

Efficacy of omalizumab in an atopic young adult with asthma and eosinophilic chronic rhinosinusitis with nasal polyps

G.L. FADDA¹, A. GALIZIA², L. MAUGERI³, R.F. CANEVARI^{4,5},
E. CROSETTI¹, G. CAVALLO¹

¹Department of Otolaryngology, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Italy

²Department of Otolaryngology, Infermi Hospital, Rivoli, Italy

³Department of Pulmonology, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Italy

⁴Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy

⁵IRCCS San Martino Hospital, Genoa, Italy

Abstract. – OBJECTIVE: Chronic rhinosinusitis (CRS) presents a multifactorial etiology due to interactions between the immune host system and external agents. It can be classified into two phenotypes based on the presence or absence of polypoid neof ormation (respectively CRSwNP and CRSsNP). According to EPOS2020, CRS is now classified into two endotypes, eosinophilic (E CRS) and non-eosinophilic (non-E CRS), based on eosinophil tissue count (more than 10 eosinophils per High Power Field, HPF).

CASE PRESENTATION: We present the case of a 31-year-old man affected by recalcitrant ECRSwNP and asthma.

RESULTS: He was treated with a combination of omalizumab and endoscopic sinus surgery. This combination led to a reduction in blood eosinophils, modified Lund-Kennedy endoscopic score, Lund-Mackay score, and Sino-Nasal Outcome Test (SNOT-22), almost 6 months after surgery.

CONCLUSIONS: In this clinical case, omalizumab regulated nasal symptoms for more than a year and with good control of the recalcitrant pattern when combined with ESS.

Key Words:

Asthma, Eosinophilic chronic rhinosinusitis, Nasal polyps, Omalizumab.

explanation for the pathophysiological mechanism underlying the onset of CRS^{2,3}. On the other hand, endotyping based on the pathogenic mechanism produces a specific picture more suitable for use in clinical practice. While pathophysiological knowledge progresses, therapeutic protocols may be adapted to address specific processes in the underlying condition⁴.

CRS is divided into two endotypes, eosinophilic (E CRS) and non-eosinophilic (non-E CRS), based on eosinophil tissue count (more than 10 eosinophils per High Power Field, HPF). Other markers to endotype CRS discussed in the literature are total serum immunoglobulin (Ig)E and blood eosinophils⁵.

Omalizumab is a monoclonal antibody which selectively targets human IgE, inducing the generation of small-sized immune complexes which inhibit binding among IgE and its high- and low-affinity receptors⁶. It has been used for a long time in asthma disease control and is also characterized by an excellent safety record and tolerability profile⁷. Due to the central role of IgE in the pathogenesis of ECRSwNP⁸, omalizumab has been widely used and studied in the management of this disease⁹⁻¹⁴.

This case report describes the efficacy of omalizumab in the management of a young adult patient with recalcitrant ECRSwNP and early-onset asthma.

Case Report

A 31-year-old man presented at our clinic in November 2018 complaining of nasal obstruction, runny nose and anosmia. He had already been treated on four occasions (2003,

Introduction

Chronic rhinosinusitis (CRS) is a very common clinical syndrome which affects 4.5-12% of the population¹. It is usually classified into two phenotypes based on the presence (CRSwNP) or absence (CRSsNP) of nasal polyps. At present, clinical findings do not provide a comprehensive

2010, 2012, 2014) with endoscopic sinus surgery (ESS). Furthermore, he had a history of atopic diseases with early-onset asthma diagnosed in September 1999 and cutipositivity for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and grasses at prick test performed in July 2017. The patient was treated with a combination of inhaled long-acting β 2-agonist (LABA) and inhaled corticosteroid (ICS) therapy until the onset of a maculopathy secondary to the use of corticosteroids, then he commenced therapy with montelukast, LABA and short acting β 2-agonist (SABA) as required.

In January 2019, during the follow-up evaluation, the patient had a Sino-Nasal Outcome Test (SNOT) score of 59, a total modified Lund-Kennedy (MLK) score of 12 and a Lund-Mackay (LM) score of 21 (Figure 1, Figure 2). Blood chemistry in December 2018 showed a blood eosinophil count of $1.06 \times 10^3/\mu\text{L}$ (14%) and total IgE of 361 kU/L. This was confirmed in January 2019 when blood chemistry returned to an eosinophil count of $1.33 \times 10^3/\mu\text{L}$ (16.8%), total IgE of 401 kU/L, and vitamin D of 15.7 ng/mL (Figure 1).

From the patient's general condition and the absence of regular pneumological follow-up, we decided to include him in our multidisciplinary team, consisting of an otolaryngologist, pulmonologist and allergist, before performing further surgery.

At the pulmonological evaluation performed in March 2019, the patient reported limited

physical activity and poor symptom control with severe exacerbations and the need to use SABA frequently. Spirometry highlighted a forced vital capacity (FVC) of 4.82 L (97%), forced expiratory volume (FEV_1) of 2.82 L (67%) and a FEV_1/FVC of 73% (Table I). Severe asthma was diagnosed.

The patient started therapy in March 2019 with monthly subcutaneous injections of 600 mg of Omalizumab, based on weight and blood IgE value. The patient was followed by evaluating SNOT-22, MLK, LM, complete blood count, total blood IgE, serum vitamin D, and respiratory function.

The patient soon experienced a marked improvement in asthma as demonstrated by spirometry and the reported improvement in symptoms and the need for on-demand therapy with SABA. This improvement was stable throughout the 18-month follow-up after initiation of therapy (Table I).

Blood chemistry tests showed a rapid decrease in eosinophilia and an increase in circulating IgE (Figure 1).

s regards the nasal sinus pathology, the patient's condition remained substantially unchanged (Figure 1, 2), so it was decided to proceed with surgery and in September 2020, 18 months after the initiation of therapy with omalizumab, the patient underwent ESS. Histological examination of the sampled tissue confirmed an eosinophilic inflammation.

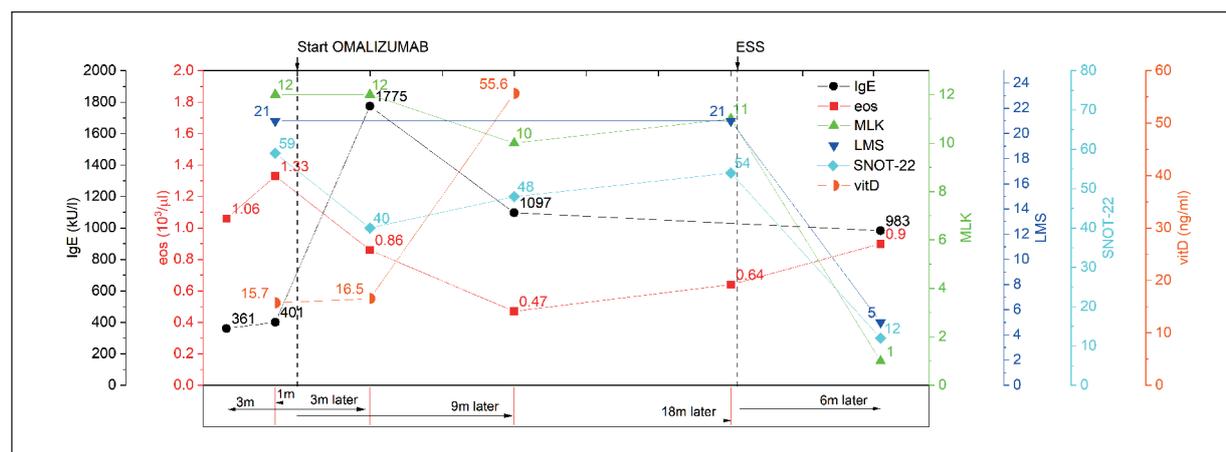


Figure 1. IgE, eos, MLK, LMS, SNOT-22 and vitD levels in relation to omalizumab therapy and ESS. After the initiation of omalizumab, there was a decrease in blood eosinophil values (from $1.33 \cdot 10^3/\mu\text{L}$ to $0.47 \cdot 10^3/\mu\text{L}$) while the IgE values increased (from 401 kU/L to 1097 kU/L). The values remained essentially stable throughout the remainder of the therapy regardless of ESS. Regarding LMS, MLK and SNOT-22 in the 18 months after therapy initiation, no significant differences were observed. However, after full ESS, there was a rapid reduction of these three values. Abbreviations: Blood eos: Blood eosinophil count, vitD: vitamin D, LM: Lund-Mackay score, m: months, MLK: modified Lund-Kennedy, SNOT-22: Sino-Nasal Outcome Test-22.

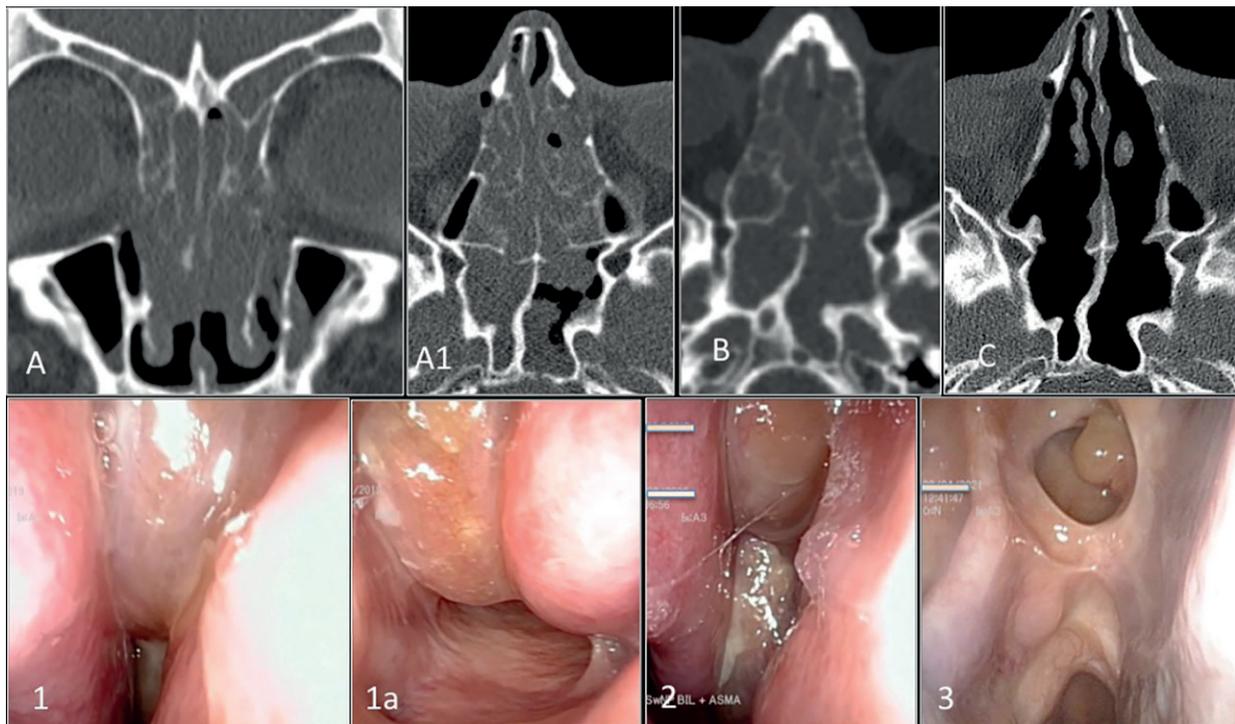


Figure 2. Endoscopic and radiological images in relation to omalizumab therapy and ESS. Panels **A**, **A1** and **1**, **1a** (2 months before omalizumab initiation): computed tomography (CT) images show a picture of pansinusitis. Endoscopic examination of both nasal cavities shows polypoid formation which completely occupies the nasal fossa (**1**= right and **1a**=left). Panels **B** and **2** (18 months after initiation of omalizumab: (**B**) Axial CT scan; (**2**) endoscopic image of the right nasal fossa. Panels **C** and **3** (6 months after ESS): a clear improvement is seen in the radiologic (**C**) and endoscopic (**3**) images.

Six months after surgery, his SNOT-22 score had decreased to 12, MLK score to 4 and LM score to 1. Blood chemistry showed an eosinophilic count of $0.9 \times 10^3/\mu\text{L}$ (9.4%) and total IgE of 983 kU/L (Figure 1, 2). The primary symptoms of asthma were still under control without corticosteroid therapy.

The patient is still continuing therapy with omalizumab. At the most recent check in September 2021, a substantially stable objective picture was demonstrated compared to the previous check and with a MLK score of 1 and SNOT-22 of 10.

Discussion

For many years, omalizumab was the only monoclonal antibody available for biological treatment of asthma. As a result of its action on IgE, it significantly improves symptoms and prevents asthma exacerbations. Thus, omalizumab administration significantly reduces both emergency department referrals and hospitalizations due to asthma exacerbations. It is also able to intervene in airway remodeling through the inhibition of IgE receptors expressed in structural

Table 1. Lung function parameters during therapy. There was a 15% increase in FEV₁/FVC after initiation of omalizumab therapy and this improvement was stable throughout the duration of therapy.

	FVC L (% Pred)	FEV ₁ L (% Pred)	FEV ₁ /FVC %
1 month before initiation of omalizumab therapy	4.82 (97%)	2.82 (67%)	73%
3 months after omalizumab	4.49 (88%)	3.14 (74%)	86%
6 months after omalizumab	4.36 (86%)	2.92 (69%)	82%
18 months after omalizumab	3.99 (79%)	2.84 (68%)	88%

Abbreviations: FVC: forced vital capacity, FEV₁: forced expiratory volume in the 1st second, L: liter, % Pred: percent predicted value.

cells such as bronchial epithelial cells and airway smooth muscle cells. Furthermore, it has a very good safety and tolerability profile^{7,11}. This is especially important since our patient had severe uncontrolled asthma and in addition, the need to stop ICS therapy which can result in significant side effects.

In accordance with the EPOS2020 guidelines, the patient had chronic polypoid rhinosinusitis with a Th2 endotype. This form is markedly linked to disease severity, asthma comorbidity, and disease recurrence after surgery. Having already undergone surgery four times, our patient showed a recalcitrant pattern of inflammation with nasal polypoid formation and the development of severe rhinosinusitis (with SNOT-22 score of 59, MLK 12, and LM 21)¹⁵.

Omalizumab has demonstrated efficacy in severe asthma and has been evaluated in studies in patients with CRSwNP with or without asthma, demonstrating its ability to ameliorate sinonasal symptoms (assessed using nasal endoscopy and computed tomography scanning)¹².

Given the poor control of asthma and the numerous recurrences of nasal polyposis before performing further ESS, in agreement with the pulmonologist, we decided to treat the patient with omalizumab. This allowed asthma control to be improved without introducing the side effects that had occurred after ICS therapy. Furthermore, we believed that modulating the patient's deviated Th2 response by using omalizumab before surgery might reduce the risk of recurrence.

After the start of administration of the drug, a subjective and objective improvement in asthma was immediately noted and an initial improvement in SNOT-22 was also seen; however, this increased at subsequent controls before surgery. SNOT-22 is based on the patient's subjective responses and therefore, we believe that the initial reduction was caused by the improvement in asthma and a placebo effect. The objective parameters used to evaluate CRS, such as MLK and LM, remained essentially unchanged.

The graph in Figure 1 shows a paradoxical increase in serum IgE values, but this is a known effect of omalizumab due to the formation of IgE-drug immunocomplexes¹⁶.

The role of vitamin D has been studied extensively in the pathogenesis of asthma; however, it does not play a definite role in the development of the disease¹⁷. Similar to what occurs with asthma, vitamin D deficiency has been associated with the development of CRS but, in this case, the data

are limited and not particularly significant and do not allow us to define its role in the development of the disease¹⁸. Our patient had a vitamin D deficiency which was corrected by oral therapy; however, current knowledge does not allow us to hypothesize a mechanism for the development of vitamin D deficiency.

As the patient was young and omalizumab proved to be effective in the management of asthma, we decided to perform a new endoscopic sinus surgical procedure and continue therapy with the biologic drug. We continued to monitor the patient's nasal sinus parameters and 6 months after surgery, he had excellent disease control as demonstrated by a SNOT-22 score of 12 and the objective parameters with an MLK of 1 and an LM of 5. At 12 months after surgery, the patient demonstrated good control of the disease, both subjective (SNOT-22 of 10) and objective (MLK of 1).

Conclusions

In this clinical case, omalizumab regulated nasal symptoms for more than a year and with good control of the recalcitrant pattern when combined with ESS. In addition, asthma symptoms were very well controlled without the need for corticosteroids. Studies with a larger sample size have already been conducted and demonstrate the efficacy of omalizumab in improving the endoscopic outcome and symptoms¹³.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Acknowledgements

The authors would like to thank Health Publishing and Services Italy S.r.l. for technical editing. This support was funded by Novartis Farma.

Informed Consent

The patient gave written informed consent for the study.

References

- 1) DeConde AS, Soler ZM. Chronic rhinosinusitis: Epidemiology and burden of disease. *Am J Rhinol Allergy* 2016; 30: 134-139.

- 2) Bachert C, Akdis CA. Phenotypes and Emerging Endotypes of Chronic Rhinosinusitis. *J Allergy Clin Immunol Pract* 2016; 4: 621-628.
- 3) Lou H, Zhang N, Bachert C, Zhang L. Highlights of eosinophilic chronic rhinosinusitis with nasal polyps in definition, prognosis, and advancement. *Int Forum Allergy Rhinol* 2018; 8: 1218-1225.
- 4) Brescia G, Alessandrini L, Marioni G. Structured histopathology for endotyping and planning rational treatment in chronic rhinosinusitis. *Am J Otolaryngol* 2021; 42: 102795.
- 5) Fadda GL, Galizia A, Galizia G, Castelnuovo P, Bignami M, Cavallo G. Multiparametric Analysis of Factors Associated With Eosinophilic Chronic Rhinosinusitis With Nasal Polyps. *Ear Nose Throat J* 2020; 6:145561320960357.
- 6) Kawakami T, Blank U. From IgE to Omalizumab. *J Immunol* 2016; 197: 4187-4192.
- 7) Pelaia C, Calabrese C, Terracciano R, de Blasio F, Vatrella A, Pelaia G. Omalizumab, the first available antibody for biological treatment of severe asthma: more than a decade of real-life effectiveness. *Ther Adv Respir Dis* 2018; 12: 1753466618810192.
- 8) Bachert C, Gevaert P, Holtappels G, Johansson SGO, Van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol* 2001; 107: 607-614.
- 9) Vennera MC, Picado C, Mullol J, Alobid I, Bernal-Sprekelsen M. Efficacy of omalizumab in the treatment of nasal polyps. *Thorax* 2011; 66: 824-825.
- 10) Pinto JM, Mehta N, Detineo M, Wang J, Baroody FM, Naclerio RM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology* 2010; 48: 318-324.
- 11) Kariyawasam HH, James LK. Chronic Rhinosinusitis with Nasal Polyps: Targeting IgE with Anti-IgE Omalizumab Therapy. *Drug Des Devel Ther* 2020; 14: 5483-5494.
- 12) Bidder T, Sahota J, Rennie C, Lund VJ, Robinson DS, Kariyawasam HH. Omalizumab treats chronic rhinosinusitis with nasal polyps and asthma together - a real life study. *Rhinology* 2018; 56: 42-45.
- 13) Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, Kaufman D, Ligueros-Saylan M, Howard M, Zhu R, Owen R, Wong K, Islam L, Bachert C. Efficacy and safety of omalizumab in nasal polyps: 2 randomized phase 3 trials. *J Allergy Clin Immunol* 2020; 146: 595-605.
- 14) Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, Hellings P, Brusselle G, De Bacquer D, van Cauwenberge P, Bachert C. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2013; 131: 110-116.
- 15) Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, Toppila-Salmi S, Bernal-Sprekelsen M, Mullol J, Alobid I, Terezinha Anselmo-Lima W, Bachert C, Baroody F, von Buchwald C, Cervin A, Cohen N, Constantinidis J, De Gaboro L, Desrosiers M, Diamant Z, Douglas RG, Gevaert PH, Hafner A, Harvey RJ, Joos GF, Kallongera L, Knill A, Kocks JH, Landis BN, Limpens J, Lebeer S, Lourenco O, Meco C, Matricardi PM, O'Mahony L, Philpott CM, Ryan D, Schlosser R, Senior B, Smith TL, Teeling T, Tomazic PV, Wang DY, Wang D, Zhang L, Agius AM, Ahlstrom-Emanuelsson C, Alabri R, Albu S, Alhabash S, Aleksic A, Aloulah M, Al-Qudah M, Alsaleh S, Baban MA, Baudoin T, Balvers T, Battaglia P, Bedoya JD, Beule A, Bofares KM, Braverman I, Brozek-Madry E, Richard B, Callejas C, Carrie S, Caulley L, Chussi D, de Corso E, Coste A, El Hadi U, Elfarouk A, Eloy PH, Farrokhi S, Felisati G, Ferrari MD, Fishchuk R, Grayson W, Goncalves PM, Grdincic B, Grgic V, Hamizan AW, Heinichen JV, Husain S, Ping TI, Ivaska J, Jakimovska F, Jovancevic L, Kakande E, Kamel R, Karpischenko S, Kariyawasam HH, Kawauchi H, Kjeldsen A, Klimek L, Krzeski A, Kopacheva Barsova G, Kim SW, Lal D, Letort JJ, Lopatin A, Mahdjoubi A, Mesbahi A, Netkovski J, Nyenbue Tshipukane D, Obando-Valverde A, Okano M, Onerci M, Ong YK, Orlandi R, Otori N, Ouenoughy K, Ozkan M, Peric A, Plzak J, Prokopakis E, Prepagarera N, Psaltis A, Pugin B, Raftopoulos M, Rombaux P, Riechelmann H, Sahtout S, Sarafoleanu CC, Seariyoh K, Rhee CS, Shi J, Shkookani M, Shukuryan AK, Sicak M, Smyth D, Sindvongs K, Soklic Kosak T, Stjarne P, Sutikno B, Steinsvag S, Tantilipikorn P, Thanaviratatananich S, Tran T, Urbancic J, Valiulius A, Vasquez de Aparicio C, Vicheva D, Virkkula PM, Vicente G, Voegels R, Wagenmann MM, Wardani RS, Welge-Lussen A, Witterick I, Wright E, Zabolotniy D, Zsolt B, Zwetsloot CP. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology* 2020; 58: 1-464.
- 16) Eckl-Dorna J. Omalizumab's Impact on Total and Allergen-Specific IgE Levels: A Polyclonal Story. *Int Arch Allergy Immunol* 2016; 169: 69-70.
- 17) Niloufer SA, Kashmira N. A Review on the Role of Vitamin D in Asthma. *Cureus* 2017; 9: e1288.
- 18) Stokes PJ, Rimmer J. The Relationship between Serum Vitamin D and Chronic Rhinosinusitis: A Systematic Review. *Am J Rhinol Allergy* 2016; 30: 23-28.