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Efficacy and use of benralizumab in patients with eosinophilic chronic rhinosinusitis

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ABSTRACT

Chronic rhinosinusitis has a multifactorial etiology resulting from a dysfunctional interaction between various environmental factors and the host immune system. The patient of case report is affected by chronic rhinosinusitis with nasal polyps and a type 2 molecular pattern, has comorbid asthma and symptoms resistant to adequate medical and surgical therapy. The patient was treated with benralizumab, a mAb that binds IL-5Rα. The therapy resulted in a reduction in blood and tissue eosinophilia, but this was not associated with an improvement in the clinical and objective rhinological picture. Instead, at the lung level, there was a marked improvement in the control of severe asthma. Therefore, the patient was undergoing revision Full FESS in association with biological drug therapy. The patient showed an immediately improvement in the clinical and objective rhinological picture and this association allowed for control of the disease almost one year after surgery.

1. Introduction

Chronic rhinosinusitis (CRS) is a clinical syndrome affecting 5–12% of the general population [1]. Both direct and indirect health care costs are high for CRS [2].

CRS has a multifactorial etiology resulting from a dysfunctional interaction between various environmental factors and the host immune system, but it is unclear what factors are important in the general population and especially in the individual patient [3–5].

The phenotypes do not provide a complete picture of all of the underlying pathophysiological mechanisms of CRS which have become increasingly relevant due to its variable association with comorbidities such as asthma and the response to different treatments including corticosteroids, surgery and biological agents [6,7]. So currently, interest is centered on identification of the inflammatory molecular pathways (endotypes) so as to allow personalized therapy.

The aim of the study was to describe the effect of Benralizumab in the management of a patient with recalcitrant chronic polypoid rhinosinusitis.

2. Case report

A 57-year-old man came to our clinic on January 7, 2019 complaining of nasal respiratory obstruction, dense nasal secretions, facial pain/pressure and anosmia with a total VAS score greater than 5 and a SNOT-22 score of 16. The patient had used systemic corticosteroids with only temporary benefit during the previous year and, on presentation, was taking Beclomethasone dipropionate and Formoterol fumarate dihydrate with two inhalations twice a day, Fluticasone furoate two puffs per day in cycles, and oral antihistamine. The patient reported allergic rhinitis with cutipositivity for dust mite and allergic asthma while denying allergic reactions to non-steroidal anti-inflammatory drugs (NSAIDs), gastroesophageal reflux disease (GERD) and other comorbidities.

In 2005 and 2009, the patient underwent Functional Endoscopic Sinus Surgery (FESS) and from May 2017 to October 2018 was treated with Omalizumab 300 mg/month, which was suspended because of poor lung and sinonasal benefits.

Rhino-endoscopy revealed a picture of bilateral chronic polypoid rhinosinusitis (CRSwNP) with a modified Lund-Kennedy score (MLK) of 12 (Fig. 1 and Fig. 2, panel 1). Biopsy of the sinonasal mucosa and polypoid tissue showed eosinophilic infiltration (>10 eosinophils/HPF).

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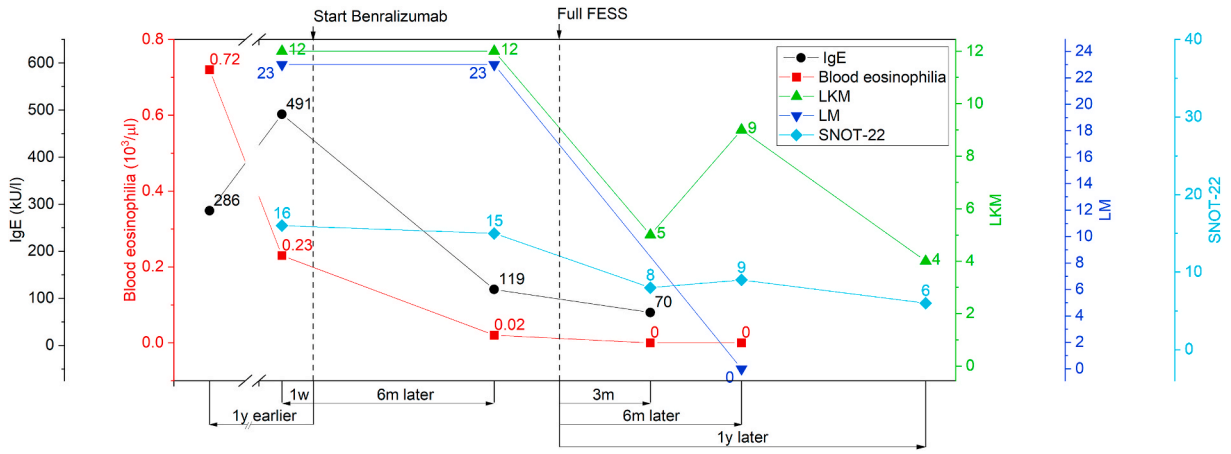

Fig. 1. Blood eosinophils, total IgE, SNOT-22, MLK, and LM in relation to benralizumab therapy and Full FESS. After the initiation of benralizumab, there was a rapid drop in blood eosinophilia values (from $0.23{\cdot}10^3$/µL to $0.02{\cdot}10^3$/µL) and total IgE (from 491 KU/L to 119 KU/L). These values were low throughout the duration of therapy. Regarding LM, MLK and SNOT-22 in the 6 months following the start of therapy, no significant differences were seen. On the other hand, after Full FESS, there was a progressive reduction of all three values. In particular, the LM at 6 months was 0 while SNOT-22 and MLK values 1 year after the intervention were 6 and 4, respectively. SNOT-22: Sino-Nasal Outcome Test-22, MLK: modified Lund-Kennedy endoscopic score, LM: Lund-Mckay score, w: weeks, m: months, y: years.

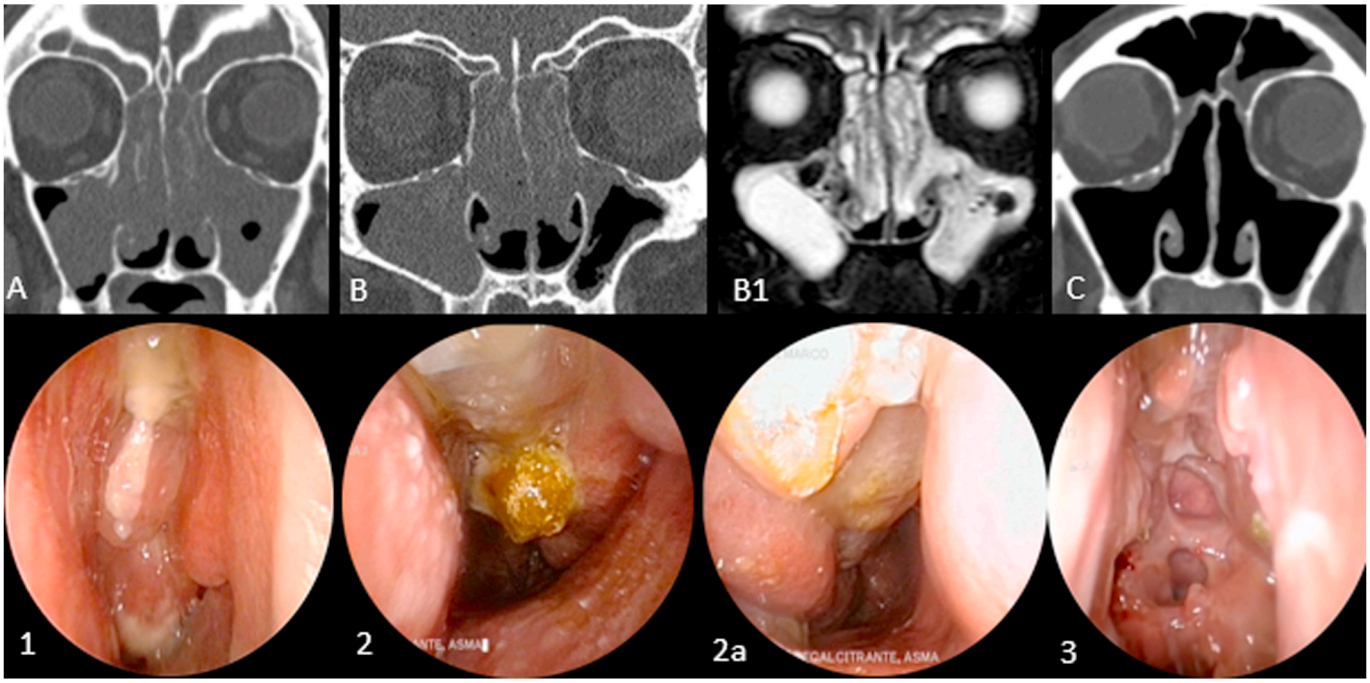

Fig. 2. Endoscopic and radiological images in relation to benralizumab therapy and Full FESS. Panels A and 1 (1 week before start of benralizumab): the CT image shows a picture of pansinusitis. Endoscopy of the left nasal fossa shows mucous secretions and a polypoid formation which completely occupies the nasal fossa. **Panels B, B1, 2, 2a** (6 months after initiation of benralizumab): the endoscopic images of the left (**2**) and right (**2a**) nasal fossa, CT scan (**B**) and MRI (**B1**) show a largely stable picture compared to the earlier one a week before the start of benralizumab (**A** and **1**). **Panels C and 3** (CT at 6 months and endoscopic follow-up 1 year after Full FESS): a clear improvement of the radiologic and endoscopic picture is seen. FESS: functional endoscopic sinus surgery, CT: computed tomography, MRI: magnetic resonance imaging.

Blood chemistry tests on January 2011 showed blood eosinophilia with 0.72×10^3/µL (7.90%) and total IgE of 286 kU/L (Fig. 1).

At the pneumological examination with spirometry performed on January 2019 during therapy with bronchodilators, a forced vital capacity (FVC) of 5.49 L (109%), forced expiratory volume (FEV1) of 3.76 L (97%), and FEV1/FVC of 66% (85% predicted) were recorded. In view of the clinical picture of severe extrinsic eosinophilic asthma, benralizumab was prescribed with 1 vial subcutaneously per month for the first 3 months and then 1 every 2 months. The patient started therapy on January 24, 2019. The patient performed a month earlier CT of the sinus cavity, that showed pansinusitis with a Lund-Mackay score (LM) of 23 (Fig. 2, panel A), and blood chemistry with eosinophilia of 0.23×10^3/µL (3.00%) and total IgE of 491 KU/L (Fig. 1).

According to the new EPOS2020 guidelines [8], the patient had a type 2 diffuse primary recalcitrant CRS with polypoid phenotype and comorbid asthma, uncontrolled from a symptomatic point of view. Rhinological follow-up included the SNOT-22 questionnaire, nasal endoscopy with MLK and blood chemistry tests.

Six months after the begin of therapy the patient performed CT scan highlighted a substantially stable picture compared to the previous one

(LM of 23). Also, the magnetic resonance imaging showed a diagnosis of pansinusitis (Fig. 2, panels B and B1). The blood chemistry tests showed blood eosinophils of 0.02 × 103/μL (0.20%) and total IgE 119 KU/L. The SNOT-22 and MLK values were 15 and 12 respectively (Figs. 1 and 2, panels 2 and 2a).

From a pneumological point of view, benralizumab therapy resulted in excellent asthma control documented by the absence of systemic and inhalation corticosteroid therapy.

On September 27, 2019, because of the persistence of symptoms and of the endoscopic picture of bilateral massive polyposis, the patient underwent Full FESS with lowering of the posterior portion of the nasal septum and of the inter-sphenoid septum. Histopathological examination of the sinonasal mucosa and polypoid tissue samples showed reduced eosinophilic infiltration (<10 eosinophils/HPF).

Three months after the intervention, eosinophilia of 0.00 × $\cdot 10^3$/μL (0.00%), total IgE of 70 kU/L, SNOT-22 of 8 and MLK of 5 were recorded (Fig. 1).

Six months later CT scan showed complete absence of opacification of sinu-nasal cavities with LM of 0 (Fig. 2, panel C). Eosinophilia of 0.00 × $\cdot 10^3$/μL (0.00%), SNOT-22 of 9 and MLK of 9 were recorded (Fig. 1).

At the check one year after surgery, we found a MLK of 4 and SNOT-22 of 6 (Figs. 1 and 2, panel 3).

3. Discussion

Multiple inflammatory mechanisms are operational, interact dynamically and cause variable patterns of tissue inflammation that are approximately related to the clinical phenotype. Recent attempts have been made to divide CRS into inflammatory endotypes, defined as distinct pathological mechanisms. These inflammatory mechanisms typically use type 1, 2 or 3 pathways alone or in combinations. Type 2 inflammation is characterized by cytokines IL-4, IL-5 and IL-13, and the activation and recruitment of eosinophils and mast cells. Patients with pure or mixed type 2 endotypes tend to be more resistant to current therapies, exhibiting a high recurrence rate compared to pure type 1 or 3 endotypes. Type 2 endotype is also more commonly associated with asthma [9,10].

According to the above, our patient, affected by CRSwNP with a type 2 molecular pattern, had comorbid asthma and symptoms resistant to adequate medical and surgical therapy.

Eosinophils play an important role in the type 2 molecular pattern and are the predominant cells in patients with CRSwNP in the Western world but this is not equally true in Asian patients [11,12]. Therefore, eosinophils are currently considered unnecessary for the presence of nasal polyposis or CRS, but tissue eosinophilia correlates with a relatively poor outcome regardless of the presence or absence of polyps. As a result, they appear to be a biomarker for severe and recalcitrant forms of CRS disease [13,14].

Although most cases of CRSwNP in Western countries show a profile of type 2 cytokines with eosinophilia of polypoid tissue, only about half showed significant polyp shrinkage with anti-IL-5 monoclonal antibody (mAb) therapy [15]. In the same study, it was demonstrated that a significant proportion of patients, who had eligible criteria for surgery, no longer needed surgery after Mepolizumab therapy. This was associated with a statistically significant reduction in the VAS score for nasal polyposis severity and the SNOT-22 score.

In a study by Gevaert et al. [16], a statistically significant reduction in the Total Polyp Score (TPS) was demonstrated in patients treated with Mepolizumab compared to the placebo group. In a case report by Pelaia et al., an improvement was demonstrated in hyposmia patients and rhinoscopy showed the disappearance of the relapsing nasal polyps [17]. In a case report by Tsurumaki et al., a reduction in nasal polyps was demonstrated both radiologically and endoscopically and patients reported improved nasal visual analog scale (VAS) scores [18].

In the Phase IIIb ANDHI trial, an improved SNOT-22 score was recorded in the benralizumab group vs. placebo [19]. In addition, a study using the oral anti-eosinophilic drug dexpramipexole, showed a greater than 90% reduction in eosinophils in blood and polyps in patients with CRSwNP without significant symptom improvement or polyp shrinkage [20].

Our patient, having already been treated with Omalizumab without benefit, was treated with benralizumab, a mAb that binds IL-5Rα, for which currently no randomized controlled trials have been conducted. The therapy resulted in a reduction in blood and tissue eosinophilia, but this was not associated with an improvement in the clinical and objective rhinological picture. On the other hand, at the lung level, there was a marked improvement in the control of severe asthma. It was therefore decided that the patient should undergo revision Full FESS in association with biological drug therapy. The patient immediately showed a marked improvement clinically and therefore a close follow-up was carried out to assess the risk of recurrence.

About 1 year after surgery, the patient showed a clear improvement with a SNOT-22 score of 6 and a MLK of 4. In addition, at the radiological level, the CT sinus scan carried out 6 months after surgery showed the absence of involvement of the paranasal sinuses.

4. Conclusion

Although eosinophils have been considered for many years to be the cells responsible for CRSwNP, more evidence is emerging that these cells are not essential for the development of the disease, but their presence is associated with severe forms that do not respond to adequate medical and surgical therapy.

In the clinical case presented in this article, the use of benralizumab did not lead to a change in the course of the disease while it resulted in an improvement in asthma. On the other hand, the association of the drug with FESS, allowed for a control of the disease almost one year after surgery.

Other studies with extensive case histories would be desirable to evaluate the efficacy of these drugs and other biological drugs and their proper use in patients with CRS.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Declaration of competing interest

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

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