Real life effects of benralizumab on airway oscillometry in severe eosinophilic asthma

Chan, Rory; Lipworth, Brian J.

Published in:
BMJ Open Respiratory Research

DOI:
10.1136/bmjresp-2022-001472

Publication date:
2023

BMJ Open Respiratory Research

Real-life effects of benralizumab on airway oscillometry in severe eosinophilic asthma

Rory Chan, Brian J Lipworth

To cite: Chan R, Lipworth BJ. Real-life effects of benralizumab on airway oscillometry in severe eosinophilic asthma. *BMJ Open Resp Res* 2023;**10**:e001472. doi:10.1136/bmjresp-2022-001472

Received 24 September 2022
Accepted 21 April 2023

Scottish Centre for Respiratory Research, University of Dundee School of Medicine, Dundee, UK

Correspondence to
Professor Brian J Lipworth; b.j.lipworth@dundee.ac.uk

ABSTRACT

Introduction Eosinophil depletion with benralizumab reduces exacerbations and improves disease control and FEV_1 in patients with severe eosinophilic asthma. However, few studies have investigated the effect of biologics on small airways dysfunction (SAD) even though the latter correlates better with poor asthma control and type 2 inflammation.

Methods 21 GINA-defined severe asthma patients who were treated with benralizumab and who had baseline oscillometry-defined SAD were included in this study. Here, SAD was diagnosed only if patients satisfied both R5–R20≥0.10 kPa/L/s and AX≥1.0 kPa/L. The mean duration of follow-up between pre-benralizumab versus post-benralizumab clinical measurements was 8 months.

Results Mean values for FEV_1% and FVC% but not $FEF_{25\%–75\%}$ significantly increased following benralizumab, along with significant reductions in Asthma Control Questionnaire (ACQ). There were no significant improvements in R5–R20, X5 or AX, while the mean (SEM) PBE count fell to 23 (14) cells/µL. In a responder analysis, n=8/21 and n=12/21 patients experienced improvements exceeding biological variability of 0.04 kPa/L/s and 0.39 kPa/L in R5–R20 and AX, respectively, in severe asthma. N=10/21, n=10/21 and n=11/21 patients experienced improvements in FEV_1, $FEF_{25–75}$ and FVC exceeding biological variability of 150 mL, 0.210 L/s and 150 mL, respectively. In contrast, n=15/21 patients experienced an improvement in ACQ greater than minimal clinical important difference of 0.5 units.

Conclusion Eosinophil depletion with benralizumab improves spirometry and asthma control but does not improve spirometry-measured or oscillometry-measured SAD in severe asthma in a real-life setting.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Phase 3 randomised controlled trials (RCTs) looking at benralizumab have demonstrated significant and modest improvements in prebronchodilator FEV_1 and Asthma Control Questionnaire (ACQ). However, the effect of benralizumab on oscillometry resistance heterogeneity (R5-R20) and reactance area (AX), in those with severe small airways dysfunction (SAD), has not been studied before.

WHAT THIS STUDY ADDS

⇒ We have confirmed findings from previous RCTs that benralizumab improves FEV_1 and ACQ and have shown that, in patients with severe SAD, benralizumab does not improve oscillometry R5–R20 and AX.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings from this pilot study suggest that eosinophil depletion alone is not sufficient to reverse the effects of severe small airways asthmatic inflammation.

INTRODUCTION

Benralizumab is a humanised IgG1κ monoclonal antibody that binds to the IL5Rα receptor on eosinophils to prevent IL5 binding and activation.[1] Eosinophil depletion with benralizumab reduces exacerbations and improves disease control and forced expiratory volume in 1 second (FEV_1) in patients with severe eosinophilic asthma.[1] However, few studies have investigated the effect of biologics on small airways dysfunction (SAD) even though the latter correlates better with poor asthma control and type 2 inflammation.[2]

One prospective study in 19 patients with severe asthma showed no improvement in resistance heterogeneity (R5–R20) or reactance area (AX), measuring peripheral airways resistance and compliance respectively, after 24 weeks of benralizumab.[3] Pointedly the mean baseline R5–R20 and AX values in this study were normal and consequently one might not expect any room for improvement. As a result, we performed a retrospective review of our severe asthma database of patients with abnormal baseline oscillometry-defined SAD treated with benralizumab.

METHODS

Oscillometry was measured prior to spirometry using Impulse Oscillometry (IOS) Masterscreen (Carefusion, Hoechberg, Germany) with measurements

Table 1 Mean differences (95% CI) in spirometry, oscillometry, type 2 inflammation and asthma control pre-benralizumab versus post-benralizumab

	Mean difference (95% CI)
FEV_1 (mL)	230 (88, 373)**
FEV_1 (%)	8.8 (3.7, 13.8)**
$FEF_{25–75}$ (L/s)	0.156 (–0.064, 0.377)
$FEF_{25–75}$ (%)	4.9 (–2.1, 11.9)
FVC (mL)	248 (102, 394)**
FVC (%)	8.4 (4.1, 12.6)***
FEV_1/FVC	1.4 (–1.3, 4.1)
R5 (kPa/L/s)	–0.03 (–0.10, 0.03)
R5 (%)	–12.0 (–30.5, 6.5)
R20 (kPa/L/s)	–0.02 (–0.06, 0.01)
R5–R20 (kPa/L/s)	–0.01 (–0.06, 0.04)
X5 (kPa/L/s)	0.05 (–0.01, 0.11)
AX (kPa/L)	–0.40 (–1.09, 2.97)
Fres (Hz)	–0.50 (–3.22, 2.21)
FeNO (ppb)	0 (–11, 11)
PBE (cells/µL)	–430 (–584, to –277)***
ACQ	–1.2 (–1.8, –0.6)***

**p<0.01, ***p<0.001.
ACQ, Asthma Control Questionnaire; AX, reactance area; $FEF_{25–75}$, forced expiratory flow rate between 25% and 75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; PBE, peripheral blood eosinophils.

performed in triplicate according to the ERS technical standards. Spirometry (Micromedical, Chatham, UK) was performed according to European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines. Fractional exhaled nitric oxide (FeNO) was measured using NIOX VERO (Circassia, Oxford, UK) according to the manufacturer's instructions and ATS guidelines. Asthma control was determined using the Asthma Control Questionnaire (ACQ). The number of severe exacerbations requiring OCS over the past year prior to benralizumab and in the 6 months subsequent to biological initiation was retrieved from medical records. FeNO, oscillometry, spirometry and ACQ were carried out contemporaneously while peripheral blood eosinophil (PBE) counts were averaged over the preceding year due to temporal variability in severe asthma. The mean (SEM) duration between benralizumab initiation and postbiological pulmonary function testing was 8 (0.7) months.

Statistical analysis using SPSS V.27 involved paired Student's t-tests to detect significant differences (95% CI) in pulmonary function, asthma control and type 2 inflammation pre-benralizumab vs post-benralizumab. Demographic values are presented as means (SEM) with an alpha error set at 0.05. Missing values (1.3% of entire dataset) were substituted using multiple imputation. Caldicott approval was obtained prior to data collection.

21 Global INitiative for Asthma (GINA) defined severe asthma patients with concomitant oscillometry-defined SAD were included in this study. Here, SAD was diagnosed only if patients satisfied both R5-R20≥0.10 kPa/L/s and AX≥1.0 kPa/L.

RESULTS

Baseline mean (SEM) patient demographics were as follows: age 56 (2), gender (F/M) 12/9, inhaled corticosteroid (ICS) beclomethasone equivalent 1895 (61) µg, body mass index 31.5 (1.3) kg/m^2, long-acting beta agonist 90%, long-acting muscarinic antagonist 62%, leukotriene receptor antagonist 52%, theophylline 24%, oral antihistamine 52%, nasal polyps 24%, ex-smokers 19%, average PBE 453 (70) cells/µL, highest PBE 659 (84) cells/µL, FeNO 45 (8) ppb, number of specific IgE 2.1 (0.4), total IgE 492 (195) kU/L, FEV_1 75 (4)%, forced expiratory flow rate between 25 and 75% of forced vital capacity ($FEF_{25–75}$) 41 (5)%, forced vital capacity (FVC) 93 (4)%, FEV_1/FVC 67 (2), R5 192 (16)%, R5 0.68 (0.05) kPa/L/s, R20 0.44 (0.03) kPa/L/s, R5–R20 0.24 (0.04) kPa/L/s, X5–0.36 (0.05) kPa/L/s, AX 3.55 (0.60) kPa/L, ACQ 2.6 (0.2) and number of exacerbations requiring OCS in past year 3.9 (0.4).

In patients with chronic rhinosinusitis with nasal polyps (CRSwNP) (n=5/21), mean nasal polyp scores and Lund Mackay scores were 6/8 and 16/24, respectively. Three patients remained on maintenance OCS following benralizumab initiation at daily doses of 1, 3 and 7.5 mg.

Mean values for FEV_1% and FVC% but not $FEF_{25–75}$% significantly increased following benralizumab, along with significant reductions in ACQ (table 1). There were no significant improvements in R5–R20, X5 or AX, while the mean (SEM) PBE count fell to 23 (14) cells/µL. Individual prebiological versus postbiological values for pulmonary function, ACQ and PBE counts are presented (figure 1).

In a responder analysis, n=8/21 and n=12/21 patients experienced improvements exceeding biological variability of 0.04 kPa/L/s and 0.39 kPa/L in R5–R20 and AX, respectively, in severe asthma.[4] A significantly higher FVC (101.2% vs 85.1% p=0.024) was detected in R5–R20 responders versus non-responders. N=10/21, n=10/21 and n=11/21 patients experienced improvements in FEV_1, $FEF_{25–75}$ and FVC exceeding biological variability of 150 mL, 0.210 L/s and 150 mL, respectively. In contrast, n=15/21 patients experienced an improvement in ACQ greater than MCID of 0.5.

In patients with baseline impaired $FEF_{25–75}$<60% (n=17/21), an increase (95% CI) amounting to 8.6% (3.2% to 13.9%) p=0.004 was detected. No correlations were detected in changes in R5–R20, AX, FEV_1 or $FEF_{25–75}$ with changes in asthma control. Four patients required

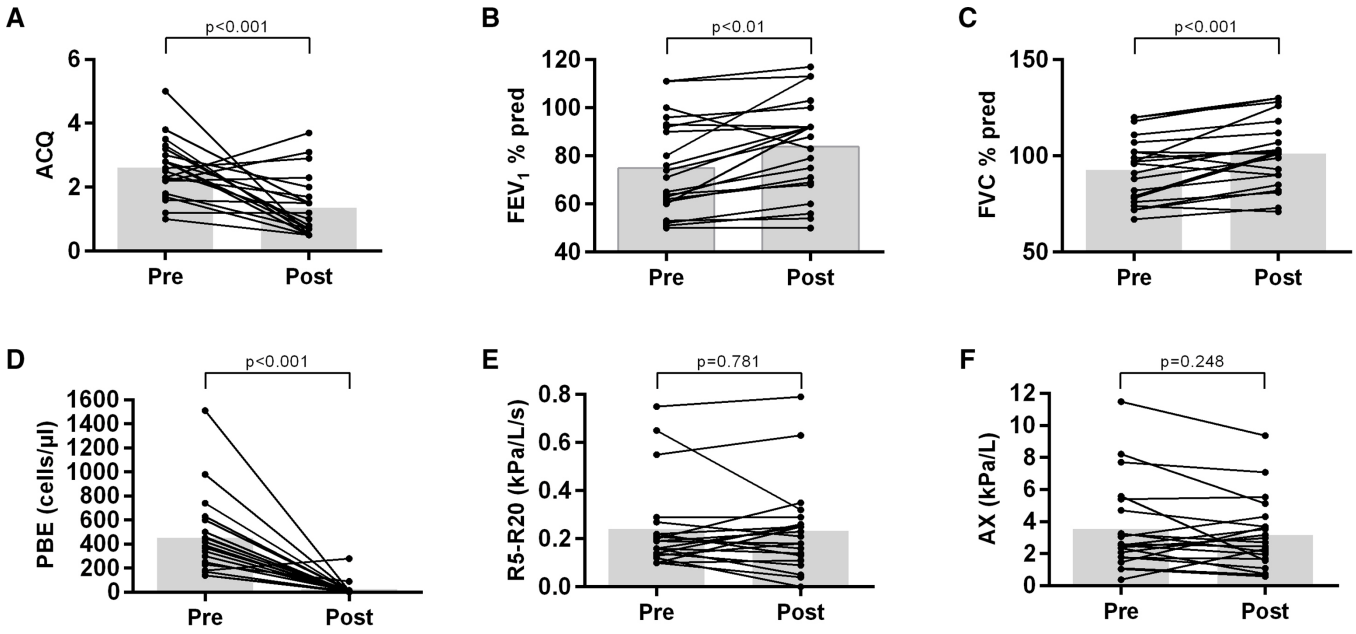

Figure 1 Before and after graph depicting individual treatment responses and means for (A) ACQ (B) FEV_1% (C) FVC% (D) PBE (E) R5–R20 and (F) AX for pre-benralizumab versus post-benralizumab therapy. ACQ, Asthma Control Questionnaire; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; AX, reactance area; PBE, peripheral blood eosinophils.

one course of rescue OCS in the 6-month follow-up period.

N=10/21 patients were taking extra fine particle size ICS inhalers. When compared with the remaining n=11/21 patients, no differences were detected in ΔFEV1%, ΔFEF25–75%, ΔR5–R20, ΔAX or ΔACQ.

DISCUSSION

Our real-life study is the first to look at the effects of benralizumab in severe asthma patients selected according to oscillometry-defined SAD. We opted for a R5–R20 cut point of 0.10 kPa/L/s as a previous prospective study[5] using computational modelling demonstrated that 0.08 kPa/L/s was most indicative of small airways constriction. Another study[6] demonstrated that R5–R20 at a cut point 0.10 kPa/L/s identified patients with impaired $FEF_{25–75}$% who had worse asthma control and more frequent exacerbations requiring OCS.

Although our cohort had severe SAD, no significant improvements in oscillometry outcomes were detected following 6 months of benralizumab. In keeping with the phase 3 trials, our patients experienced significant improvements in FEV_1 amounting to 230 mL meeting the MCID in asthma.[7] This occurred in conjunction with significant mean improvements in ACQ scores surpassing MCID of 0.5 units more than twofold.[8] Similar to findings from another real-life study,[9] our patients experienced a significant mean improvement in FVC amounting to 248 mL suggesting partial reversal of lung hyperinflation, exceeding biological variability of 150 mL.[4] Despite being somewhat underpowered, R5–R20 responder analysis still identified higher prebiological FVC% predicted in responders. It has previously been discussed[10] that severe asthma patients with detectable hyperinflation could be exhibiting a pathophysiological process that increases small airway closure but this requires more research to fully elucidate.

One multicentre observational study[11] demonstrated a significant 17% improvement in $FEF_{25–75}$ after 6 months of benralizumab where median baseline $FEF_{25–75}$ and PBE were 38% and 705 cells/µL, respectively. Another real-life study[9] showed that $FEF_{25–75}$ improved by 0.820 L/s over 24 weeks in severe eosinophilic asthma patients (median baseline 810 cells/µL) exceeding biological variability value[4] for a clinically relevant effect. Although our severe asthma cohort had comparable baseline demographics, we did not detect a significant improvement in $FEF_{25–75}$ raising the question whether this could be due to our lower mean baseline PBE count of 453 cells/µL. This is perhaps relevant as the degree of small airways inflammation is generally related to airway remodelling and progression of asthma.[12] A subgroup analysis in 17 of our patients with $FEF_{25–75}$<60% showed a significant improvement amounting to 0.271 L/s aligning with the results of the aforementioned studies and exceeding biological variability of 0.210 L/s.

We recognise the limitations of this study including its retrospective nature and relatively small numbers of patients although similar to currently published studies. However, we hope that the novelty of only including patients with genuine SAD as a starting point might mitigate this. Furthermore, the absence of any change in FeNO following benralizumab

therapy supports the notion that spirometry improvements were likely due to anti-IL5Rα rather than alterations in ICS compliance. N=10/21 patients took extra fine particle size ICS inhalers while all patients in this study still exhibited severe SAD at baseline so there would theoretically be plenty room for improvement. In this regard, the small airways are of utmost importance in achieving optimal asthma control as a significant proportion of patients with preserved FEV_1% still have evidence of underlying SAD.[13]

In conclusion, eosinophil depletion with benralizumab improves spirometry and asthma control but does not improve spirometry-measured or oscillometry-measured SAD in severe asthma in a real-life setting. We hope that the results of this pilot study will form the basis for larger prospective studies that can definitively answer the question of whether benralizumab improves oscillometry defined SAD in severe asthma.

Contributors RC and BJL jointly contributed to idea conception, data collection, analysis and writing all versions of the manuscript. BJL is responsible for the overall content as the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests RC reports personal fees (talks) and support attending ERS from AstraZeneca, personal fees (consulting) from Vitalograph, and personal fees (talks) from Thorasys. BJL reports non-financial support (equipment) from GSK; grants, personal fees (consulting, talks and advisory board), other support (attending ATS and ERS) and from AstraZeneca; personal fees (talks and consulting) from Sanofi, personal fees (consulting, talks and advisory board) from Circassia in relation to the submitted work; grants, personal fees (consulting, talks, advisory board), other support (attending ERS) from Teva, personal fees (talks and consulting), grants and other support (attending ERS and BTS) from Chiesi, personal fees (consulting) from Lupin, personal fees (consulting) from Glenmark, personal fees (consulting) from Vectura, personal fees (consulting) from Dr Reddy, personal fees (consulting) from Sandoz; grants, personal fees (consulting, talks, advisory board), 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 BJL is presently an employee of AstraZeneca.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

REFERENCES

1 Chan R, RuiWen Kuo C, Lipworth B. Pragmatic clinical perspective on Biologics for severe refractory type 2 asthma. *J Allergy Clin Immunol Pract* 2020;8:3363–70.
2 Kuo CR, Chan R, Lipworth B. Impulse Oscillometry Bronchodilator response and asthma control. *J Allergy Clin Immunol Pract* 2020;8:3610–2.
3 Shirai T, Akamatsu T, Hirai K, *et al*. Oscillometry improves earlier than Spirometry after Benralizumab initiation in severe asthma. *Allergy* 2020;75:2678–80.
4 Chan R, Misirovs R, Lipworth B. Repeatability of impulse Oscillometry in patients with severe asthma. *Eur Respir J* 2022;59:2101679.
5 Foy BH, Soares M, Bordas R, *et al*. Lung computational models and the role of the small Airways in asthma. *Am J Respir Crit Care Med* 2019;200:982–91.
6 Chan R, Lipworth B. Interactions between Spirometry and Oscillometry in patients with moderate to severe asthma. *Eur Respir J* 2022;60:2200543.
7 Santanello NC, Zhang J, Seidenberg B, *et al*. What are minimal important changes for asthma measures in a clinical trial *Eur Respir J* 1999;14:23–7.
8 Juniper EF, O'byrne PM, Guyatt G h, *et al*. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902.
9 Pelaia C, Busceti MT, Crimi C, *et al*. Real-life effects of Benralizumab on exacerbation number and lung Hyperinflation in Atopic patients with severe eosinophilic asthma. *Biomed Pharmacother* 2020;129:110444.
10 Sorkness RL, Bleecker ER, Busse WW, *et al*. Lung function in adults with stable but severe asthma: Air trapping and incomplete reversal of obstruction with Bronchodilation. *J Appl Physiol (1985)* 2008;104:394–403.
11 Nolasco S, Crimi C, Pelaia C, *et al*. Benralizumab effectiveness in severe eosinophilic asthma with and without chronic Rhinosinusitis with nasal polyps: A real-world multicenter study. *J Allergy Clin Immunol Pract* 2021;9:4371–80.
12 Bjermer L. The role of small airway disease in asthma. *Curr Opin Pulm Med* 2014;20:23–30.
13 Manoharan A, Anderson WJ, Lipworth J, *et al*. Small airway dysfunction is associated with poorer asthma control. *Eur Respir J* 2014;44:1353–5.