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Original article

Effects of benralizumab in a population of patients affected by severe eosinophilic asthma and chronic rhinosinusitis with nasal polyps: a real-life study

Carla Santomasi[1], Enrico Buonamico[1], Silvano Dragonieri[1], Lucia Iannuzzi[2], Andrea Portacci[1] Nicola Quaranta[2], Giovanna Elisiana Carpagnano[1]

[1]Respiratory Diseases, University of Bari "Aldo Moro", Bari, Italy; [2]Otolaryngology Unit, Department of Basic Medical Science Neuroscience and Sence Organs, University of Bari "Aldo Moro", Bari, Italy

Abstract. *Background and aim:* Chronic rhinosinusitis with nasal polyps (CRSwNP) is a frequent comorbidity in severe eosinophilic asthma (SEA), which may contribute to the loss of asthma control. CRSwNP and SEA share a T2-mediated mechanism and the use of some anti-asthma monoclonal antibodies has recently been extended to CRSwNP. Unlike dupilumab and omalizumab, benralizumab approval for CRSwNP is ongoing. We aimed to evaluate the efficacy of benralizumab efficacy on SEA and on CRSwNP in patients affected by both pathologies in a real-life setting. *Methods:* 17 patients affected by both SEA and CRSwNP participated to our study. At baseline (T0) and at one year after benralizumab initiation (T1), all participants underwent spirometry, exhaled nitric oxide (FeNO), Asthma Control Test (ACT), nasal endoscopy with Nasal Polyp Score (NPS), nasal cytology and Sino-Nasal Outcome Test 22 (SNOT 22). The continuous oral corticosteroid therapy (OCS), the number of year exacerbations and the need for sinus surgery were also evaluated for each patient. *Results:* At T1, a marked reduction of SNOT-22, NPS, nasal eosinophils and neutrophils count were shown compared to T0. Moreover, at T1 ACT was significantly increased and FeNO, exacerbations/year and mean OCS dosage were significantly reduced compared to T0. *Conclusions:* Our real-life study demonstrates the efficacy of benralizumab not only on SEA but also on nasal cytology and on nasal polyposis, confirming that patients affected by both SEA and CRSwNP may receive a considerable benefit from anti-IL5 receptor, treating both the comorbidities at once. (www.actabiomedica.it)

Key words: nasal cytology, eosinophils, severe asthma, nasal polyposis, benralizumab

Introduction

Severe asthma is associated with high social and health burden (1). Comorbidities like chronic rhinoconjunctivitis, chronic rhinosinusitis with nasal polyps (CRswNP), obesity and gastro-esophageal reflux disease (GERD) are often linked to the loss of control in severe asthmatics (1). These comorbidities worsen asthma control, raise the need for systemic corticosteroid usage and as-needed bronchodilator therapy, determining an augmented risk of side-effects and leading to a worsening in quality of life and a heavier social-health burden (2,3).

Since CRswNP is a frequent comorbidity in the severe eosinophilic asthma (SEA) subtype, it is important to evaluate severe asthma patients for this pathology in the need of defining the most appropriate therapy (1-4).

The link between SEA and CRswNP can be explained by their common inflammatory pathways, both being T2-inflammation mediated conditions (5,6).

In the last years five monoclonal antibodies, omalizumab, mepolizumab, benralizumab, reslizumab

and dupilumab, have been introduced in severe asthma therapeutic algorithm, all targeting T2-inflammation mediators. Omalizumab and dupilumab have been recently approved for CRswNP, whereas mepolizumab and benralizumab are still undergoing randomized control trials to verify their effects on CRswNP (1,7,8).

Recently, our group have investigated the effect of benralizumab on nasal cytology in rhinosinusitis and nasal polyps, showing its relevant effect after six months of therapy on nasal eosinophils and on nasal polyps, which were present in all individuals (9). Based on the above, the aim of the current study was to extend our observations by evaluating the effect of one year therapy with benralizumab on asthma clinical and functional parameters, nasal polyps and eosinophils count in nasal cytology in a group of patients with coexisting SEA and CRswNP.

Materials and methods

Patients

A total number of 17 patients participated to our study. Subjects were enrolled from the severe asthma outpatient clinic of the University Hospital Policlinico, Bari, Italy, from January 2019 to December 2020.

Inclusion criteria were the following: SEA diagnosed following GINA 2021 guidelines (1); CRswNP diagnosed by CT scan and/or by optical nasal endoscopy and refractory to nasal topic corticosteroid therapy; age between 18 and 80 years; presence of eligibility criteria for benralizumab: blood eosinophils > 300/mm^3, at least two asthmatic exacerbations during the previous years despite maximum inhaler therapy or continuous oral corticosteroid (OCS) therapy in addition to inhaler therapy; production of a valid written or oral informed consent.

Exclusion criteria were the following: previous biologic therapy; not type 2 Severe Asthma; SEA that did not meet the eligibility criteria for benralizumab; absence of CRSwNP; age <18 years or> 80 years; established diagnosis of Churg-Strauss; refusal to participate to the study.

The local Institutional Review Board approved this study (approval number: 6716) and informed consent from individual patients was obtained. The experiment was performed in accordance with the Helsinki Declaration of 1975 and following the standards of Good Clinical Practice.

Study design

We conducted an observational, prospective, monocentric study. Patients attended our center for two visits, at baseline (T0) and after one year from the first visit (T1). All participants started biologic therapy with benralizumab immediately after T0.

For every patient detailed clinical data were recorded such as general characteristics, comorbidities, allergic status, smoking habit, inhaled therapy, and number of previous sinus surgery.

At both T0 and T1, all subjects performed the following investigations: blood eosinophil count, total serum Ig-E, respiratory function assessment with pre-post bronchodilator spirometry, exhaled nitric oxide (FeNO) test, asthma symptoms assessment with Asthma Control Test (ACT), OCS therapy with daily dosage, number of previous year exacerbations, ENT examination with nasal endoscopy for obtaining Nasal Polyp Score (NPS), nasal cytologic sampling, CRswNP symptoms assessment with Sino-Nasal Outcome Test 22 (SNOT 22). In addition, the need for sinus surgery was assessed for each patient at T1.

Lung function assessment

All lung function tests were performed with Jaeger™ Masterscreen Body (CareFusion Germany), following the last ATS/ERS lung function guidelines (10).

FeNO measurement

FeNO test was performed with an electrochemical analyzer (HypairFeNO Medisoft Exp'air, 2010) according to ATS-ERS recommendations for online measurement of FeNO in adults (11). FeNO was measured during slow exhalation from total lung capacity against a positive pressure to generate an exhalation flow rate of 50 mL/s.

Nasal endoscopy

Nasal endoscopy was carried out by mean of a flexible fiberscope (Karl Storz, Germany, diameter 3.4 mm). None of the patients received local anesthesia or nasal decongestion. The NPS was calculated for each patient depending on endoscopic findings (12).

Nasal cytology

Nasal Cytology was performed by scraping the middle part of the inferior turbinate. For the sampling we used a sterile disposable curette (Nasal scraping®, Ep Medica (RA), Italy). The sample was immediately smeared on a glass slide, air dried and then stained with May–Grunwald–Giemsa preparation. The following reading by an optical microscope Nikon E600 (Nikon, Ontario, Canada) allowed us to identify the presence of inflammatory cells (neutrophils, eosinophils, lymphocytes and mast cells) in nasal mucosa. We analyzed a minimum of 50 microscopic fields at x 1000 in oil immersion and the count of each cell type was expressed by a semi-quantitative grading (from 0 to 4) (13,14). During the nasal cytological examination at T0, the clinical-cytologic grading was also calculated for each patient. Since CRswNP is a pathology with an elevated risk of relapse and poor control despite conventional therapy, negative prognostic factors responsible of relapses and lack of symptoms control were identified (15). Many studies demonstrated that allergy, asthma, and acetylsalicylate (ASA) sensitivity are determining factor for negative outcomes. The correlation between these clinical parameters and nasal cytology results (nasal eosinophilia, neutrophilia, mastocytosis) led to the development of a score, called clinical-cytologic grading (CCG), whose value defines the relapse prognostic index, classified in low, intermediate, or high (Table 1) (16).

Table 1. Clinical-cytologic grading (CCG) determinants. The sum of all values determines the score of relapse prognostic index (RPI) (15).

Grading	Item	value
Clinical	ASA sensitivity	1
Clinical	Asthma	1
Clinical	Allergy	1
Clinical	ASA sensitivity + Asthma	1
Cytologic	Nasal neutrophilia	1
Cytologic	Nasal mastocytosis	1
Cytologic	Nasal eosinophilia	2
Cytologic	Nasal eosinophilia + mastocytosis	4

Score ≤ 3, low risk; score 4 – 6, intermediate risk; score ≥ 7, high risk

Statistical analysis

All continuous variables were tested for normality with Shapiro-Wilk normality test. Variables with parametric distribution were expressed as mean (± standard deviation) whereas non- parametric variables were expressed in median (interquartile range). Comparison between groups were made as follows: unpaired student t test for parametric unpaired values; paired student t test for parametric paired values; Mann-Whitney test for nonparametric unpaired values; Wilcoxon signed-rank test for nonparametric paired values. Correlations were made by Pearson correlation test in case of variables with parametric distribution and by Spearman rank correlation test in case of variables with parametric distribution. A p value < 0,05 was considered as statistically significant.

Results

We enrolled 17 patients that met inclusion criteria. All patients assumed high dose corticosteroids inhaler therapy. General population characteristics are shown in table 2.

After one year-treatment with benralizumab patients showed a significant reduction in SNOT-22 values ($p < 0.01$) as well as NPS ($p < 0.05$). Also, nasal cytology test showed a significant reduction in eosinophils ($p < 0.01$) and neutrophils ($p < 0.05$) (table 3, figure 2).

Moreover, ACT was markedly increased at T1 ($p < 0.05$) and FeNO values were significantly decreased ($p < 0.05$). Only FEV1% showed an increase at T1 which was not statistically significant. Both previous year exacerbation number ($p < 0.05$) and mean

OCS dosage ($p < 0.01$) were significantly reduced (table 3, figure 2).

Regarding nasal polyps, only 1 patient (5.8%) required surgery after treatment with benralizumab.

Conversely, the correlation between the variations from T0 to T1 of ACT and SNOT-22 ($p = 0.8$), ACT and NPS ($p = 0.63$), FEV1% and SNOT-22 ($p = 0.22$) and FEV1% and NPS ($p = 0.55$) were not significant.

Table 2. General population characteristics at baseline.

Age (yrs)	55.29 (± 12.28)
Male (% total)	28%
Aeroallergens sensitivity (% total)	38%
Previous year exacerbations (n.)	0.75 (± 1.18)
OCS chronic therapy (% total)	61%
OCS dosage (mg of prednisone)	0 (0 – 2,5)
Previous sinus surgery (% total)	50%
Clinical-cytologic grading	5.81 (± 2.29)
Sinus Surgery (n.)	3.94 (± 1.59)
SNOT-22	45.19 (± 69.03)
Nasal eosinophilia (% total)	55%
Nasal neutrophilia (% total)	55%
ACT	18.67 (± 3.94)
FEV1 (%pred)	77.5 (± 20.9)
Blood eosinophil count (cells/mcL)	412 (± 115)
Total serum IgE (IU/ml)	128 (± 82)
FeNO (ppb)	53.2 (± 70.1)

Discussion

To the best of our knowledge, this is the first study conducted on patients affected by severe eosinophilic asthma (SEA) and chronic rhinosinusitis with nasal polyps (CRswNP), which demonstrates benralizumab efficacy not only on asthma but also on clinic, volumetric and cytologic characteristics of nasal polyps.

Benralizumab is a monoclonal antibody that selectively blocks the α subunit of the IL-5 receptor, a cytokine widely implicated in the genesis of type 2 inflammation (16).

Benralizumab efficacy on SEA has already been assessed by three placebo-controlled, double blind, parallel groups randomized controlled trials (RCT) that were used as registration studies, demonstrating benralizumab efficacy in lowering annual exacerbation rate and mean OCS dosage, in increasing mean FEV1 and asthma control assessed by 6 items Asthma Control Questionnaire (ACQ-6) (18-20).

Similarly, real-life studies confirmed benralizumab efficacy on SEA: Kavanagh et al in a 2020 retrospective observational study showed a reduction in exacerbation, significant amelioration of asthmatic symptoms assessed by ACQ-6 and quality of life assessed by mini asthma quality of life questionnaire (mAQLQ) and significant improvement in FEV1 values, whereas FeNO levels did not significantly decrease (21).

Our findings retrace those of Kavanagh and colleagues, showing a significant improvement of asthma

Table 3. Comparison between T0 and T1.

Variables	**Baseline**	**T1**	**p**
SNOT-22	61.5 (32.5-75.75)	21.5 (14.7-44)	<0.01
Sinus Surgery (n.)	4 (3-5)	2.5 (1-4.25)	<0.05
ACT	19 (16-22.25)	23 (22-25)	<0.05
FEV1 (% pred)	85.5 (± 23.01)	89.25 (± 22.83)	ns
Nasal eosinophils (grading)	1 (0-3)	0 (0-0)	<0.01
Nasal neutrophils (grading)	2 (0-2)	0 (0-1)	<0.05
OCS dosage (mg)	5 (0-5)	0 (0-2.5)	<0.01
Previous year exacerbations (n.)	0 (0-2)	0 (0-0)	<0.05
FeNO (ppb)	49 (21.5-83.5)	24.5 (12.75-43.5)	<0.05

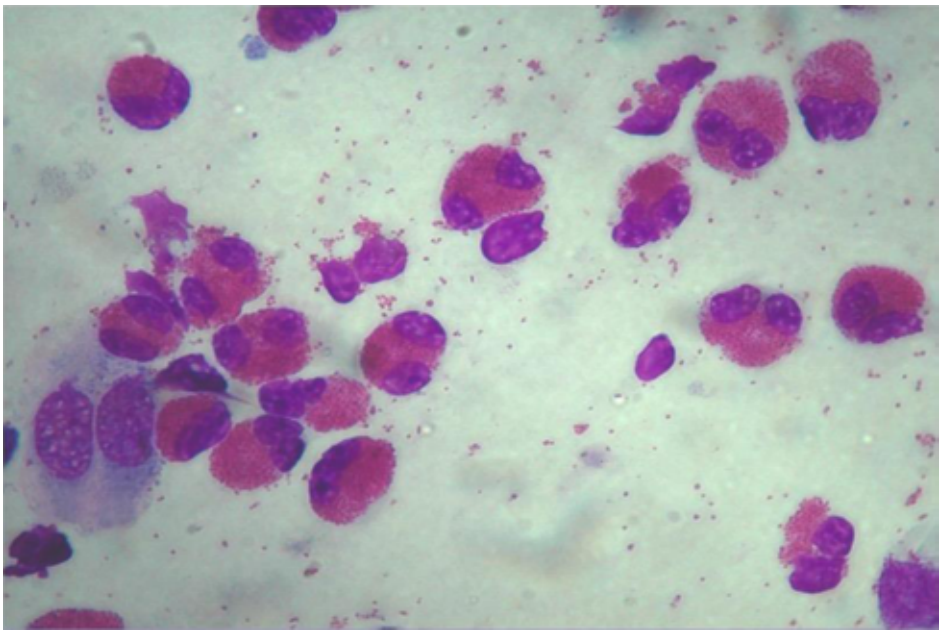

Figure 1. Cytological nasal sample under microscope at high-power magnification showing numerous eosinophils, partly degranulated, with absence of ciliated epithelial cells.(MGG; 1000x magnification).

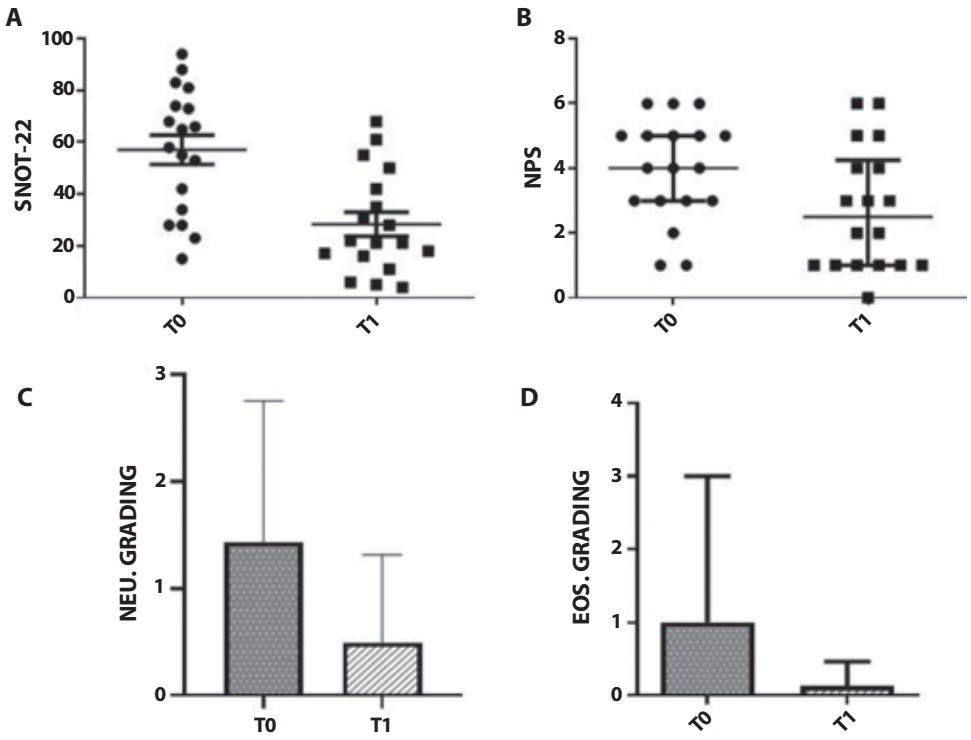

Figure 2. Comparison between T0 and T1 concerning NP parameters. A: Sino-Nasal Outcome Test 22 (SNOT-22, $p<0.01$); B: Nasal Polyp Score (NPS, $p<0.05$); C: nasal neutrophils ($p<0.05$); D: nasal eosinophils ($p<0.01$).

control assessed by ACT, a marked reduction of exacerbations and mean OCS dosage, whereas no significant FEV1 improvement was reported. The latter can be due to the smaller sample size, which may have determined the lack of significance despite the improvement of mean FEV1. In our population, differently from Kavanagh study, FeNO values were significantly lowered at T1. Indeed, FeNO is an important biomarker used in clinical practice for the evaluation of SEA control and its reduction in our study seems to further confirm the clinical efficacy of benralizumab, as already shown also in real-life settings (22).

About CRswNP treatment, Benralizumab efficacy has been explored in two recent RCTs: Harrison et al. in ANDHI trial showed that, in a subpopulation of SAE patients with physician-diagnosed NP, benralizumab significantly reduced SNOT-22 alongside with asthma clinical and functional values (23). Furthermore, Takabayashi et al in a phase II RCT on a population of 56 patients with eosinophilic chronic rhinosinusitis demonstrated that 42,2% of patients in the benralizumab group experienced a reduction of at least 2 points in NPS after 24 weeks compared to 9,1% in placebo group (24). Nevertheless, Bagnasco et al, in a multi-centered real-life study evaluated benralizumab efficacy in 59 patients affected by severe uncontrolled asthma, showing a significant improvement in asthma related outcomes, except for lung function and FeNO values, and a significant reduction in SNOT-22 in a subset of patients (n = 34) affected also by nasal polyposis (25). Similarly, Nolasco et al. showed, in a population of 137 late-onset SEA patients, an improvement in asthma related outcomes (this time including lung function) and in a subgroup of 79 patients with CRswNP a significant reduction in SNOT-22 (26). Finally, Lombardo et al. showed, in a population of 10 patients affected both by severe asthma and CRswNP, a significant amelioration not only in clinical SNOT-22 score, but also in NPS and Lund-Mackay CT score after 24 weeks of treatment with benralizumab (27).

Besides assessing CRswNP-related clinical amelioration with benralizumab, our study also aimed to associate these clinical data with endoscopic findings. In particular, we found a significant reduction in both SNOT-22 and NPS, confirming previous evidence on nasal polyps' volume reduction over time (24-27).

The clinical-endoscopic correlation appears to be supported by our interesting finding of a significant benralizumab-driven decrease in both eosinophilic and neutrophilic inflammatory infiltrate of the nasal mucosa. As far as we know, there is no study in the literature where the efficacy of Benralizumab, in terms of nasal cytology, has been demonstrated. Only our previous study, conducted on a smaller cohort of patients, showed similar results to our population (9). The reduction in nasal eosinophils can be easily explained since 85% of CRSwNPs have nasal eosinophilic infiltration linked to TH2 inflammation and elevated levels of IL-5 have been shown in some studies (6,28). Differently, the neutrophilic infiltrate is an interlocutory finding and has been linked to refractoriness of CRswNP (29). The evidence of significant neutrophilic infiltrate reduction after treatment with benralizumab may highlight its deep and effective local anti-inflammatory role.

A further innovative finding from our study is related to the relapse prognostic index (RPI). The CRswNP is characterized by a high risk of relapse, that happens in about 40% of the cases within one year after sinus surgery, and uncontrolled symptoms despite conventional therapy (15). In fact, since in our study the mean clinical-cytologic grading (CCG) at baseline was 5.81 which corresponds to an intermediate RPI, we expected a certain number of relapses and poor control of NP at T1. Despite this, we obtained a significant improvement in all the NP parameters and only one of our patients required post-biological surgery, confirming the therapeutic efficacy of benralizumab on NP.

Moreover, we also correlated both endoscopic and clinical amelioration of CRswNP values with ACT and FEV1 variations from baseline to one-year visit. However, statistical analysis did not show any significance, probably due to the scarce numerosity of our population, or to the different mechanism of benralizumab in bronchial and nasal districts with different local inflammation features.

Our study has some limitations. First, the relatively small size of our population, which is due to the nature of this study, that is observational and monocentric. Second, the absence of the CT-driven Lund-Mackay score as a further staging score for nasal

polyps, which was arbitrarily not included due to the risk of ionizing radiations.

To conclude, this study conducted on patients with SEA and CRswNP, demonstrates benralizumab efficacy not only on asthma but also on clinic, volumetric and cytologic characteristics of nasal polyps, confirming that patients affected by both SEA and CRswNP may receive a considerable benefit from anti-IL5 receptor, treating both the comorbidities at once. Therefore, the evaluation of clinical characteristics and comorbidities, including the CRswNP, in patients with SEA, is useful for building a more personalized therapy.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Correspondence:
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Silvano Dragonieri
Respiratory Diseases, University of Bari "Aldo Moro
Piazza Giulio Cesare, 11 Bari, Italy
E-mail: silvano.dragonieri@uniba.it