Original paper

Omalizumab in middle-aged or older patients with severe allergic asthma-COPD overlap

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Abstract

Introduction: Biological therapies used for severe asthma may be useful even for middle-aged or older patients who have a history of severe allergic asthma with a chronic obstructive pulmonary disease (COPD) overlap phenotype.
Aim: To show omalizumab efficacy in severe allergic asthma-COPD overlap disease.
Material and methods: We report our data of a retrospective study on 11 patients (mean age: 67.18 years) with a positive history of severe allergic asthma treated with omalizumab. They all presented limited reversibility of airway obstruction and signs of chronic bronchitis at radiological examinations, as in asthma-COPD overlap. Omalizumab improved conditions in terms of reduced exacerbations as well as asthma control test (ACT) and Asthma Quality of Life Questionnaire (AQLQ) scores.
Results: Clinical improvement was seen already in the first year with significantly increased ACT scores ($p < 0.0001$) and a significantly decreased number of exacerbations ($p < 0.001$). Furthermore, our data showed a significant inverse correlation over time between the number of exacerbations and ACT ($r = –0.83$, $p < 0.0001$), AQLQ symptoms ($r = –0.87$, $p < 0.0001$), forced expiratory volume in 1 s (FEV_1) ($r = –0.71$, $p < 0.001$) and FEV_1/forced vital capacity (FVC) ($r = –0.43$, $p = 0.04$). There also was a positive correlation between ACT and FEV_1 ($r = 0.74$, $p < 0.0001$), ACT and AQLQ symptoms ($r = 0.93$, $p < 0.0001$), FEV_1 and AQLQ symptoms ($r = 0.67$, $p < 0.001$). All parameters continued to improve during the second year of treatment.
Conclusions: Omalizumab may be relevant as a therapeutic option even in middle-aged and older patients with severe asthma.

Key words: severe allergic asthma-COPD overlap, middle aged-older patients, omalizumab.

Introduction

The term "asthma-chronic obstructive pulmonary disease (COPD) overlap" has been suggested to be used in patients commonly seen in clinical practice with features of asthma and COPD [1].

Asthma and COPD include several different phenotypes, such as eosinophilic COPD, asthma with smoking and severe asthma in older patients with incomplete airflow reversibility or COPD patients who have a significant response to bronchodilators [2]. Patients with features of both asthma and COPD are treated as patients with asthma, with inhaled corticosteroids (ICS) in association to long-acting bronchodilators (LABA), to reduce the risk of severe exacerbations and death. Treatment with LABA in monotherapy or in association with long-acting muscarinic agents (LAMA) even if indicated in COPD, could increase the risk of severe life-threatening exacerbations in asthma [3, 4].

Asthma and COPD overlap (ACO) in middle-aged or older patients may have a common underlying mechanism as T2 inflammation involving Th2, eosinophils and in general allergic pathways [5, 6]. It has been reported that differential diagnosis of asthma, COPD and ACO could be exploited measuring fractional exhaled nitric oxide (FENO) as this is a biomarker of airway inflammation; therefore FENO is expected to be increased in asthma and ACO patients rather than in COPD patients [7].

Biological therapies which target these pathways are used for the treatment of severe refractory asthma but for asthma-COPD overlap data are needed [8].

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Omalizumab is an effective therapy for patients with severe allergic asthma binding to serum IgE and reducing mast cell, basophil, dendritic and B cell responses [9–11]. Furthermore, it has been shown to reduce the bronchial reticular basement membrane thickness and eosinophil infiltration, typical of severe asthma re-modelling [12].

Aim

As to date there have been limited data available on the efficacy of omalizumab in populations with overlapping asthma and COPD, we report our experience with omalizumab in eleven patients with a positive history of allergic severe asthma due to sensitization to at least one perennial allergen, who started treatment with a limited reversibility of airway obstruction and signs of chronic bronchitis at radiological examination.

Material and methods

We present a retrospective study on 11 patients (6 females and 5 males), who were referred to our Allergy Unit for a positive history of allergic asthma with frequent exacerbations.

All eleven patients were non-smokers, had developed asthma in childhood, adolescence or young adulthood and were now either middle aged or older (mean age: 67.18 years). They had asthma symptoms with cough, hoarseness, intermittent chest tightness, daily and nocturnal wheezing, reported activity limitations because of dyspnoea and had needed emergency department visits for asthma exacerbations. Other chronic disorders, such as heart failure or lung diseases, as well as asthma comorbidities were not present. Asthma treatment consisted in high-dose ICS + LABA but patients reported 2 ≥ exacerbations/year requiring OCS. Spirometry tests showed persistent airflow limitations as the forced expiratory volume in 1 s (FEV_1) was < 80% of the predicted value and the bronchodilation test negative as the FEV_1 did not increase by at least 12%/200 ml within 30 min after inhalation of 400 µg of salbutamol.

All patients had positive allergic skin tests to perennial allergens of the Mediterranean area, either *house dust mites* or *Parietaria judaica* pollens; total IgE levels were 35–1500 KU/l.

Therefore, as all 11 patients had a history of long-standing allergic asthma and presented persistent airflow limitations, the diagnosis was of asthma-COPD overlap with an allergic phenotype. Omalizumab treatment was started by calculating the necessary dose of omalizumab for each individual patient according to the baseline weight and total IgE levels. Omalizumab injections were given subcutaneously with a maximum dose of 600 mg twice monthly.

Patients' medical history in the previous year, before starting omalizumab treatment, was collected, including disease status, current treatment, lung function and medical resource use.

Data were collected over a 2-year period: all patients were evaluated at T0, before starting omalizumab treatment, T1 (at 1 year) and T2 (at 2 years) in terms of Asthma Control Test (ACT), a 5-item quick test that provides a numerical score to assess asthma control in the previous 4 weeks (a lower score represents uncontrolled asthma), number of exacerbations, FEV_1, FEV_1/FVC, that is the ratio which represents the proportion of vital capacity that can be exhaled in the first second of forced expiration and Asthma Quality of Life Questionnaire (AQLQ) scores. The AQLQ score is the mean of 32 disease-specific quality of life questions which relate to the previous 2 weeks and assess four domains including symptoms, activity limitations, emotional function and environmental stimuli, with a lower AQLQ representing greater impairment of the health status.

All eleven patients, therefore, had the characteristics of patients with ACO.

Primary outcome was the change in symptom control measured by ACT, reduction in the number of exacerbations, increase in AQLQ scores and increase in FEV_1, FEV1/FVC parameters.

The study was approved by the Ethics Committee of the University Hospital "G. Martino" of Messina, Italy (registration number 15/19).

Statistical analysis

Data analyses were carried out using SPSS 22 (IBM Corporation, Armonk, NY, USA) and R v3.6.1. Descriptive parameters are expressed as median and interquartile range (IQR). Differences in ACT, FEV_1, FEV_1/FVC, number of exacerbations and AQLQ were analysed using the Friedman test and Wilcoxon test for paired non-parametric data. To evaluate the overall correlation, we used the repeated measures correlation [13–15]. Results were considered statistically significant with $p < 0.05$.

Results

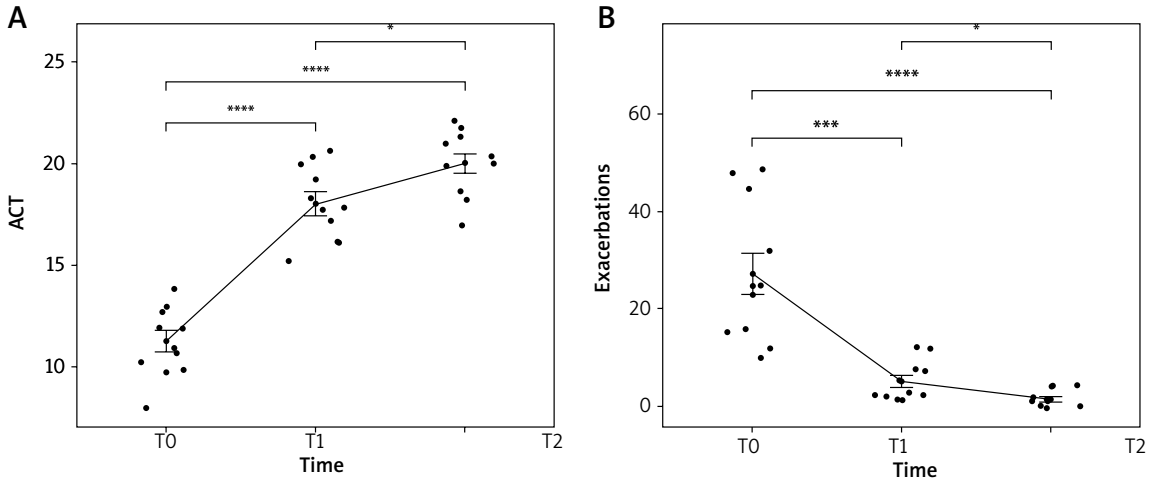
No significant differences and correlations in gender and age were found in our population of patients with ACO treated with omalizumab. Routine blood tests were within normal range, including blood count, liver and renal function and inflammation markers. All 11 patients presented statistically significant improvement of severe allergic asthma for values of ACT, number of exacerbations, FEV_1 and AQLQ symptoms, limitations, emotive functions and environmental stimuli from T0 to T2. Only FEV1/FVC did not increase in a statistically significant manner. All differences of parameters between T0, T1 and T2 are reported in Table 1.

All 11 patients followed omalizumab treatment regularly with complete adherence to the prescribed schedule.

The ACT score increased significantly from T0 to T1 ($p < 0.0001$), T1 to T2 ($p < 0.01$) and the number of exac-

Table 1. Median values and interquartile ranges (IQR) extracted for T0, T1, T2 for ACT, AQLQ, exacerbations, FEV_1, FEV_1/FVC parameters and *p*-value of non-parametric Friedman test

Parameter	T0	T1	T2	Test	*P*-value
ACT	11 (2.5)	18 (3)	20 (1.5)	Friedman	< 0.0001
No. of exacerbations	25 (23)	3 (5.5)	1 (3)	Friedman	< 0.0001
FEV_1	55 (15.5)	59 (17.5)	65 (21)	Friedman	< 0.01
FEV_1/FVC	84 (15.5)	86 (21)	87 (24.5)	Friedman	0.16
AQLQ symptoms	21 (4.5)	46 (12)	53 (9.5)	Friedman	< 0.0001
AQLQ activity limitations	26 (4)	45 (9.5)	48 (9)	Friedman	< 0.0001
AQLQ emotive functions	11 (4)	18 (2)	18 (3)	Friedman	< 0.001
AQLQ environmental stimuli	10 (2.5)	15 (2.5)	14 (1.5)	Friedman	< 0.0001



,,*** and **** indicate significance of Wilcoxon rank sum test with p-value < 0.1, < 0.01, < 0.001 and < 0.0001.*

Figure 1. Jitter plots shows ACT (A) and the number of exacerbations (B) measured at T0, T1 and T2

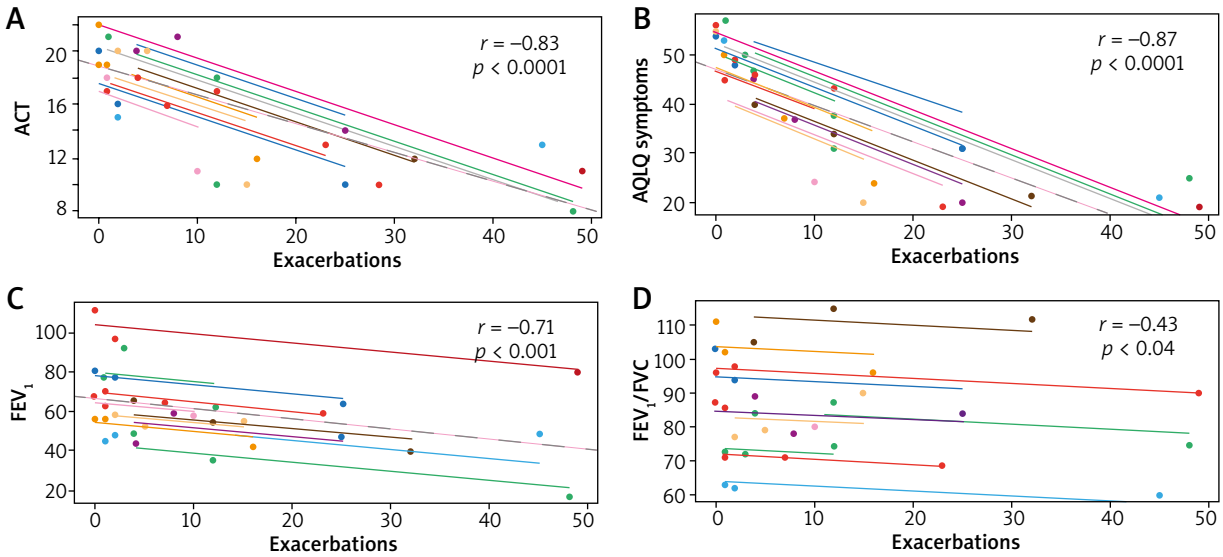


Figure 2. A – Overall correlation between exacerbations and ACT with $r = -0.83$, $p < 0.0001$. **B** – Correlation between exacerbations and AQLQ symptoms with $r = -0.87$, $p < 0.0001$. **C** – Overall correlation between exacerbations and FEV_1 with $r = -0.71$, $p < 0.0001$. **D** – Overall correlation between exacerbations and FEV_1/FVC with $r = -0.43$, $p = 0.04$. Observations from the same participant are given in the same colour, with corresponding lines to show the linear fit of multiple measures (T0, T1, T2) for each participant

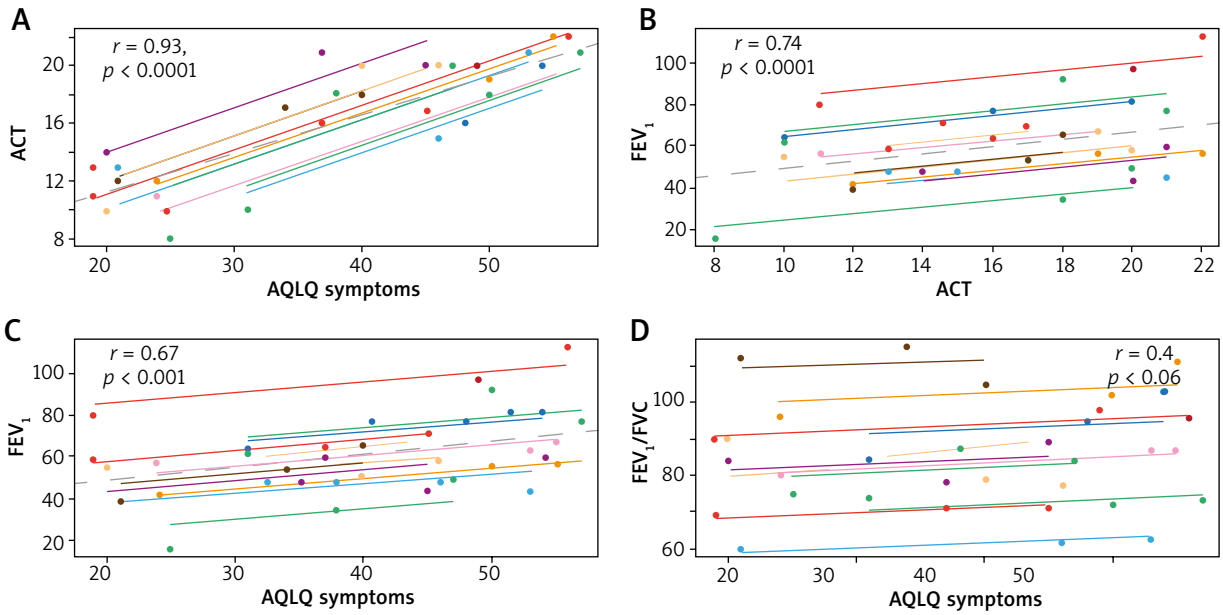


Figure 3. A – Overall correlation between AQLQ symptoms and ACT with $r = 0.93$, $p < 0.0001$. **B** – Correlation between ACT and FEV_1 with $r = 0.74$, $p < 0.0001$. **C** – Overall correlation between AQLQ symptoms and FEV_1 with $r = 0.67$, $p < 0.001$. **D** – Overall correlation between AQLQ symptoms and FEV_1/FVC with $r = 0.40$, $p = 0.06$. Observations from the same participant are given in the same colour, with corresponding lines to show the linear fit of multiple measures (T0, T1, T2) for each participant

erbations decreased significantly over time from T0 to T1 ($p < 0.001$) and T1 to T2 ($p < 0.01$) as shown in Figure 1. In addition, all AQLQ parameters increased significantly from T0 to T1 ($p < 0.0001$). No significant differences in FEV_1 and FEV_1/FVC were found over time. Additionally, a significant inverse correlation was observed over time between the number of exacerbations and ACT ($r = –0.83$, $p < 0.0001$), exacerbations and AQLQ symptoms ($r = –0.87$, $p < 0.0001$), exacerbations and FEV_1 ($r = –0.71$, $p < 0.001$), exacerbations and FEV_1/FVC ($r = –0.43$, $p = 0.04$) as shown in Figure 2. We also observed a positive correlation between AQLQ symptoms and ACT ($r = 0.93$, $p < 0.0001$), ACT and FEV_1 ($r = 0.74$, $p < 0.000$), AQLQ symptoms and FEV_1 ($r = 0.67$, $p < 0.001$), AQLQ symptoms and FEV_1/FVC ($r = 40$, $p = 0.06$) as shown in Figure 3.

Radiologic diagnostic tests, such as either chest X-rays or computed tomography (CT) were performed at T0. Scan images showed signs of chronic bronchitis such as increased air trapping, typical of emphysema, or increased wall thickness, typical of fibrosis.

None of the 11 patients discontinued omalizumab during the 2-year follow-up due to adverse events. Overall omalizumab treatment was well tolerated with only slight pain in the injection site during subcutaneous injection in 2 female patients out of the 11 patients studied.

Discussion

Asthma-COPD overlap in middle-aged or older patients is characterized by airway obstruction typical of asthma and limited reversibility typical of COPD, therefore it is described as difficult to manage and phenotype [16].

At present it is treated with ICS/LABA in association with ipratropium bromide as a LAMA in add-on treatment but, according to severity, different therapeutic approaches are needed [17]. One specific treatment in the presence of allergic sensitization to perennial allergens, such as house dust mites [18] and in the Mediterranean area, *Parietaria judaica* pollens [19], is anti-IgE treatment with omalizumab [20].

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody, which prevents free IgE from binding to their high and low affinity receptors on effector cells interfering with the allergic cascade in patients with severe allergic asthma [21].

While the role of IgE in severe asthma has already been well established, the role of omalizumab in COPD populations is still under study [21, 22]. Stoll *et al.* [23] showed how COPD and allergic asthma are characterized by a similar over-expression of the high-affinity IgE receptor on plasmacytoid dendritic cells. In another study [24], IL-17, a key role cytokine in asthma pathogenesis was higher in COPD patients. Moreover, Th2 inflammation

might be present in COPD and, therefore, omalizumab treatment is beneficial in this population [25].

At present, data on omalizumab treatment in asthma-COPD overlap populations are limited as patients with the diagnosis of COPD are usually excluded from clinical trials [26, 27].

Furthermore, it is still difficult to define an asthma-COPD overlap status in real-life settings [28]. The clinical diagnosis up to now was based on the positive history for asthma and lung function measurements with FEV_1/FVC < 0.7 or FEV_1 < 80% of predicted value, in the presence of an obstructive spirometry airflow curve with a negative bronchodilation test [29]. The presence of a positive history for allergic respiratory diseases with sensitization to inhalant allergens can also help to distinguish asthma-COPD overlap from COPD [30].

In our study, omalizumab treatment was efficacious for patients with asthma-COPD overlap, non-responsive to ICS/LABA with LAMA as add-on treatments. The study data are on 11 patients, non-smokers, with the history of severe allergic asthma, positive specific IgE to perennial allergens such as dust mites and *Parietaria judaica* pollens with signs of COPD at chest X-rays or CT.

Our data showed that patients treated with omalizumab might improve their condition in terms of reduced exacerbations, increased FEV_1, improved ACT and AQLQ. Clinical improvement, in our patients, correlated, especially after the first year of therapy, with significantly increased ACT scores ($p < 0.0001$) and significantly decreased number of exacerbations ($p < 0.001$). Furthermore, patients' quality of life significantly improved in the first year of omalizumab treatment as AQLQ scores significantly increased ($p < 0.001$). Spirometry parameters, such as FEV_1, increased even if not statically significantly, and no bronchial reversibility was achieved. Bronchodilator-mediated reversibility is usually proposed as a diagnostic criterion to differentiate asthma from COPD, but it does not rule out asthma-COPD overlap and does not consider that reversibility may not be present in severe asthma [5]. Nevertheless, in our study all real-life indicators, such as the number of exacerbations, ACT and AQLQ scores, significantly improved with omalizumab as an add-on therapy continuing to improve during the second year of treatment. Omalizumab, therefore, ensured that the goals of asthma-COPD overlap treatment were reached, such as prevention of exacerbations, symptoms relief and quality of life improvement.

Data reported in our study, unfortunately, have some bias as they were collected retrospectively and on a small group of patients. Nevertheless, they show the coexistence of asthma-COPD overlap in middle-aged or older patients refractory to conventional pharmacological therapies, sensitized to at least one perennial allergen and responders to omalizumab as an add-on treatment.

Conclusions

In our study, treatment with omalizumab resulted in asthma control and improved quality of life in a small population of middle-aged or older patients with asthma-COPD overlap.

Future studies on omalizumab efficacy in populations with the same characteristics will provide additional insights for treatment of patients who have features of both asthma and COPD with an allergic phenotype.

Conflict of interest

The authors declare no conflict of interest.

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