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

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ABSTRACT

Introduction  Eosinophil depletion with benralizumab reduces exacerbations and improves disease control and FEV₁ 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 FEV₁ % and FVC% but not FEF₂₅–₇₅ % 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=9/21 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 FEV₁, FEF₂₅–₇₅ 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.

INTRODUCTION

Benralizumab is a humanised IgG1κ monoclonal antibody that binds to the IL₅Rα receptor on eosinophils to prevent IL₅ binding and activation. Eosinophil depletion with benralizumab reduces exacerbations and improves disease control and forced expiratory volume in 1 second (FEV₁) 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.

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. 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

<table>
<thead>
<tr>
<th>Mean difference (95% CI)</th>
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<tbody>
<tr>
<td>FEV(_1) (mL)</td>
<td>230 (88, 373)**</td>
</tr>
<tr>
<td>FEV(_1) (%)</td>
<td>8.8 (3.7, 13.8)**</td>
</tr>
<tr>
<td>FEF(_{25-75}) (L/s)</td>
<td>0.156 (−0.064, 0.377)</td>
</tr>
<tr>
<td>FEF(_{25-75}) (%)</td>
<td>4.9 (−2.1, 11.9)</td>
</tr>
<tr>
<td>FVC (mL)</td>
<td>248 (102, 394)**</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>8.4 (4.1, 12.6)***</td>
</tr>
<tr>
<td>FEV(_1)/FVC</td>
<td>1.4 (−1.3, 4.1)</td>
</tr>
<tr>
<td>R5 (kPa/L/s)</td>
<td>−0.03 (−0.10, 0.03)</td>
</tr>
<tr>
<td>R5 (%)</td>
<td>−12.0 (−30.5, 6.5)</td>
</tr>
<tr>
<td>R20 (kPa/L/s)</td>
<td>−0.02 (−0.06, 0.01)</td>
</tr>
<tr>
<td>R5−R20 (kPa/L/s)</td>
<td>−0.01 (−0.06, 0.04)</td>
</tr>
<tr>
<td>X5 (kPa/L/s)</td>
<td>0.05 (−0.01, 0.11)</td>
</tr>
<tr>
<td>AX (kPa/L)</td>
<td>−0.40 (−1.09, 2.97)</td>
</tr>
<tr>
<td>Fres (Hz)</td>
<td>−0.50 (−3.22, 2.21)</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>0 (−11, 11)</td>
</tr>
<tr>
<td>PBE (cells/µL)</td>
<td>−430 (−584, to −277)***</td>
</tr>
<tr>
<td>ACQ</td>
<td>−1.2 (−1.8, −0.6)***</td>
</tr>
</tbody>
</table>

**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.

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. There were no significant improvements in R5−R20, X5 or AX, while significant reductions in ACQ (table 1). There were no significant improvements in R5−R20, X5 or AX, while significant reductions in ACQ (table 1).

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)%.

Mean values for FEV\(_1\), FVC, FEF\(_{25-75}\), R5, R5−R20, X5 and AX exceeded biological variability of 0.04 kPa/L/s and 0.39 kPa/L in R5−R20 and AX, respectively, in severe asthma.

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\(_1\), FVC and PEF% 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.

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 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 (1.5% 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.
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 \( \Delta \text{FEV1\%} \), \( \Delta \text{FEF25–75\%} \), \( \Delta \text{R5–R20} \), \( \Delta \text{AX} \), or \( \Delta \text{ACQ} \).

**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 meaningful improvements in ACQ scores surpassing MCID of 0.5 units more than twofold.\(^8\) Similar to findings from another real-life study,\(^3\) our patients experienced a significant mean improvement in FVC amounting to 150 mL.\(^4\) Despite being somewhat underpowered, R5–R20 responder analysis still identified higher prebiological FVC\% predicted in responders. It has previously been discussed\(^9\) that severe asthma patients with detectable hyperinflation could be exhibiting a pathophysiological process that increases small airway closure and this results in 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 FEV1% 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.

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