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Brief Report

Patient-Reported Outcomes with Benralizumab in Patients with Severe Eosinophilic Asthma and Severe Chronic Rhinosinusitis with Nasal Polyps

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Abstract: Introduction: Chronic rhinosinusitis with nasal polyps (CRSwNP) and severe eosinophilic asthma (SEA) are common comorbidities characterised by type 2 inflammation associated with increased expression of interleukin 5. **Methods:** Eight patients with SEA and severe CRSwNP attended the Scottish Centre for Respiratory Research as part of a clinical trial (EudraCT number 2019-003763-22). Following an initial 4-week run-in period (baseline) when patients took their usual inhaled and intranasal corticosteroid treatment for SEA and CRSwNP, they all received subcutaneous benralizumab 30 mg q4w for 12 weeks. **Results:** Following 12 weeks of benralizumab, no significant differences were detected in nasal global symptom visual analogue score (VAS), hyposmia VAS, total nasal symptom score, or peak nasal inspiratory flow. In contrast, Asthma Control Questionnaire significantly improved along with near-complete depletion of peripheral blood eosinophils by 99%, while eosinophil-derived neurotoxin fell by 72%. **Conclusions:** Greater improvements in patient-reported outcomes related to asthma were observed than with CRSwNP in response to benralizumab.

Keywords: benralizumab; asthma; nasal polyps; eosinophils; patient-reported outcomes

Citation: Chan, R.; Stewart, K.; Misirovs, R.; Lipworth, B. Patient-Reported Outcomes with Benralizumab in Patients with Severe Eosinophilic Asthma and Severe Chronic Rhinosinusitis with Nasal Polyps. *Sinusitis* **2023**, *7*, 1–5. https://doi.org/10.3390/sinusitis7010001

Academic Editor: Eleonora Nucera

Received: 31 October 2022
Revised: 30 December 2022
Accepted: 19 March 2023
Published: 29 March 2023

1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) and severe eosinophilic asthma (SEA) are common comorbidities characterised by type-2 inflammation associated with increased expression of interleukin-5. Phase-3 biologic trials have all demonstrated varying degrees of efficacy in improving key patient outcomes, including endoscopic nasal polyp score (NPS) and patient-reported outcomes (PROs) in CRSwNP [1]. Real-life experience with mepolizumab has demonstrated better clinical outcomes in SEA than in CRSwNP [2]. The purpose of this study was to report on asthma and CRSwNP PROs in patients receiving anti-IL5rα therapy with benralizumab.

2. Methods

Eight patients with SEA and severe CRSwNP attended the Scottish Centre for Respiratory Research as part of a clinical trial (EudraCT 2019-003763-22) [3]. Following an initial 4-week run-in period (baseline) when patients took their usual inhaled and intranasal corticosteroid treatment, all received subcutaneous benralizumab 30 mg q4w for 12 weeks. Patients were asked to rate individual nasal symptoms at baseline and week 12 to create the composite total nasal symptom score (TNSS), with a maximum score of 12 subjectively denoting the most severe impairment [4]. Hyposmia and global symptom visual analogue scales were also recorded to determine subjective nasal symptomatic burden, with higher scores suggesting more severe impairment (max score 100 mm). An In-Check peak nasal inspiratory flow (PNIF) meter (Clement Clarke International Ltd., Harlow, UK) was used to measure nasal airway obstruction, noting the best-of-three value. Asthma control was determined using the 6-point Asthma Control Questionnaire (ACQ). Patients

were asked to perform domiciliary early morning peak expiratory flow (PEF) readings using a Mini-Wright peak-flow meter (Clement Clarke, Harlow, UK). Ethical approval was obtained from the East of Scotland research ethics committee 2 (19/ES/0134) prior to any study procedures.

3. Results

Baseline patient demographics were as follows: F/M, 1/7; mean age 54 yrs; body mass index 29 kg/m^2; aspirin-exacerbated respiratory disease 38%; ICS beclomethasone equivalent dose 2000 μg; number of positive specific IgEs 2; total IgE 383 kU/L; Lund–Mackay (LM) score 19/24; NPS 6/8; long-acting beta agonist 100%; long-acting muscarinic antagonist 50%; leukotriene receptor antagonist 50%; theophylline 13%; oral antihistamine 63%; intranasal corticosteroids 100%; and intranasal antihistamine 38%.

Following 12 weeks of benralizumab, no significant differences were detected in nasal global symptom visual analogue score (VAS), hyposmia VAS, total nasal symptom score (TNSS), or PNIF (Table 1). In contrast, ACQ significantly improved along with near-complete depletion of peripheral blood eosinophils by 99%, while eosinophil-derived neurotoxin fell by 72%. Six and two patients experienced improvements in TNSS and PNIF, respectively, surpassing minimal clinically important difference (MCID), whilst seven and four patients experienced improvements in ACQ and PEF, respectively, that exceeded MCID (Figure 1).

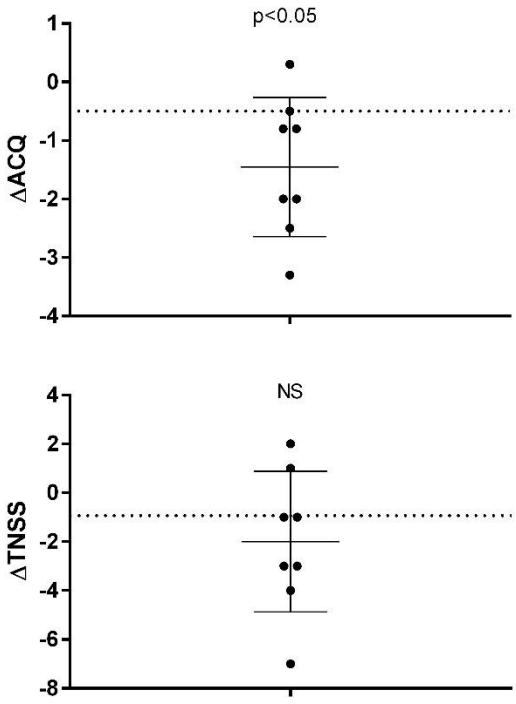

Figure 1. Individual changes in ACQ and TNSS post benralizumab therapy. Mean (95%CIs) values are shown. Dotted lines represent the MCIDs of 0.5 and 0.94 for ACQ and TNSS, respectively.

Table 1. Differences in asthma and nasal polyp outcomes after 12 weeks of benralizumab therapy.

	Baseline (Post Run-In)	Week 12 (Post Benralizumab)	Mean Diff (CI) at Week 12
Nasal global symptom VAS (mm)	78	62	−17 (−44, 10)
Hyposmia VAS (mm)	81	68	−13 (−29, 3)
TNSS	7	5	−2 (−4, 0)
PNIF (L/min)	101	109	7 (−22, 36)

Table 1. *Cont.*

	Baseline (Post Run-In)	Week 12 (Post Benralizumab)	Mean Diff (CI) at Week 12
ACQ-6	3.0	1.5 *	−1.5 (−2.4, −0.5)
Diary card PEF (L/min)	416	466	50 (−21, 121)
PBE (cells/μL)	669	4 **	−665 (−1003, −327)
EDN (ng/mL)	75.8	13.4 ***	−62.4 (−85.0, −39.9)
FeNO (ppb)	71	83	12 (−24, 47)

* $p < 0.05$ ** $p < 0.01$, *** $p < 0.001$. EDN: eosinophil-derived neurotoxin; PBE: peripheral blood eosinophils.

4. Discussion

We observed greater improvements in PROs related to asthma than CRSwNP in response to benralizumab. The mean improvement in TNSS amounted to 2 points, which exceeded the MCID of 0.94 by two-fold [5], although this was not statistically significant (Table 1). In contrast, mean ACQ improvements significantly surpassed the MCID of 0.5 units by three-fold. Improvements in PEF exceeded the MCID of 19 L/min, which was not significant [6], whilst those for PNIF did not exceed the MCID of 20 L/min [7]. Furthermore, despite numerical improvements in both hyposmia and nasal global symptom VAS scores, these did not exceed the conventional MCID of 23 mm [8]. As expected with benralizumab, peripheral blood eosinophil counts were almost completely (99%) depleted, but there was a numerical increase in FeNO, possibly inferring that patients may have inadvertently reduced their ICS dose due to improved asthma control. Eosinophil-derived neurotoxin is a degranulation protein found in eosinophils that has been shown to be more associated with asthma control than blood eosinophil count [9]. Furthermore, eosinophil-derived neurotoxin is more closely related to asthma symptoms and airway hyperresponsiveness than other degranulation proteins, such as eosinophil cationic protein [10].

Notably, the OSTRO trial in CRSwNP with benralizumab showed a small but significant 9% overall reduction in the co-primary outcomes of NPS, along with a 10% reduction in the nasal blockage score. The OSTRO trial over 40 weeks failed to show significant differences in 22-point sino-nasal outcome test (SNOT-22) or University of Pennsylvania smell identification test scores, or requirements for rescue medical or surgical polypectomy. In that study, mean ACQ score was not significantly reduced in patients with comorbid asthma, although there was a 47% lower asthma exacerbation rate. The modest effects of benralizumab on CRSwNP are perhaps counterintuitive, as patients with concomitant asthma and CRSwNP have higher peripheral blood eosinophils than those with asthma alone [11]. We appreciate that our findings are somewhat limited due to the small patient numbers in terms of not being powered a priori for PROs. Nonetheless, despite this, we observed statistically and clinically relevant improvements in asthma control. We did not perform nasal endoscopy after benralizumab, although one could argue that the 0.57 mean difference in NPS from a mean baseline of 6.14 reported in OSTRO would not have been detected in our severe CRSwNP patients who had an NPS of 6/8 and an LMS of 19/24. Pointedly, VAS scores have been shown to correlate well with SNOT-22 [12], with the latter showing no statistically or clinically relevant changes with benralizumab after 40 weeks in OSTRO.

5. Conclusions

In conclusion, we found that eosinopenia with anti-IL5Rα benralizumab therapy is associated with greater improvements in asthma PROs compared to those for CRSwNP in patients with concomitant asthma and nasal polyps.

Author Contributions: R.C. was responsible for collecting and analysing all data. R.C., K.S., R.M. and B.L. were responsible for idea conception and drafting all versions of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: The authors declare that the supply of benralizumab they received from the AstraZeneca company has not influenced their research at any level and that the outcome has been their independent, unbiased conclusion, unrelated to their association with AstraZeneca, and that there are no ethical concerns. The study has not been directly funded or influenced by AstraZeneca.

Institutional Review Board Statement: Ethical approval was obtained from the East of Scotland Research Ethics Committee (19/ES/0134) prior to any data collection.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data can be made available upon reasonable request.

Conflicts of Interest: R.C. reports personal fees (talks) and supporting attending ERS from AstraZeneca; and personal fees (talks) from Thorasys. Stewart has no relevant conflict of interest. Misirovs has no relevant conflict of interest. Lipworth reports non-financial support (equipment) from GSK; grants, personal fees (consulting, talks, and advisory board), other support (attending ATS and ERS) from AstraZeneca; grants, personal fees (consulting, talks, advisory board), and other support (attending ERS) from Teva; personal fees (consulting) from Sanofi; personal fees (consulting, talks, and advisory board) from Circassia in relation to the submitted work; personal fees (consulting) from Lupin; personal fees (consulting) from Glenmark; personal fees (consulting) from Reddy; personal fees (consulting) from Sandoz; grants, personal fees (consulting, talks, advisory board), and other support (attending BTS) from Boehringer Ingelheim; grants and personal fees (advisory board and talks) from Mylan outside of the submitted work; and the son of B.L. is presently an employee of AstraZeneca.

Abbreviations

ACQ	asthma control questionnaire
CI	confidence interval
CRSwNP	chronic rhinosinusitis with nasal polyps
FeNO	fractional exhaled nitric oxide
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IL	interleukin
LM	Lund–Mackay
MCID	minimal clinically important difference
NPS	nasal polyp score
PEF	peak expiratory flow
PNIF	peak nasal inspiratory flow
PRO	patient-reported outcome
SEA	severe eosinophilic asthma
SNOT-22	22-point sino-nasal outcome test
TNSS	total nasal symptom score
VAS	visual analogue score

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