

Omalizumab treatment in Samter's triad: case series and review of the literature

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Abstract. – **OBJECTIVE:** Samter's triad is the combination of asthma, aspirin sensitization, and nasal polyposis. Few data are available on the use of omalizumab in this disease. The study aimed to describe the impact of omalizumab on clinical and functional parameters and the quality of life of a series of patients with Samter's triad. Moreover, we aimed to provide a review of the literature on this topic.

PATIENTS AND METHODS: We retrospectively described four patients with Samter's triad undergoing omalizumab therapy. Clinical, functional, and immunological data of these patients were collected at baseline and follow-up.

RESULTS: Reduction of asthma exacerbations and salbutamol rescue therapy were observed in all patients after anti-IgE treatment together with an improvement in the quality of life. A significant improvement in FEV₁, FVC, and FEF25-75 was observed. No major side-effects were observed. A total of 14 studies regarding omalizumab in aspirin-exacerbated respiratory diseases were included in the review, comprising 78 patients. All studies reported a good efficacy in improving asthma control; restoration of aspirin tolerance was repeatedly reported.

CONCLUSIONS: The results of our case series and review of the literature suggest that omalizumab effectively improves asthma control, lung function tests, and quality of life in patients with Samter's triad.

Key Words:

Omalizumab, Samter's triad, Therapy, Anti-IgE.

by massive infiltration of mastocytes, basophils, and eosinophils of the rhinosinus and respiratory mucosa, determining an over-production of leukotrienes and prostaglandins (in particular, LTE₄ and PGD₂)⁴, whose action is further enhanced by the upregulation of specific receptors⁵. From the clinical point of view, the onset of asthma in the AERD generally occurs in the third-fourth decade of life with persistent, difficult-to-control asthma and a predisposition for early bronchial remodelling⁶. The standard medical treatment is based on inhaled and/or systemic steroids, combined with anti-leukotrienes, inhaled bronchodilators, and aspirin desensitization protocols^{7,8}. This approach may not be sufficient, and patients may present unsatisfactory quality of life with major drug-induced side effects. Biological therapies approved for severe asthma could, therefore, be interesting in this context.

Omalizumab is a recombinant anti-IgE humanised monoclonal antibody⁹. Its efficacy in improving symptoms and reducing exacerbation rate in patients with severe asthma, resulting in a significant "steroid-sparing" effect, has been repeatedly demonstrated^{10,11}. However, no clinical trials have yet been conducted in this specific setting. Here we describe a case series of four patients with Samter's triad, treated with omalizumab to evaluate its clinical effect, followed by a review of the literature concerning this topic.

Introduction

The combination of asthma, nasal polyposis, and sensitization to aspirin is currently known as Samter's triad¹. It was first described in 1922 by Widal et al² and is an aspirin-exacerbated respiratory disease (AERD), affecting 15% of all patients with severe asthma³. From the pathogenetic point of view, AERD is characterized

Patients and Methods

We retrospectively collected four patients (3 males, 53 ± 14 years old) with Samter's triad, who were followed at our Centre. Clinical, demographic, functional, hematochemical, and immunological data were collected prior to initiation of omalizumab therapy and at follow-up (13 ± 5.1 months). The clinical control of asthma and nasal

polyposis was assessed by the Asthma Control Test (ACT) and Sino Nasal Outcome Test-22 (SNOT22) questionnaires. The study design was approved by the Ethics Committee of Siena University (Italy).

Clinical, functional, serological, and demographic features are reported in Table I. Patient 1, 2, and 4 started omalizumab therapy due to severe asthma associated with atopic sensitization to perennial allergens. Patient 3 was on therapy with omalizumab at the dose approved for Spontaneous Chronic Urticaria (CSU)¹², as he showed no sensitization to perennial allergens and no flow limitation at pulmonary function tests (PFTs). No patient had ever performed aspirin desensitization or specific allergen immunotherapy due to severe asthmatic symptoms. At baseline, all patients were on treatment with a high dose of inhaled corticosteroids (ICS) associated with inhaled long-acting β -2 agonists (LABA) and montelukast; all except for patient 3 were also in treatment with long-acting muscarinic receptors antagonists (LAMA) (tiotropium). Patient 4 was also treated with daily oral steroids (OCS) to maintain an acceptable control of asthma and nasal disease, while the other patients performed recurrent cycles of OCS. Concerning functional parameters, all patients (except for patient 3) showed mild-to-moderate obstructive impairment. All patients reported at least two moderate or severe asthmatic exacerbations requiring high doses of OCS and antibiotics in the previous year of omalizumab therapy. Regarding nasal polyposis, patient 1, 2, and 3 underwent functional endoscopic sinus surgery (FESS) twice, once and twice, respectively. Patients 1, 2, and 4 were on chronic therapy with combined intranasal steroids and azelastine, while patient 3 was taking only nasal steroid spray.

At follow-up (13 ± 5.1 months, *media* \pm *SD*), there was a notable clinical improvement of asthma and nasal polyposis control, certified by ACT and SNOT22 scores' improvement and by a significantly reduced use of rescue bronchodilator therapies. Of the three patients on treatment with as-needed salbutamol, two did not resort to rescue therapy at all; and patient 4 reduced salbutamol from an average of 5 to 2 weekly doses. Concerning exacerbations of asthma, only patient 4 reported a single mild episode associated with an acute viral rhinitis. All patients with FEV1 < 80% of predicted at baseline, showed a significant improvement at follow-up, with normalization of lung parameters in 2/3 cases. Regarding mainte-

nance therapy, no patient was taking OCS, and patient 4 reduced daily ICS dose (from 750 to 400 μ g/day, beclometasone equivalent). Surgical nasal polypectomy or FESS was not necessary during omalizumab therapy. No considerable modifications of intranasal treatment were made during the observation period. Eosinophilic blood counts showed a clear reduction in all patients. Omalizumab was very well tolerated, and no medium or severe side effects were observed: in the first 2 months of omalizumab therapy, a single patient reported frontal headache that subsequently resolved spontaneously.

Discussion and Review of the Literature

Omalizumab is a recombinant monoclonal antibody (mAb) that binds the Fc ϵ portion of the immunoglobulin (Ig)E antibodies. It reduces the total IgE levels preventing interaction with the high-affinity receptors (Fc ϵ RI) expressed on the surface of the target cells, receptor expression and the resulting inflammatory cascade^{13,14}. Omalizumab has been licensed since 2003 by the Food and Drug Administration (FDA) and since 2005 by European Medicines Agency (EMA) for the treatment of moderate-to-severe allergic asthma in adults and adolescents (≥ 12 years) with sensitization to a perennial allergen and symptoms not controlled by inhaled corticosteroids (ICS).

The clinical efficacy and safety of omalizumab in severe asthma have already been extensively demonstrated in many studies^{11,12,15}. Several clinical trials have also investigated the utility of omalizumab for the treatment of different IgE-related diseases besides allergic asthma, such as allergic rhinitis, food and drugs allergy, allergic bronchopulmonary aspergillosis, atopic dermatitis, eosinophilic granulomatosis with polyangiitis (EGPA) or mastocytosis¹⁶⁻²², with promising results. In our case series, omalizumab proved to be a safe and effective treatment in a specific syndrome such as Samter's triad. The reduction in asthma exacerbation and decreased use of OCS revealed a significant improvement in disease control and quality of life, as certified by an increase in ACT score. Moreover, SNOT-22 declined significantly, along with peripheral eosinophilic count. These results confirm the systemic overall effectiveness of omalizumab in reducing the burden of eosinophilic and inflammatory activity, as already reported in the literature^{23,24}. Our data²⁵ confirms the effectiveness of omalizumab in improving sino-nasal clinical and radiological outcomes in these patients, as previously demonstrated, even

Table 1. Demographic features, clinical, immunological and functional data of the 4 patients included in the case series.

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Gender, age (yrs)	M, 57	M, 43	M, 38	F, 74
Smoking status, pack /year	Former smoker, 2 p/y	Never smoker	Former smoker, 7 p/y	Former smoker, 2 p/y
BMI (kg/m ²)	24.6	22.6	26.5	24.8
Medical comorbidities	BPH	None	CSU	Arterial hypertension
Total serum IgE (kUA/l)	103	181	136	35
Sensibilization to perennial allergens	DP	DP	None	DP
Months of omalizumab therapy	6	11	15	20
Baseline eosinophilic cell count (cell/mm ³)	11% (1000)	7% (400)	4.3% (470)	8% (600)
Follow-up eosinophilic cell count (cell/mm ³)	4% (450)	5% (330)	4% (400)	6% (330)
Clinical features				
N° exacerbations in the year before omalizumab (moderate/severe)	2 (2/0)	3 (2/0)	2 (1/1)	4 (3/0)
N° exacerbations during omalizumab (moderate/severe)	0 (0/0)	0 (0/0)	0 (0/0)	1 (1/0)
Salbutamol (puff/month) pre-omalizumab	2	12	0	20
Salbutamol (puff/month) during omalizumab	0	0	0	8
OCS dosage (mg/die): baseline – follow-up	0-0	0-0	0-0	6.25-0
ACT score: baseline – follow-up	20-24	15-19	19-25	16-20
SNOT-22: baseline – follow-up	30-22	32-30	24-7	26-22
PFTs				
FEV ₁ % (l) baseline – follow-up; % variation	66 (1.9)-88 (2.6); +31%	78 (3.3)-91 (3.8); +15%	100 (4.1)-100 (4.1); 0%	70 (1.5)-92 (2); +31%
FVC % (l) baseline – follow-up; % variation	79 (2.9)-97 (3.6); +22%	79 (4.9)-106 (5.4); +10%	104 (5)-104 (5.1); +2%	96 (2.5)-118 (3); +20%
FEV ₁ /FVC baseline – follow-up; % variation	67-72; +7%	66-70; +6%	79-79; 0%	60-65; +8%
FEF 25-75 % (l/s) baseline – follow-up; % variation	35 (1.2)-54 (1.9); +55%	44 (1.9)-53 (2.3); +21%	81 (3.7)-82 (3.8); +2%	34 (0.8)-47 (1.2); +41%

BPH: benign prostatic hyperplasia; BMI: body mass index; CSU: Chronic spontaneous urticaria; DP: Dermathophagoides pteronyssinus; OCS: oral corticosteroids; ACT: Asthma Control Test; SNOT: Sino Nasal Outcome Test.

compared with the surgical approach²⁶. With this case series, we supported the potential utility of omalizumab in the management of AERDs: however, in our patients, its efficacy may be explained by the fact that 3/4 patients were sensitized to perennial allergens.

In literature, there are limited studies on this topic. The only specific available evidence of omalizumab use in Samter's triad comes from two case reports^{27,28} and a single case series of 3 patients²⁹. All these studies reported a good efficacy of omalizumab in improving asthma control. Moreover, in the case series, omalizumab significantly decreased eosinophilic cationic peptide, exhaled nitric oxide, interleukin-1 β , and C-reactive protein levels, although these results were not associated with a significant improvement of nasal polyposis.

Other small-sized observational studies or case series investigated the utility of omalizumab in the clinical management of patients with AERDs, therefore including also Samter's triad cases. Tiotiu et al³⁰ recently described a cohort of 21 patients with severe asthma and nasal polyps, including 9 subjects with aspirin intolerance. The results are in line with our data, showing a good clinical and radiological response associated to a decrease of peripheral eosinophilic cell count. The same findings were reported in a multi-center randomized placebo-controlled trial of omalizumab in patients with asthma and nasal polyposis, even though the outcomes related to AERDs were not specifically assessed³¹. Hayashi et al³² confirmed the reliability of omalizumab in a small cohort of patients with AERDs. Interestingly, the authors also reported a significant reduction in the urinary concentrations of LTE₄ and PGD₂, suggesting a specific activity of omalizumab in modulating this subtype of inflammation.

Concerning aspirin hypersensitivity, three case reports have first described the effectiveness of omalizumab in restoring the tolerance to aspirin^{28,33,34}. These promising results were subsequently detected in a case series by Phillips-Angles et al³⁵ in which FANS tolerance was restored in 4 out of 6 patients. The underlying mechanisms for which omalizumab may be specifically effective in AERDs are not clear. Omalizumab is able not only to bind and inactivate serum free IgE, but also to detach IgE from Fc ϵ RI in basophils, dendritic cells, and mast cells³⁶. The consequent surface IgE downregulation may determine a decrease production of LTs and other mediators by mast cells and basophils, that are

crucial in the pathogenesis of AERDs. A specific activity in restoring aspirin tolerance *per se* by omalizumab is further supported by a case report of a non-asthmatic woman affected with chronic spontaneous urticaria³⁷. Our results are in line with these previous results, supporting the beneficial effect of omalizumab in reducing mast cell and eosinophilic inflammatory burden and aspirin-induced respiratory diseases.

Finally, some authors investigated the potential use of omalizumab to prevent adverse events during aspirin desensitization, reporting conflicting results. The first case report by Guillén et al³⁸ showed positive results, while a retrospective single-center study by Waldram et al³⁹, including 9 patients treated with omalizumab, did not show any difference in terms of safety. However, in a randomized controlled trial recently published by Lang et al⁴⁰, omalizumab use was associated with a significant reduction of adverse events during desensitization, suggesting a potential implementation of the drug on this setting.

Conclusions

Despite the limited data available in the existing literature, omalizumab has proved to be effective and safe for the use in patients with Samter's triad. The evidence that omalizumab decreases mast cell and basophils activity, inducing a reduction of LTE₄ production, suggests that its activity goes beyond the inhibition of the free serum IgE. Therefore, the use of omalizumab in patients with Samter's triad, and, in general, with AERDs, may be proposed as a valid therapeutic option. A randomized clinical trial to confirm these previous results is strongly needed.

Conflict of Interest

The study was developed at Siena University and it was unfunded. The authors have no conflict of interest to declare.

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