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

Rory Chan, Brian J Lipworth

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=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 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>Parameter</th>
<th>Mean difference (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>FEV1 (mL)</td>
<td>230 (88, 373)**</td>
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<tr>
<td>FEV1 (%)</td>
<td>8.8 (3.6, 13.8)**</td>
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<tr>
<td>FEF25–75 (L/s)</td>
<td>0.156 (−0.064, 0.377)</td>
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<tr>
<td>FEF25–75 (%)</td>
<td>4.9 (−2.1, 11.9)</td>
<td></td>
</tr>
<tr>
<td>FVC (mL)</td>
<td>248 (102, 394)**</td>
<td></td>
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<tr>
<td>FVC (%)</td>
<td>8.4 (4.1, 12.6)***</td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>1.4 (−1.3, 4.1)</td>
<td></td>
</tr>
<tr>
<td>R5 (kPa/L/s)</td>
<td>−0.03 (−0.10, 0.03)</td>
<td></td>
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<tr>
<td>R5 (%)</td>
<td>−12.0 (−30.5, 6.5)</td>
<td></td>
</tr>
<tr>
<td>R20 (kPa/L/s)</td>
<td>−0.02 (−0.06, 0.01)</td>
<td></td>
</tr>
<tr>
<td>X5 (kPa/L/s)</td>
<td>0.05 (−0.01, 0.11)</td>
<td></td>
</tr>
<tr>
<td>AX (kPa/L)</td>
<td>−0.40 (−1.09, 2.97)</td>
<td></td>
</tr>
<tr>
<td>Fres (Hz)</td>
<td>−0.50 (−3.22, 2.21)</td>
<td></td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>0 (−11.11)</td>
<td></td>
</tr>
<tr>
<td>PBE (cells/µL)</td>
<td>−430 (−584, to −277)</td>
<td></td>
</tr>
<tr>
<td>ACQ</td>
<td>−1.2 (−1.8, −0.6)***</td>
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*p<0.01, ***p<0.001.

ACQ, Asthma Control Questionnaire; AX, reactance area; FEF25–75, forced expiratory flow rate between 25% and 75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; PBE, peripheral blood eosinophils.

**p<0.01, ***p<0.001.

ACQ, Asthma Control Questionnaire; AX, reactance area; FEF25–75, forced expiratory flow rate between 25% and 75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; PBE, peripheral blood eosinophils.

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/m², 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, FEV1 75 (4)%, forced expiratory flow rate between 25 and 75% of forced vital capacity (FEF25–75) 41 (5)%., forced vital capacity (FVC) 93 (4)%., FEV1/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 (CRSsNP) (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 FEV1% and FVC% but not FEF25–75% 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. In patients with baseline impaired FEF25–75<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, FEV1, or FEF25–75, with changes in asthma control. Four patients required...
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 \( \Delta FEV1\% \), \( \Delta FEF25–75\% \), \( \Delta R5–R20 \), \( \Delta AX \) or \( \Delta ACQ \).

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 significant mean 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 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 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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Competing interests  RC reports personal fees (talks) and support attending ERS from Chiesi, personal fees (consulting, talks and advisory board) from Circassia in relation to the submitted work; grants, personal fees (consulting, talking, advisory board) from Boehringer Ingelheim, grants and other support (attending ERS) and from Teva, personal fees (talks and consulting) from Sanofi, personal fees (consulting, talks and advisory board) from Cincinatti in relation to the submitted work; grants, personal fees (consulting, talking, advisory board), other support (attending ERS) 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, talking, advisory board), other support (attending ERS) from AstraZeneca; personal fees (consulting, talking, advisory board) from Sanofi, personal fees (consulting, talks and advisory board), grants and other support (attending ERS and BTS) from Chiesi, personal fees (consulting) from Lupin, personal fees (consulting) from Glencar, personal fees (consulting) from Vectura, personal fees (consulting) from Dr Reddy, personal fees (consulting) from Sanofit; grants, personal fees (consulting, talking, 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.

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REFERENCES