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Benralizumab improves patient reported outcomes and functional parameters in difficult-to-treat patients with severe asthma: Data from a real-life cohort

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ABSTRACT

In the last decade, an increasing number of randomized controlled trials (RCTs) on biologic therapy in patients with severe asthma have included patient-reported outcomes (PROs) as secondary efficacy measures. The majority of these RCTs showed a benefit in symptoms and quality of life. However, the magnitude of this benefit remains uncertain, because it rarely exceeded the minimal important difference (MID), owing to a significant improvement in the control group (placebo effect). Real-life studies on biologic therapies assessing PRO are scarce. They may support and integrate RCT results through their different experimental design.

This real-life retrospective study provides data on 15 patients with difficult-to-treat severe eosinophilic asthma treated with benralizumab up to 6 months. Asthma quality of life questionnaire (AQLQ) and asthma control test (ACT) were assessed and administered at each visit to minimize the Hawthorne effect. Changes in general accepted efficacy measures, such as forced expiratory volume in 1 s (FEV_1), peak expiratory flux (PEF), exacerbation rate and blood eosinophils, from baseline were also assessed.

AQLQ and ACT improved from 3.9 ± 0.4 to 5.2 ± 0.4 and from 15.6 ± 5.7 to 18.1 ± 5.6, respectively. FEV_1 increased of about 250 ml (+14%). PEF increased from 288 ± 107 to 333 ± 133 l/min. The number of exacerbations requiring OCS courses decreased from 2.8 ± 2.2 to 0.5 ± 0.8. Eosinophil counts dropped to 25.6 ± 15 cells/microliter.

In conclusion, most patients reported improvements in AQLQ and ACT greater than MID, suggesting that these outcome represent a sensitive tool in real-life effectiveness studies. Our approach reduced the limitations of transition questions and the Hawthorne effect, increasing findings reliability.

1. Introduction

Efficacy and safety of benralizumab as add-on treatment in patients with severe eosinophilic asthma has been shown in registration randomized controlled trials (RCTs) [1–3]. In contrast, effectiveness studies, providing data more relevant to the circumstances under which patients are routinely treated, are scarce because of the recent introduction of benralizumab in clinical practice [4]. Furthermore, an evaluation of health-related quality of life outcomes is often missing in real-life studies, whereas, in the last decade, RCTs have started to include the measurement of patient-reported outcomes (PROs) as outcome measures, such as the Asthma Control Test (ACT) and the Asthma Quality of Life questionnaire (AQLQ). These tools provide information on the impact of the disease and its treatment on patient's life and may be useful to assess the proportion of patients who can perceive a definite improvement in their condition.

In registration RCTs [1–3,5,6] a small improvement in ACT and AQLQ compared to placebo was reported. The difference between *verum* and placebo were statistically significant in specific subgroups of patients, but the clinical benefit of these small improvements remains uncertain.

The aim of the present study was to evaluate, in a real-life settings,

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effectiveness of benralizumab in difficult-to-treat patients despite best therapies at maximal doses or previous monoclonal antibodies courses (omalizumab, mepolizumab), through the assessment of health-related quality of life outcomes. Lung function parameters and exacerbation rate were also assessed to compare the results of PROs to the accepted general efficacy measures used in clinical studies.

2. Methods

This real-life retrospective analysis was conducted on patients from 2 Italian tertiary referral centers (Bari University Hospital; Foggia University Hospital). Between May 2019 and March 2020, fifteen patients with severe eosinophilic asthma were consecutively treated with benralizumab. Patients complained of persistent respiratory symptoms, though they were on regular treatment with high dosages of inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) combination, with or without leukotriene receptor antagonists (LTRA) or long-acting muscarinic antagonists (LAMA), and most of them also received add-on treatment with monoclonal antibodies (omalizumab, mepolizumab). Patients were included if they had 1) blood eosinophil value > 300 cells/microliter and either 2) at least 2 exacerbations requiring intravenous/intramuscular or oral corticosteroid (OCS) or hospitalization, or 3) continuous treatment with OCS despite the maximum inhaled therapy. There were no exclusion criteria, thus patients with respiratory comorbidities or smokers were included.

Benralizumab was administered in an outpatient clinic settings according to the standard schedule (30 mg administered subcutaneously at 4-week intervals for 3 times and every 8 weeks, thereafter).

AQLQ, ACT, exacerbation rate, OCS courses, pulmonary function parameters, such as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), forced expiratory flow at 25–75% of FVC (FEF 25–75); peak expiratory flow (PEF), were regarded as the efficacy end points. To help patients to consider all possible relevant items in order to complete AQLQ, they were presented with the prompts reported in the original AQLQ version [7]. Data were collected from patients' medical records that were prospectively filled at each administration visits at week 0 (baseline), 4, 8, 16, 24.

Informed consent for the retrospective analysis was obtained from participants. Comparisons between means were made using the Student's t-test. The Pearson's correlation coefficient was used to measure the strength of linear association between variables. Statistical analysis was performed by STATA 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

3. Results

The clinical characteristics of the study population and the type of pharmacological treatment before starting benralizumab are reported in Table 1. Fifteen consecutive patients (mean age 55.2 ± 14 years; 100% female; mean duration of asthma from initial diagnosis: 9.6 ± 5.7 years) with severe eosinophilic asthma (mean eosinophil count at baseline, 458 ± 318 cells/microliter), poorly controlled by conventional treatment or previous monoclonal antibody treatment, underwent benralizumab treatment and were followed-up. Thirty-six moderate exacerbations (requiring OCS; 2.4 ± 2.2 exacerbations per patients on average) and 2 severe exacerbations (requiring emergency room access) were reported in the 12 months before benralizumab treatment in this population. Ten out these 15 patients had been previously treated with either omalizumab or mepolizumab, with poor efficacy. Five patients had been treated with both antibodies. Benralizumab had been started 2–3 months upon discontinuation of the previous monoclonal antibodies (Table 1). One patient was OCS-dependent (prednisone, 15 mg/day); five patients had OCS comorbidities (Table 1); 11 patients had other respiratory comorbidities, such as rhinitis, nasal polyposis, bronchiectasis (Table 1). The mean ACT and AQLQ scores at baseline were 15.6 ± 5.7 and 3.9 ± 0.4, respectively.

Table 1
Clinical characteristics of the patients (n = 15, all females) prior to benralizumab.

	Patients
Mean age ±SD, year	55.2 ± 14
Mean body weight ±SD, Kg	75.3 ± 19.4
Mean body mass index ±SD, Kg/m2	30.1 ± 8.2
Mean age asthma diagnosis ±SD, year	44.5 ± 14.4
Mean disease length	9.6 ± 5.7
Smokers, n (%)	1 (6.6%)
Peripheral blood eosinophil count, n ± SD, cell/microliter	458 ± 318
Median total serum IgE level (IQR), kU/L	168 (87.5, 523.2)
Pulmonary function tests	
- Mean FVC ± SD, L	2.2 ± 0.6
- *Mean FVC ± SD, % predicted*	*80 ± 16.7*
- Mean pre-bronchodilator FEV1 ± SD, L	1.55 ± 0.6
- *Mean pre-bronchodilator FEV1 ± SD, % predicted*	*67.7 ± 20.5*
- Mean reversibility in FEV1, % (range)	18 (0–43)
- Mean FEV1/FVC ratio ± SD, %	0.71 ± 0.13
- *Mean FEF 25–75, % predicted*	51.7 ± 38.9
- PEF (L/min)	288 ± 106
Exacerbations in the 12 months before benralizumab, n (mean ± SD)	
- requiring systemic corticosteroid treatment	36 (2.4 ± 2.2)
- requiring emergency room access	2 (0.1 ± 0.4)
- requiring hospitalization	0
Drug use	
- ICS/LABA, n (%)	15 (100%)
- LAMA, n (%)	4 (26.6%)
- Leukotriene receptor antagonist, n (%)	11 (73.3%)
Comorbidities	
- Rhinitis, n (%)	13 (85.7)
- Polyposis, n (%)	3 (20)*
- Bronchiectasis, n (%)	3 (20)
- Atopic dermatitis, n (%)	4 (26.5)
- Gastro-esophageal reflux, n (%)	5 (33.3)
Anosmia, n (%)	3 (20)
OCS comorbidities (osteoporosis, diabetes, cataract), n (%)	5 (33.3)
Previous monoclonal antibody treatment	10 (66.6)
- omalizumab, n (%)	8 (53.3)
- mepolizumab, n (%)	7 (46.6%)
Mean ACT score at baseline ± SD	15.6 ± 5.7
Mean AQLQ score at baseline ± SD	3.9 ± 0.4

SD, standard deviation; IQR, interquartile range; FVC, forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FEF 25–75, forced expiratory flow at 25–75% of FVC; PEF, peak expiratory flow; OCS, oral corticosteroids; ICS, inhaled corticosteroids; LABA, long-acting beta2-adrenergic agonist; LAMA, long-acting muscarinic antagonist; ACT, asthma control test; AQLQ, asthma quality of life questionnaire. *Two patients underwent functional endoscopic sinus surgery.

At March 2020, 11 patients had been treated for at least 6 months (of these, 9 were previously treated with omalizumab/benralizumab), 3 patients had been treated for less than 6 months, two patients dropped-out for side effects (headache, gastritis). Thus, 14 patients were finally evaluated. One patient was excluded due to early side effects.

After the observation period, AQLQ significantly increased from 3.9 ± 0.4 to 5.2 ± 0.4 ($p < 0.05$) (Fig. 1). This increase (+1.3 points) is higher than the minimal important difference (MID) for AQLQ (0.5 points) [8,9]. We also observed an increase in ACT, which was greater than MID, although not statistically significant (pre-benralizumab, 15.6 ± 5.7; post-benralizumab, 18.1 ± 5.6; p = NS) (Fig. 1) [10]. However, 4 patients reported an increase of at least 5 points (Fig. 1). The main activities that patients reported to be less limited under benralizumab were: work activities, talking, walking and social activities (Table 2).

Two patients with nasal polyps partially and transiently recovered from anosmia. FEV_1 showed an average increase of about 250 ml (+14%) from baseline (Fig. 1). Three patients did not show reversibility in FEV_1 in the 12 months before benralizumab (Table 1); of these, one recovered reversibility after benralizumab. FEF 25–75 improved from 51.7% to 69.7%. PEF increased from 288 ± 107 l/min to 333 ± 133 l/

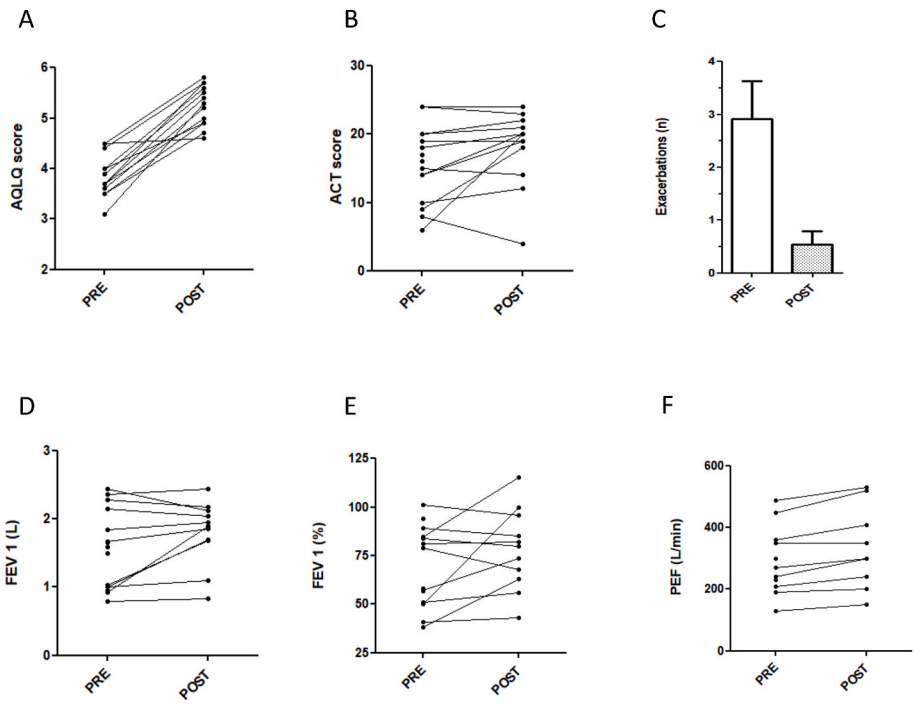

Fig. 1. Effect of benralizumab on AQLQ score (A), ACT score (B), number of exacerbations (C), FEV_1-L (D), FEV_1% (E), PEF (F).

Table 2
Patient-specific activities reported as important in determining asthma control.7

Activities	Patients
Home maintenance	6
Talking	5
Walking	4
Social activities	4
Carrying out activities at work	3
Sleeping	2
Playing with children	2
Having sexual intercourse	2
Laughing	1
Gardening	1
Running upstairs	1
Exercising	1
Dancing	1
Singing	1
Bicycling	1

min after benralizumab (Fig. 1). We also observed a decrease in the number of exacerbations requiring OCS courses from 2.8 ± 2.2 to 0.5 ± 0.8 ($p < 0.05$) (Fig. 1), with 7 out of 14 patients without any exacerbation. No exacerbation requiring emergency room access or hospitalization was observed under benralizumab. Finally, as expected, the eosinophil counts dropped down to 25.6 ± 15 cells/microliter ($p < 0.05$).

No correlation was found between patients' age and changes in AQLQ, FEV_1 (and FEV_1%), number of exacerbations, ACT, eosinophil count and PEF ($r < 0.2$ in all analyses).

4. Discussion

This analysis showed that benralizumab is effective in improving PROs (AQLQ mainly) and functional outcomes and in reducing the number of exacerbations. These findings are consistent with the results of RCTs, but within a real-life contest, suggesting that the treatment is effective in the diversity of patients in the routine care. It should be emphasized that, differently from registration RCTs, the benefit reported by our patients was observed in a difficult-to-treat cohort, with important comorbidities (e.g. bronchiectasis), and a history of previous omalizumab and/or benralizumab treatment (2/3 of cases) [1,2].

AQLQ and ACT have been increasingly used in the recent years to measure the impact of treatment on health related quality of life. Assessment in registration RCTs revealed that improvements in AQLQ and ACQ responses are smaller than one might expect, since the difference between *verum* and *placebo* groups in the score improvement from the baseline to the end of treatment was below the accepted MID of 0.5 and 2.2 points for AQLQ and ACT, respectively (about 0.2 point increase in AQLQ or ACT compared to placebo) [1,2]. In our series, we reported a modest improvement of ACT, but a significant improvement of AQLQ from the baseline to the assessment time-point, the magnitude of which is comparable to that reported in registration RCTs (about 1.5 point increase in the treatment group).

Whether this difference can be considered clinically meaningful in our observational cohort has to be carefully evaluated.

The first consideration is that our study is not a comparative effectiveness evaluation, lacking a control group; therefore, we cannot estimate the placebo contribution additional to the net drug effect. However, it should be noted that most of our patients had undergone previous treatments with one or even two other monoclonal antibodies. Thus, it is conceivable that they might have had lower expectations from the drug, possibly minimizing the placebo effect.

Furthermore, this is a retrospective evaluation. Therefore, it is unlikely that results might be biased by the Hawthorne effect (a change in the behavior of an individual that results from their awareness of being observed), that, in contrast, might be particularly pronounced in RCTs and in observational prospective studies, resulting in improvements of all outcomes from baseline and, thus, a reduced possibility to demonstrate a benefit in the treatment group [11]. This might have minimized the placebo effect too in our cohort.

Another strength of this analysis is that ACT and AQLQ were administered at each scheduled visit, reducing the methodological weakness of transition questions (e.g. patient reports of their previous health status may be influenced by their current health status), which is critical in reliably measuring patient-reported outcomes [12–14].

Finally, it has been suggested that even if the mean difference

between treatment and control is small (e.g. less than MID), treatments may have an important impact on some/many patients. An aid to interpret the importance of the results is to express the treatment benefit as the proportion of patients who have either improved, remained the same or have deteriorated, provided that the difference between the groups meet criteria for significance [15]. In our series, all but one patient reported an improvement in AQLQ and 4 patients reported a significant improvement in ACT (≥5 points; MID = 2.2), suggesting that there was a benefit (assessed by one or the other tool) that was appreciable by most of the patients (Fig. 1). This result seems to suggest a real treatment benefit, even in the absence of a control.

These real-life data are consistent with those from the Bora long-term double-blind extension trial, which included patients from the Sirocco and Calima RCTs who were willing to continue benralizumab treatment for 1 year (both from *verum* and placebo groups). This study showed an improvement of AQLQ only in patients who had previously received placebo (who had a lower AQLQ score at baseline), not in those who had received *verum* [16].

Similar findings were also reported in a recently published real-life study, showing an improvement of AQLQ and ACT6 exceeding the MID, after 1-year treatment with benralizumab [17].

Finally, lung function parameters and exacerbation rate were also assessed in this study. This was also useful to correlate the benefit reported by using PROs analyses to the benefit obtained from the accepted general efficacy measures used in clinical studies.

Regarding the exacerbation rate reduction, although the observation period was shorter in our study, we reported a remarkable benefit, with 8 out of 14 patients without any exacerbation requiring OCS treatment. Moreover, none of the patients accessed emergency room or was hospitalized. The exacerbation rate of our cohort (0.5 exacerbations per patient) was comparable to that reported in the registration RCTs (about 0.6) for the treatment group, confirming the treatment benefit in a real-life cohort including more severe patients. In fact, patients with moderate to severe disease were included in the registration RCTs and the percentage of patients already treated with monoclonal antibodies was 3% [1] to 10% [2], whereas the results of this study were drawn from a population of severe uncontrolled asthma (all patients with severe asthma; 2/3 of patients previously treated with monoclonal antibodies). Unfortunately, based on these data we were unable to detect any difference between patients previously under mepolizumab and those under omalizumab, because 8 out of these patients had already switched from omalizumab to mepolizumab before commencing benralizumab.

Same considerations are valid for FEV_1 improvement observed in our patients, whose magnitude is comparable to that reported in Sirocco and Calima RCTs [1,2].

This evidence is consistent with another real-life report showing parallel improvements in PROs, lung function and annualized exacerbation rate [17].

As for reversibility in FEV_1, one out of the three patients who did not show reversibility in the 12 months before benralizumab (Table 1), showed a reversibility after benralizumab.

Regarding symptom improvement, two patients partially and transiently recovered from anosmia, whereas other 2 patients fully recovered after functional endoscopic sinus surgery (FESS). This might support the preliminary evidence of an affect of benralizumab in delaying the recurrence of nasal polyps. However, a longer observation period is necessary to observe a clear benefit in patients with nasal polyps who did not undergo FESS.

Regarding daily activities more easily performed by the patients after bernalizumab, home maintenance, walking, talking, social and work activities were scored by at least 3 patients (3–6 patients).

It was recently shown by a meta-regression analysis of data from RCTs that age does not affect the effectiveness of anti-IL5 monoclonal antibodies in patients with severe asthma [18]. In our series we confirm that age does not affect the effectiveness of benralizumab in the real-life, supporting the use of the drug in patients with different age range.

Some safety concerns were reported in our population. Two patients discontinued treatment for apparently treatment-related side effects (gastritis and headache). Another patient complained of gastritis symptoms (but she is still under treatment). The 2 specific side effects reported in our patients were also recorded in registration RCTs; the frequency of gastritis (8%) [1] was similar between treated patients and controls, whereas the frequency of headache (8–9%) [1,2] was about 2 times higher in the treatment group compared to placebo. The side effects observed in our study subsided in the 2 patients who discontinued benralizumab and were present in the one still under treatment.

The main limitation of this study is that the sample size was too small to draw firm conclusions. Other reports are, thus, needed to confirm these findings.

In conclusion, treatment with benralizumab should be considered in difficult-to-treat patients, even after failure of other biological treatments. Most patients reported an improvement in AQLQ suggesting that this outcome appears sensitive in real-life studies for effectiveness evaluation. We believe that the clinical characteristics of the patients analyzed and the methodology used in this study might have reduced the impact of placebo effect. However, appropriate methods to estimate placebo effect are needed to reliably evaluate the magnitude of improvement in patient reported outcomes benefit in the real-life [7,8].

Author contributions

DDB and LM developed the concept of this study. EM and MA collected the data for the study. The first draft of the manuscript was written by DDB and thoroughly revised by LM. MA and EN provided critical revision of the manuscript. MFC provided financial support and critical revision of the manuscript.

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Declaration of competing interest

We declare that we have no conflict of interest.

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