A multicenter approach to evaluate omalizumab effectiveness in Samter's triad

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Abstract

Omalizumab proved to be very effective in improving control of severe atopic asthma. Many small-sized studies suggested a potential role for omalizumab in the management of aspirin-exacerbated respiratory disease. The aim of this study is to describe the effectiveness of omalizumab in a multicentre group of patients with Samter's triad. We retrospectively enrolled eight patients (5 females) with Samter's triad who underwent at least one year of omalizumab therapy. Clinical data, functional parameters and questionnaires for asthma and nasal polyposis control were collected at baseline and follow-up. We observed a significant reduction of moderate-to-severe asthma exacerbations, together with an increase of FEV1 and a reduction of steroids intake. An improvement in asthma control and nasal symptoms was also reported. This multicenter study confirms the effectiveness of omalizumab in patients affected by Samter's triad. Omalizumab may represent a potential therapeutic option for the management of this disease.

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Introduction

Aspirin-exacerbated respiratory diseases (AERDs) is a group of respiratory disorders characterized by a non-IgE mediated immunological intolerance to acetylsalicilic acid. Among AERDs, the most recognizable disease entity is the so-called Samter's triad: bronchial asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP) and intolerance to aspirin or other NSAIDs. Firstly described by Widal [1], the majority of patients affected by Samter's triad shows specific clinical features, with a typical onset in the third-fourth decade of life [2]. Asthma is often refractory to inhaled therapy, including high dose inhaled corticosteroids (ICS) plus long-acting beta2-agonist and/or antimuscarinic agents, while CRSwNP can be massive, requiring multiple surgical treatments [3,4].

Due to these clinical features, Samter's triad is estimated to contribute to the 15% of severe asthmatic population, and, therefore, may be considered a specific indication for biologic treatment [5]. However, limited data is available on this topic [6]. Among biologic drugs approved for the treatment of asthma, anti-IgE omalizumab was reported to significantly improve asthma control and quality of life in these patients, even though only in limited and monocentric case-series [7–9]. Moreover, a significant reduction in urinary concentrations of LTE4 and PGD2 in patients treated with omalizumab was reported, suggesting a specific activity of this drug in regulating this specific type of inflammation [10].

The aim of this multicentre study was to investigate the effectiveness of omalizumab in terms of clinical and functional improvement in patients affected by Samter's triad.

Methods

Study design and population

In this multicentre study, we retrospectively recruited patients diagnosed with Samter's triad and treated with omalizumab.

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Patients were enrolled from three Centres: Respiratory Diseases Unit of Siena University, Immunology and Cell Therapies Unit and Interdisciplinary Internal Medicine of the Careggi University Hospital, Florence, Italy. Demographic, clinical, functional, immunological and therapeutic data was collected and entered in an ad hoc created electronic database shared by all the centres. Clinical data comprised asthma exacerbation rate and severity. Specific questionnaires for evaluation of asthma and CRSwNP control (Asthma Control Test, ACT, and 22-item SinoNasal Outcome Test, SNOT22) were reviewed from clinical records.

Pulmonary functional tests (PFTs) were collected at baseline and after 1 year of therapy. Informed consent was acquired from every patient included in the study.

PFTs

The following lung function parameters were recorded according to ATS/ERS standards [11,12], with corrections for temperature and barometric pressure: FEV1, FVC, FEV1/FVC, PEF, FEF 25-75%.

Statistical analysis

Data was expressed as mean ± standard deviation (SD). Non parametric tests (Mann-Whitney and Wilcoxon ranked test) were used to perform data analysis. Microsoft Excel and Graphpad Prism 5.0 for Windows were used for statistical analysis and to plot the figures.

Results

We retrospectively enrolled 8 patients (5 females, 54.8±11.6 years old) in this study. Demographic features, clinical and immunological parameters and functional data are reported in Table 1.

The majority of our patients were non-smoker females: the clinical onset of disease fell in the fourth decade of life, as expected. Despite general moderate-to-high dosage of ICS and oral corticosteroids (OCS) assumption as maintenance therapy in 3/8 patients, we observed a suboptimal control of asthma before therapy, as reported by moderate-severe exacerbation annual rate. Baseline ACT was available in all cases, while SNOT22 score was collected in 6/8 patients.

Baseline post bronchodilator PFTs showed a mild obstructive impairment of lung volumes, on average.

In our population, 5 patients did not show sensibilization to perennial allergens and were treated with omalizumab at the dosage of 300 mg/die because affected by chronic spontaneous urticaria (CSU). No significant differences in terms of age, sex, eosinophil

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Table 1. Demographic and clinical features, immunological and functional parameters of the study population at baseline, stratified according to atopic status.

Parameters	Total population	Non-atopic	Atopic	p-value*
Number	8	5	3	
Female sex (F)	5	3	2	1.00
Age (years)	56.7 ± 11.9	54.2 ± 10.4	61 ± 13.4	0.5714
Smoking status (pack/year)	1.3 ± 2.3	1.8 ± 2.7	0.6 ± 0.9	0.8633
- Current	1	1	0	
- Former	2	1	1	
- Never	5	3	2	
BMI (kg/m^2)	23.5 ± 1.6	24 ± 1.5	22.8 ± 1.5	0.5714
Age at onset (years)	37.6 ± 16.3	36.4 ± 8.8	39.6 ± 24	0.6528
Immunological data				
Total serum IgE (IU/ml)	167.9 ± 122.9	142.3 ± 65.1	202 ± 166	0.8571
Eosinophil cell count cell/mm^3	507.1 ± 307.3	602.5 ± 342.7	380 ± 180	0.6286
(%)	6.1 ± 3.6	6.5 ± 4.4	5.5 ± 2.8	0.8571
Clinical features				
No of moderate-severe exacerbations	2.8 ± 1.1	2.4 ± 0.5	4 ± 0.8	0.0668
ACT score	17.8 ± 4.6	19.4 ± 5	15.3 ± 2	0.4534
SNOT22 score	29 ± 8.8	29.5 ± 10.4	28 ± 4	1.00
PFTs°				
FEV1 l	2.3 ± 0.9	2.4 ± 0.9	2 ± 0.8	0.5714
(%)	(77.2 ± 14.4)	(82.5 ± 14.4)	(68.3 ± 9.4)	0.3929
FVC l	3.6 ± 1.2	3.4 ± 1.2	3.3 ± 1.1	0.7857
(%)	(95.3 ± 8.5)	(94.3 ± 10.9)	(96.8 ± 0.4)	0.7000
FEV1/FVC	64.6 ± 8.2	67.9 ± 7	59.1 ± 6.2	0.2500
PEF l/min	6.5 ± 2.2	6.9 ± 2.4	5.8 ± 1.4	0.5714
(%)	82.2 ± 12.5	87 ± 14.3	75 ± 1.4	0.4563
FEF 25-75% l/s	1.6 ± 1	1.9 ± 1.1	1.1 ± 0.5	0.4000
(%)	45.4 ± 22.9	54.9 ± 25.1	32.8 ± 10	0.4250

*p-value calculated between atopic and non-atopic subgroups; °all functional data was measured post-bronchodilator.

cell count and serum total IgE were found between CSU and not-CSU patients.

At follow-up (454.8 ± 208.7 days, mean ± SD), we observed a significant improvement of asthma control, as showed by the reduction of moderate-to-severe exacerbation rate (p=0.0103), with 4/8 patients not reporting any respiratory events during the treatment (Figure 1). Regarding inhalation therapy, we reported a non significant reduction of ICS dosage and Short-Acting Beta Agonists (SABA) as rescue therapy (p=0.2500 and p=0.0975, respectively). Among the three patients with OCS as maintenance therapy, 1 patient discontinued steroid assumption and 1 patient halved daily dosage. The third one discontinued OCS, but experienced two moderate exacerbations requiring temporary reintroduction of OCS. None of the patients took aspirin or other NSAIDs during the observation time.

Concerning PFTs, we observed a significant increase of post-bd FEV1, both in absolute and percentage of predicted values (p=0.0156 and p=0.0078, respectively) (Figure 2), while other functional parameters (FVC, PEF, FEF25-75 and FEV1/FVC ratio) improved, without reaching statistical significance (Table 2).

Regarding clinical questionnaires, our results showed an improvement of ACT and SNOT22 scores (p=0.0355 and p=0.0313, respectively) (Figure 3). None of the patients underwent sinus surgery during the observation time. None of the patients discontinued omalizumab therapy due to side effects. No significant averse events were reported during the observation time.

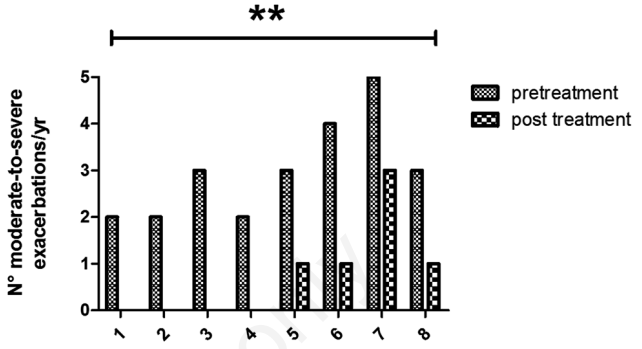
Discussion

In the present study, we described the experience of 8 patients affected by Samter's triad treated with omalizumab. Study population was recruited in three Centres specialized in diagnosis and management of severe asthmatic patients. Our results suggest a reliable effectiveness of omalizumab in improving asthma control, reducing exacerbation rate and need for OCS and relieving also CRSwNP symptoms.

The potential efficacy of omalizumab in this specific setting of patients has been already reported in literature [7,9,10,13]; however, all published studies were monocentric and predominantly consisted of case reports or little-sized case series. To our knowledge, this is the first multicenter study assessing this topic and, therefore, despite our limited sample size, provides further strength on the potential utility of omalizumab in Samter's triad. Moreover, 5 out of 8 patients included in the study didn't show any sensitization to perennial allergens and were treated with omalizumab due to CSU, showing the same results in terms of clinical efficacy on asthma control. On this field, our study confirmed and enlarged the result of a previous case report, describing the effectiveness of omalizumab in a non-atopic 15-year old female patient affected with Samters-triad and CSU [14]. Therefore, despite the limited evidence due to small samples size and pediatric setting, our study suggests that omalizumab could be useful in the management of patients

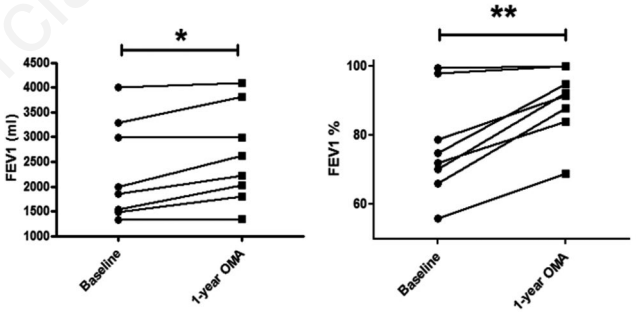
Table 2. Comparison of pulmonary functional parameters between baseline and 1-year of omalizumab treatment.

PFT parameters	Baseline	1-year omalizumab	p-value*
FEV1 l (%)	2.3 ± 0.9 (77.2 ± 14.4)	2.6 ± 0.9 (89.7 ± 9.2)	0.0156 0.0078
FVC l (%)	3.6 ± 1.2 (95.3 ± 8.5)	3.8 ± 1 (109.3 ± 9.1)	0.1563 0.1250
FEV1/FVC	64.6 ± 8.2	68 ± 7.5	0.0585
PEF l/min (%)	6.5 ± 2.4 82.2 ± 12.5	7.3 ± 2.4 93.8 ± 7.5	0.1250 0.1250
FEF 25-75% l/s (%)	1.6 ± 1.1 45.4 ± 22.9	1.7 ± 1.0 48.9 ± 19.6	0.2188 0.5625



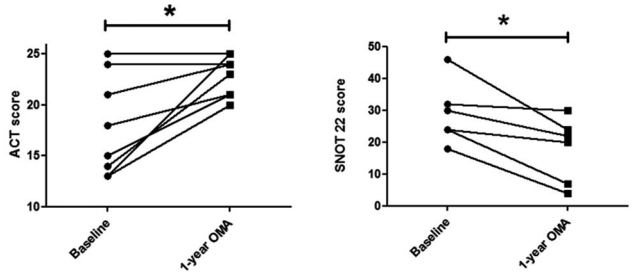
**, P= 0.0103.

Figure 1. Comparison of moderate-to-severe exacerbation events before and after one year of treatment with omalizumab.



*, P=0.0156; **, P=0.0078.

Figure 2. Evaluation of post-bronchodilator FEV1 (on the left: absolute values; on the right: percentage of predicted values) at baseline and at 1-year of follow-up.



*, P<0.05.

Figure 3. Comparison of ACT and SNOT22 scores before and after one year of treatment with omalizumab.

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affected by Samter's triad, regardless their atopic status. The specific effects of omalizumab in the pathogenesis of Samter's triad have not been clarified, probably due to the limited available data. However, pleiotropic effects of omalizumab in multiple IgE and non-IgE mediated diseases have been repeatedly demonstrated (such as non-atopic and non eosinophilic asthma), supporting further areas of application for this biological treatment. About Samter's triad, a single study demonstrated a significant reduction of specific disease biomarkers (such as urinary cysteinyl leukotriene) after treatment exposure, suggesting the potential of omalizumab in interfering with arachidonic acid metabolism [10].

Unfortunately, few data is available on the efficacy of other biological therapies on Samter's triad; conflicting results have been published on mepolizumab efficacy, while dupilumab showed promising results on sinus symptoms [6,15,16].

Interestingly, we also observed a significant improvement of CRSwNP symptoms and none of our patients underwent to sinus surgery during the observation time. Although it was limited by sample size, SNOT22 values between atopic and non atopic patients did not show any differences at statistical analysis. These data are surely interesting and are in line with previous reports, that demonstrated the efficacy of omalizumab in reducing symptomatic burden of CRSwNP, regardless the atopic status of patients [14,15]. On this topic, two phase III RCTs (POLYP 1 and 2), evaluating the efficacy of omalizumab on CRSwNP regardless diagnosis of asthma or atopic status, have been recently completed and results will shortly be published (NCT03280550 and NCT03280537).

This study has some limitations. First, the sample size, despite its multicenter design. Second, the retrospective nature of the study is typically exposed to referral and reporting bias, although the participating Centres are all highly experienced in the management of severe asthma, ensuring an accurate selection of patients.

In conclusion, this multicenter study confirms the efficacy of omalizumab in a specific disease entity as Samter's triad, regardless the atopic status of the patients. However, a larger, multicenter and prospective study is needed to strengthen these findings and confirm the therapeutic indication for omalizumab in this specific subgroup of asthmatic patients. The potential utility of omalizumab in the management of CRSwNP has been assessed and will be further evaluated in oncoming RCTs.

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