mass index (kg/m^2)	27.5 ± 5.4
FEV_1 (% predicted)	53.6 ± 14.6
FEV_1/FVC (%)	56.3 ± 9.5
Total serum IgE (IU/ml)	289.1 ± 164.7
Monthly dose of omalizumab (mg)	440.6 ± 168.5

Statistical analysis

All data are expressed as mean ± standard deviation (SD). Statistical analysis of the results was performed using SPSS (SPSS Inc., Chicago, IL, USA). Furthermore, student t-test was used to evaluate data referring to lung function. A p value lower than 0.05 was considered as significant.

Results

All 16 patients with uncontrolled, exacerbation-prone and oral steroid-dependent allergic asthma, who were selected to start add-on anti-IgE therapy between March 2007 and February 2010, experienced a marked reduction of both daily symptoms and nocturnal awakenings due to asthma. Furthermore, no patient needed to be hospitalized

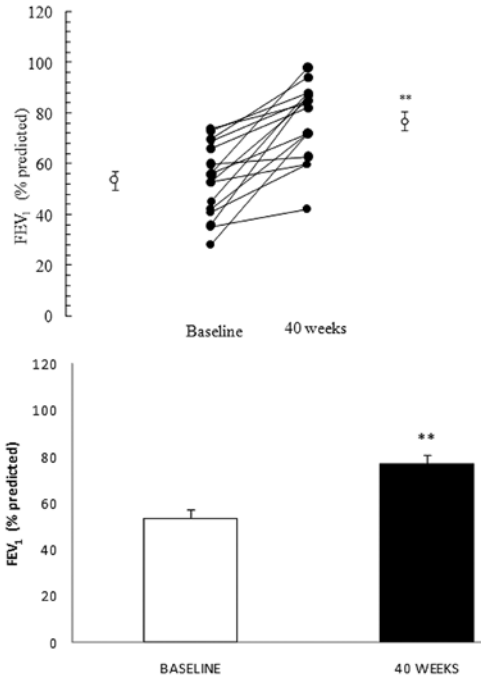

Figure 1. Effect of omalizumab on FEV_1. Top: individual values of FEV_1 recorded before (baseline) and after treatment with omalizumab (40 weeks). Bottom: mean percentage FEV_1 values, recorded at baseline (white column) and after 40 weeks of add-on treatment with omalizumab (black column). ** $p < 0.01$.

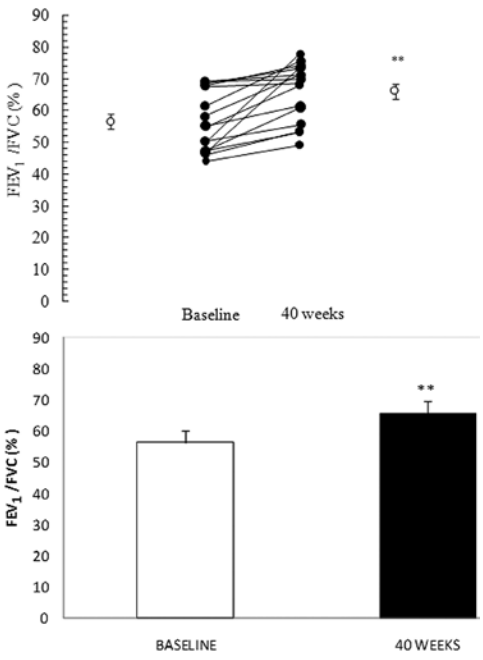

Figure 2. Effect of omalizumab on FEV_1/FVC ratio. Top: individual values of FEV_1/FVC recorded before (baseline) and after treatment with omalizumab (40 weeks). Bottom: mean FEV_1/FVC values, recorded at baseline (white column) and after 40 weeks of add-on treatment with omalizumab (black column). ** $p < 0.01$.

during the observation period. These relevant clinical improvements were paralleled by a drastic decrease in the use of inhaled SABA bronchodilators as rescue medications whose consumption dropped, after 40 weeks of add-on treatment with omalizumab, from 8.4 ± 3.5 to 1.6 ± 1.1 daily inhalations. A more moderate effect of omalizumab was reported by our patients about the utilization of ICS/LABA combinations, whose daily doses of their corticosteroid and bronchodilator components underwent a reduction from 1,192.5 ± 134.0 to 761.2 ± 183.9 μg and from 56.0 ± 30.6 to 41.6 ± 35.7 μg, respectively. With regard to the impact of omalizumab treatment on lung function, after 40 weeks all patients maintained the already achieved improvement of airway obstruction, documented by relevant changes in both FEV_1 and FEV_1/FVC (forced vital capacity) ratio, whose mean values increased versus baseline from 53.6 ± 14.6 to 77.0 ± 14.9% pred. ($p < 0.01$) (Figure 1) and from 56.3 ± 9.5 to 65.8 ± 9.2% ($p < 0.01$) (Figure 2), respectively. Among the 16 patients enrolled in this study, 13 have been followed-up for at least 56 weeks, and in these subjects the changes in lung function resulted to be stabilized or further improved throughout the observation period (data not shown).

All patients experienced a remarkable attenuation of both frequency and severity of their acute asthma exacerbations, whose mean monthly numbers decreased from 1.1 ± 0.6 to 0.2 ± 0.4 ($p < 0.01$) (Figure 3). In 13 patients this effect contributed to allow the interruption, after a gradual dose tapering, of the continuous or almost continuous use of oral corticosteroids, and the remaining 3 subjects were anyway able to reduce their daily maintenance dose of prednisone. Therefore, in this study population the overall consumption of prednisone sharply fell, with respect to pre-omalizumab treatment, from 22.6 ± 5.0 to 1.2 ± 2.9 mg/day ($p < 0.01$) (Figure 4). The lack of necessity to take oral corticosteroids lasted well beyond 40 weeks in those subjects who have been monitored for longer periods, thus allowing especially to some female patients to lose weight as a result of the reversal of corticosteroid systemic side-effects. In particular, with respect to baseline values a weight reduction was detected after 40 weeks of treatment with omalizumab in 9 of 12 female patients (from 65.1 ± 7.6 kg

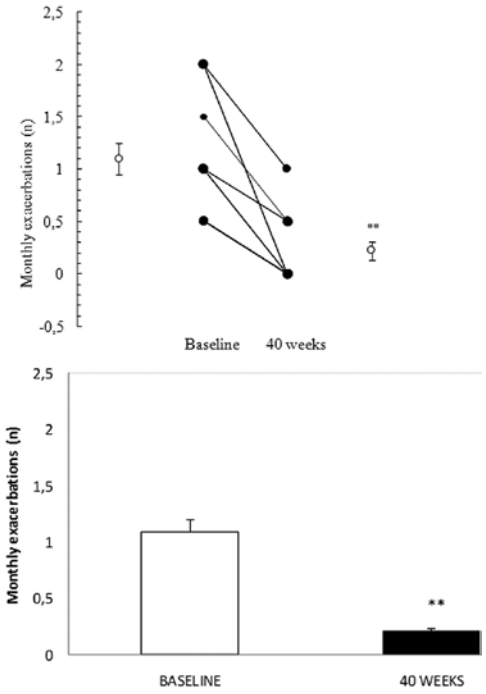

Figure 3. Effect of omalizumab on monthly exacerbations of asthma. Top: individual numbers of monthly exacerbations reported before (baseline) and after treatment with omalizumab (40 weeks). Bottom: mean monthly numbers of exacerbations, reported at baseline (white column) and after 40 weeks of add-on treatment with omalizumab (black column). ** $p < 0.01$.

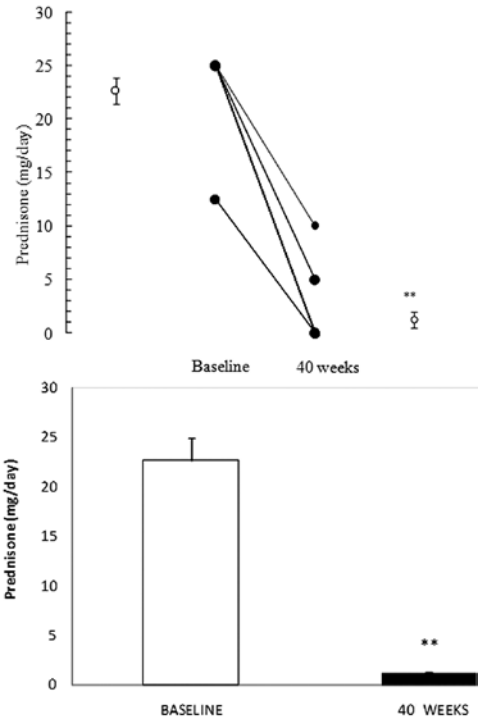

Figure 4. Effect of omalizumab on daily prednisone use. Top: individual daily dosages of prednisone, assessed before (baseline) and after treatment with omalizumab (40 weeks). Bottom: mean prednisone daily dosages, assessed at baseline (white column) and after 40 weeks of add-on treatment with omalizumab (black column). ** $p < 0.01$.

to 59.2 ± 8.7 kg). Moreover, in our patients anti-IgE therapy contributed to improve their exercise tolerance and psychological status, which showed a marked tendency to depression and anxiety before starting add-on omalizumab treatment. Furthermore, in 5 patients who persistently had increased blood numbers of eosinophils (15.9 ± 8.0% of total WBC count; absolute number: 1,588.0 ± 956.9/µl) despite a long-lasting therapy with inhaled and systemic corticosteroids, the peripheral counts of these cells decreased down to near normal levels (6.3 ± 2.3% of total WBC count; absolute number: 462.0 ± 262.3/µl) after 16 weeks of omalizumab treatment.

With regard to the adverse events attributable to omalizumab, in our study only slight local reactions at the level of injection sites, characterized by erythema, warmth and bruising, were detected in two patients. However, these reactions were restricted to the first two to three drug administrations, and resolved quickly and spontaneously without any pharmacologic treatment. On the basis of all such evaluations, the overall efficacy and tolerability of omalizumab were rated as excellent or good by both patients and physicians.

Discussion and conclusion

All 16 allergic asthmatic patients enrolled in the present observational study expressed a particular subphenotype of severe asthma, characterized by very frequent exacerbations and by an impaired lung function. Such a "exacerbation-prone asthma" often requires, in addition to high dosages of inhaled LABA and corticosteroids, also an almost continuous oral intake of the latter drugs. Furthermore, some of these patients may also have a peripheral blood eosinophilia, refractory to both inhaled and systemic corticosteroids. Because asthma is difficult to be controlled by optimal standard treatments in patients like those enrolled in our descriptive investigation, they can potentially benefit from IgE-targeted therapies. Indeed, IgE are crucially involved in the immunopathologic

mechanisms underlying allergic asthma [36]. Consistently with these considerations, after 40 weeks of add-on treatment with omalizumab we observed in all our 16 patients a very drastic reduction in the frequency of asthma exacerbations, associated with a striking decrease in the consumption of oral corticosteroids. Such effects were paralleled by a better control of asthma symptoms, as well as by a marked reduction in the use of rescue bronchodilators. These patients also experienced a substantial decrease in the loss of working hours and days, which together with better exercise tolerance and psychological conditions contributed to the reported overall improvement in quality of life, consistent with previous findings [34]. It is also noteworthy that omalizumab improved chronic airflow limitation, as shown by the relevant increases of FEV_1 and FEV_1/FVC ratio. Such a globally favorable pharmacodynamic pattern of omalizumab is further corroborated by its excellent tolerability and safety profile. Moreover, in the subgroup of these difficult-to-treat asthmatic subjects who were also characterized by the presence of increased blood eosinophil numbers, omalizumab induced a marked reduction of peripheral eosinophil counts.

The very effective therapeutic action of omalizumab can reasonably result from its capacity to markedly dampening allergic airway inflammation. Indeed, omalizumab binds free IgE regardless of their antigen specificity, thereby being potentially useful for both perennial and seasonal allergies as well as for their exacerbations [16]. It is well known that, in addition to aeroallergens, other frequent triggers of acute asthma exacerbations are respiratory viruses [37]. In particular, viral infections can cause the production of virus-specific IgE, and also an increased expression of high affinity IgE receptors on lung dendritic cells [38]. Therefore, an interference of omalizumab with virus-induced IgE responses could also contribute to the remarkable inhibitory effect of this drug on asthma exacerbations, detected by us and many other authors [21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]. With regard to airflow limitation, a decrease in free IgE does not necessarily affect FEV_1 and FEV_1/FVC ratio [39]. Indeed, the effects of omalizumab on FEV_1 are quite controversial, and many studies have shown no significant change in such a functional parameter [28]. However, some increases in FEV_1 have been occasionally recorded after several weeks of treatment with omalizumab [25, 40]. Furthermore, according to a recent open-label study performed on patients with uncontrolled severe allergic asthma, randomized to receive best standard anti-asthma therapy with or without omalizumab, in comparison with control values a significant increase in percentage predicted FEV_1 has been observed throughout a 1-year period of anti-IgE treatment [41]. Our present results suggest a possible association between the reduction in exacerbation frequency, elicited by omalizumab, and the recorded improvement of airflow limitation. This observation is consistent with the reported relationship between recurrence of asthma exacerbations and deterioration of lung function [42]. In particular, the exacerbation-prone subphenotype may be characterized by a vicious pathogenic circuit sustained by exacerbation-driven inflammation leading to bronchial narrowing, which in turn predisposes to repetitive exacerbation cycles. Such a self-perpetuating airway injury can thus be interrupted by omalizumab. The dramatic decrease in asthma exacerbation rate, observed in our study during treatment with omalizumab, made it also possible to stop or reduce oral administration of corticosteroids. This finding confirms the oral corticosteroid-sparing potential of omalizumab, reported by recent analyses carried out in Italian, French and German patients with severe allergic asthma [32, 33]. Taken together, such data thereby emphasize the effectiveness of omalizumab in attenuating or even abrogating the eventual morbidities due to the chronic use of systemic corticosteroids in inadequately controlled, severe atopic asthma. In comparison with the extraordinary capacity of omalizumab to limit oral corticosteroid use, we noticed a more moderate effect of anti-IgE therapy in lowering the required dosages of ICS-LABA combinations; therefore, this observation is consistent with the role of omalizumab as add-on treatment, absolutely not alternative to or substitutive for standard inhaled anti-asthma therapeutic strategies.

Finally, omalizumab was able to reverse peripheral blood eosinophilia in those five patients, included in our study, who exhibited this particular feature. Peripheral blood

eosinophils are considered reliable inflammatory markers in allergic asthma, and they are reportedly sensitive to the inhibitory action of omalizumab [43, 44, 45]. In this regard, it is notable that a very recent pooled analysis of data referring to several trials involving patients with moderate-to-severe persistent allergic asthma treated with omalizumab, has found some degree of correlation between omalizumab-induced decrease in peripheral blood eosinophils and various clinical and functional outcomes; the latter included a reduced requirement for management of exacerbations with oral steroid bursts, an increased FEV_1 and a positive global evaluation of treatment effectiveness by investigators [45]. Interestingly, our eosinophilic patients maintained high blood eosinophil counts in spite of continuous or almost continuous treatments with systemic corticosteroids, known to be strong inducers of eosinophil apoptosis. This implies that such patients were characterized by a steroid-refractory blood eosinophilia [46]. Conversely, these same asthmatic subjects resulted to be sensitive to the anti-eosinophilic action of omalizumab. This effect is probably due to a powerful induction of eosinophil apoptosis. In fact, omalizumab can significantly increase the staining of peripheral eosinophils with apoptotic markers such as annexin V [47]. The pro-apoptotic action of omalizumab is associated with a decrease in T cell production of granulocyte macrophage colony stimulating factor (GM-CSF), an important mediator involved in eosinophil growth and survival [47]. In this regard, it is noteworthy that in addition to reducing blood eosinophil counts, omalizumab is also capable of decreasing eosinophil numbers in both induced sputum and bronchial biopsies obtained from asthmatic subjects [48].

In conclusion, our clinical, functional, and hematologic observations referring to some outpatients with difficult-to-treat allergic asthma, are consistent with several other recently published real-life trials performed in various European countries. Like all real-life observational investigations, also the present descriptive study lacks a placebo control. However, despite this unavoidable limitation, our findings further confirm that omalizumab can be used as a very effective and well tolerated additional treatment in the management of exacerbation-prone, oral steroid-dependent atopic asthma. Therefore, availability of omalizumab in medical practice represents a true advance in the management of severe persistent allergic asthma. Indeed, this drug makes it possible to significantly improve disease control in many of those atopic patients who, though receiving an optimized standard treatment, still experience a persistence of respiratory symptoms and a high frequency of asthma exacerbations. However, further and longer studies are needed in order to evaluate whether an anti-IgE therapy might also effectively prevent and/or attenuate the development of immunologically-mediated bronchial structural changes (airway remodeling) and the related progressive functional decline, thus possibly affecting the natural history of exacerbation-prone, difficult-to-treat asthma.

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