Real-World Effectiveness of Benralizumab in Severe Eosinophilic Asthma

Joanne E. Kavanagh, MBChB; Andrew P. Hearn, MBBS; Jaideep Dhariwal, PhD; Gráinne d'Ancona, MsC; Abdel Douiri, PhD; Cris Roxas, MSc; Mariana Fernandes, MSc; Linda Green, MSc; Louise Thomson, MSc; Alexandra M. Nanzer, PhD; Brian D. Kent, MD; and David J. Jackson, PhD

BACKGROUND: Benralizumab is an IL5-receptor monoclonal antibody licensed for the treatment of severe eosinophilic asthma (SEA). It has demonstrated efficacy in clinical trials in reducing asthma exacerbation rates and maintenance oral corticosteroids (mOCSs).

RESEARCH QUESTION: What is the real-world effectiveness of benralizumab and what baseline characteristics are associated with response to therapy?

STUDY DESIGN AND METHODS: We assessed outcomes in all SEA patients who began benralizumab treatment at our specialist center. At each dosing visit, exacerbation history, mOCS dose, spirometry, and Asthma Control Questionnaire (ACQ6) and Mini-Asthma Quality of Life Questionnaire (mAQLQ) scores were recorded. Response to treatment was defined as a reduction of $\geq$ 50% in annualized exacerbation rate (AER) or in mOCS dose after 48 weeks of treatment. Super response was defined as zero exacerbations and no mOCSs for asthma.

RESULTS: One hundred thirty patients were included in the analysis. At 48 weeks, a 72.8% reduction in AER was noted, from 4.92 $\pm$ 3.35 per year in the year preceding biologic treatment to 1.34 $\pm$ 1.71 per year ($P < .001$), including 57 patients (43.8%) who were exacerbation-free with benralizumab. In those receiving mOCSs (n = 74 [56.9%]), the median daily prednisolone dose fell from 10 mg (interquartile range, 5-20 mg) to 0 mg (interquartile range, 0-5 mg; $P < .001$), and 38 of 74 patients (51.4%) were able to discontinue mOCS therapy. Clinically and statistically significant improvements were found in ACQ6 scores, mAQLQ scores, and FEV_1. Overall, 51 patients (39%) met the super responder definition and 112 patients (86%) met the responder definition. The optimal regression model of super responders vs other responders included baseline characteristics associated with a strongly eosinophilic phenotype and less severe disease. Eighteen patients (13.8%) were nonresponders to benralizumab. Evidence of chronic airway infection was observed in 6 of 18 patients, and an increase in the blood eosinophil count consistent with the development of anti-drug antibodies was observed in 5 of 18 patients.

INTERPRETATION: In a large real-world SEA cohort, benralizumab led to significant improvements in all clinical outcome measures. A lack of response was seen in a minority of patients and should be a focus for future investigation. CHEST 2020; ■(■):■-■

KEY WORDS: benralizumab; eosinophil; real world; response; severe asthma

ABBREVIATIONS: ACQ6 = Asthma Control Questionnaire 6; ADA = antidrug antibody; FENO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; IQR = interquartile range; mAQLQ = Mini-Asthma Quality of Life Questionnaire; mOCS = maintenance oral corticosteroid; ppb = parts per billion; SEA = severe eosinophilic asthma

AFFILIATIONS: From the Guy's Severe Asthma Centre (J. E. Kavanagh, A. P. Hearn, J. Dhariwal, G. d'Ancona, C. Roxas, M. Fernandes, L. Green, L. Thomson, A. Nanzer, and D. J. Jackson), Guy's and St Thomas' Hospitals, the Asthma UK Centre (J. E. Kavanagh, A. P. Hearn, and D. J. Jackson), the Department of Medical Statistics (A. Douiri), King's College London, London, England; the Department of Respiratory Medicine (B. D. Kent), St. James' Hospital, and the School of Medicine (B. D. Kent), Trinity College, Dublin, Ireland.

Some of these data were presented previously in abstract form (Kavanagh J, Roxas C, Thomson L, Fernandes M, Green L, d'Ancona G, et al. *Thorax*. 2019;74(Suppl 2):A138).

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: David J. Jackson, PhD, Asthma UK Centre, School of Immunology & Microbial Sciences, King's College London; Guy's Severe Asthma Centre, Guy's Hospital, Guy's & St. Thomas' NHS Trust, London SE1 9RT, England; e-mail: David.jackson@gstt.nhs.uk

DOI: https://doi.org/10.1016/j.chest.2020.08.2083

Severe uncontrolled asthma affects approximately 3% to 5% of all adult patients with asthma and is characterized by ongoing symptoms and recurrent exacerbations, despite adherence to high-dose inhaled therapies.[1] These patients often show evidence of significant type 2 airway inflammation—identifiable by elevated blood and airway eosinophil counts and fractional exhaled nitric oxide (FENO) levels—that is only partially responsive to inhaled corticosteroids (ICSs). This historically has left these patients reliant on maintenance oral corticosteroids (mOCSs) to achieve a reasonable degree of disease control. The recent introduction of biologic therapies targeting key mediators of type 2 (T2) inflammation including IgE,[2] IL-5/5 receptor,[3-5] and IL-4/13[6] therefore provided the first opportunity for these patients to improve their day-to-day symptom control and reduce exacerbation risk without the excess morbidity and mortality associated with oral corticosteroid exposure.[7,8]

The monoclonal antibody benralizumab binds to the IL-5 receptor expressed on eosinophils, eosinophilic precursors and basophils, resulting in the rapid apoptosis and near complete depletion of these cells through enhanced antibody-mediated cytotoxicity.[9] Three phase 3 randomized controlled trials have assessed the clinical efficacy of benralizumab in patients with uncontrolled severe eosinophilic asthma (SEA): CALIMA[9] and SIROCCO[10] both demonstrated significant reductions in exacerbations as well as improvements in lung function, asthma control, and quality-of-life measures, whereas ZONDA[11] recruited patients with SEA requiring mOCS therapy and demonstrated a median reduction in daily mOCS dose of 50% vs placebo alongside a 70% reduction in the annualized exacerbation rate.

However, it is recognized that patients recruited to phase 3 trials of biologic agents are not fully representative of severe asthma clinic populations. Trial cohorts often seem to have moderate to severe disease, rather than genuinely severe asthma, as evidenced by large improvements in symptoms, lung function, and exacerbation frequency in the placebo arm of these studies.[10,12-14] This perhaps reflects the resolution of airway inflammation with improved ICS adherence and more focussed clinical care after trial entry. Similarly, trial recruitment criteria often exclude patients with fixed airflow obstruction, significant smoking history, and medical comorbidities.[14] Consequently, real-world data are highly desirable to confirm the effectiveness of these therapies in severe asthma clinic populations. Currently, these data are lacking for benralizumab in SEA. Herein, we present real-world experience of this therapy in a large cohort of SEA patients who have undergone extensive investigation and confirmation of severe eosinophilic asthma before commencement of benralizumab.

Methods

Study Design and Approval

We performed a retrospective analysis of all patients with SEA who commenced treatment with benralizumab between May 2018 and April 2019 at our tertiary referral asthma center in the United Kingdom. Ethical approval was gained from the London—Bloomsbury Research Ethics Committee (Identifier: 15/LO/0886).

Study Participants

All patients were reviewed by an asthma physician, fulfilled the ERS/ATS definition of severe asthma,[15] and had confirmed adherence to background therapy (via ICS or long-acting β2 agonist prescription record, FENO suppression testing, paired blood prednisolone and cortisol levels, or a combination thereof). Patients subsequently began benralizumab therapy if they had an eosinophil count of $\geq 0.4 \times 10^9$/L in the preceding 12 months and a minimum of three exacerbations in the prior year, an eosinophil count of $\geq 0.3 \times 10^9$/L in the preceding 12 months and a minimum of four exacerbations in the prior year, were receiving mOCS therapy, or a combination thereof. Exacerbations were defined as a worsening in asthma control requiring $\geq$ 3 days of oral prednisolone treatment (or a doubling of prednisolone dose if receiving mOCS therapy). The benralizumab dose was 30 mg sc every 4 weeks for the first three doses, and then 30 mg sc every 8 weeks. Baseline exacerbation frequency was determined by a combination of patient report and confirmation by review of primary care and hospital prescription records. Patients who did not complete $\geq$ 24 weeks of benralizumab treatment were excluded from the analysis.

Clinical Outcomes and Analysis

Clinical assessment was performed at each benralizumab dosing visit. Data collected at these time points included: clinic spirometry, FENO, blood eosinophil count, Asthma Control Questionnaire 6 (ACQ6) score,[16] Mini-Asthma Quality of Life Questionnaire (mAQLQ) score,[17] mOCS dose, and number of exacerbations since the last clinic visit. Patient demographic data were collected from the electronic patient record. Patients were classified as responders or nonresponders after 48 weeks of treatment, with response being defined as $\geq$ 50% reduction in the annualized exacerbation rate or, for patients requiring mOCS therapy, $\geq$ 50% reduction in daily mOCS dose. Patients requiring a mOCS dose of $\leq$ 5 mg for adrenal insufficiency were classified as not requiring mOCS therapy for asthma. A further analysis was undertaken of super responders, representing a subgroup of the responders who no longer required mOCS therapy for asthma and were completely exacerbation-free. All patients who did not complete a full year of treatment because of a lack of response automatically were classified as nonresponders.

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Statistical Analysis

Data were analyzed using SPSS version 24 software (IBM SPSS). Figures were generated using GraphPad Prism version 8 software (GraphPad Software). Data are given as mean (SD) if normally distributed or median (interquartile range [IQR]) if nonparametric. Parametric variables were compared using Student *t* tests (paired or independent) and nonparametric variables using Mann-Whitney *U* tests (unrelated) or Wilcoxon signed-rank tests (related). Categorical variables were analyzed by the χ^2 test or Fisher exact test where appropriate. Additional analyses of responders were conducted using logistic regression. Variable selection using subsampling methodology was conducted to construct the optimal regression model. Differences were considered significant at $P < .05$. All P values are two-sided.

Results

A total of 136 patients began benralizumab therapy, with 6 patients excluded from the analysis because they stopped treatment before 24 weeks: 3 did not complete clinic follow-up; 2 stopped because of presumed medication-related adverse events; and 1 stopped because of pregnancy. A further 7 patients stopped between 24 and 48 weeks because of suboptimal response; these patients were included in the analysis. The baseline characteristics of the included patients (n = 130) reflected those of severe eosinophilic asthma populations: 61.5% of patients were women, the average

TABLE 1] Baseline Characteristics (N = 130)

Variable	Data
Age, y	52.8 ± 14.0
Female sex	80 (61.5)
BMI, kg/m^2	31.1 ± 7.1
Atopy[a]	96 (73.8)
Adult-onset disease (≥ 18 y)	68 (52.3)
Nasal polyposis	39 (30.2)
Smoking history (n = 128)	...
Never smoker	88 (68.8)
Former smoker	38 (29.7)
Current smoker	2 (1.6)
Pack-year history (for former or current smokers; n = 31[b])	20.76 ± 14.3
Coexistent COPD	9 (7.0)
Peak blood eosinophil count in the year preceding anti-IL5-receptor therapy, cells × 10^9/L	0.6 (0.4-0.9)
Baseline blood eosinophil count, cells × 10^9/L	0.2 (0.1-0.4)
FENO, ppb	45 (26-78)
Exacerbation rate in year before anti-IL5 or IL5-receptor therapy	4.92 ± 3.35
Previous omalizumab treatment	16 (12.3)
Previous anti-IL5 treatment	48 (36.9)
High-dose ICS or LABA treatment	130 (100.0)
Receiving mOCS therapy	74 (56.9)
Median mOCS dose, prednisolone, mg/d[c]	10 (5-20)
FEV_1, L	1.76 ± 0.69
FEV_1, % predicted	63.8 ± 20.6
ACQ6 score	2.90 ± 1.39
mAQLQ score	3.46 ± 1.49

Data are presented as No. (%), mean ± SD, or median (interquartile range). ACQ6 = Asthma Control Questionnaire 6; FENO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; mOCS = maintenance oral corticosteroid; mAQLQ = Mini-Asthma Quality of Life Questionnaire; ppb = parts per billion.

[a]Defined as raised specific IgE to ≥ 1 common aero-allergen or a clinical history of eczema.

[b]Data unavailable for 9 patients.

[c]Calculated from the subgroup receiving mOCS therapy at baseline (n = 74).

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age was 52.8 ± 14.0 years, and the mean BMI was 31.1 ± 7.1 kg/m^2 (Table 1). All patients were prescribed high-dose ICS or long-acting β2 agonist, with 57% requiring mOCS therapy. Despite high-dose corticosteroid therapy, asthma control was poor, as manifested by recurrent exacerbations, airflow obstruction, persistent type 2 airway inflammation, and impaired patient-reported outcome measures. Regarding previous treatments, 12.3% of patients had received omalizumab previously, whereas 36.9% had received previous anti-IL5 therapy with mepolizumab, reslizumab, or both.

After 48 weeks of treatment with benralizumab, overall disease control improved significantly (Table 2). A 72.8% reduction in annualized exacerbation rate was noted, from 4.92 ± 3.35 to 1.34 ± 1.71 per year ($P <$ .001), with parallel improvements seen in lung function (change in FEV_1, 140 mL; $P <$ .001), ACQ6 score (from 2.90 ± 1.39 to 2.15 ± 1.41; $P <$ .001), and mAQLQ score (from 3.46 ± 1.49 to 4.35 ± 1.51; $P <$ .001) (Fig 1). Improvements in both patient-reported outcome measures exceeded the accepted minimal clinically important difference of 0.5 and were seen as early as 4 weeks after initiation of treatment. Peripheral blood eosinophil counts were suppressed, but no significant change was seen in median FENO levels. Benralizumab generally was well tolerated, with only two patients discontinuing because of apparent side effects.

Among patients requiring mOCS therapy at baseline, a median reduction in mOCS dosage of 100% was achieved at 48 weeks (Fig 2A): 51.4% were able to discontinue all mOCSs, and 70.3% were no longer taking mOCSs for asthma (this includes additional patients who continued to take a small dose for adrenal insufficiency) (Fig 2B). However, 12.2% were unable to reduce mOCS therapy or required an increase in mOCS dosage despite benralizumab therapy (Table 3).

When defined as a ≥ 50% reduction in either exacerbation frequency or daily mOCS dose, 86.2% of patients showed a significant response to treatment with benralizumab. Nonresponders were more likely to be women (83.3% vs 58.0%; $P = .041$) and to show lower median baseline FENO of 29 parts per billion (ppb; IQR, 19-48 ppb) vs 48 ppb (IQR, 26-82 ppb) vs responders ($P = .048$). No significant differences otherwise were noted in baseline demographic or clinical characteristics, comorbidities, lung function, or measures of inflammation (Table 4).

In total, 51 patients (39%) were super responders, defined as zero exacerbations and no mOCS therapy for asthma. Comparing super responders with responders who did not meet the super-responder criteria, super responders showed higher peak blood eosinophil counts in the year before benralizumab treatment, 0.70 cells × 10^9/L (IQR, 0.5-1.1 cells × 10^9/L) vs 0.5 cells × 10^9/L (IQR, 0.45-0.7 cells × 10^9/L; $P = .010$), and higher baseline eosinophils, 0.30 cells × 10^9/L (IQR, 0.1-0.5 cells × 10^9/L) vs 0.1 cells × 10^9/L (IQR, 0.0-0.4 cells × 10^9/L; $P = .035$). They also were more likely to have adult-onset disease (65% vs 41%; $P = .015$) and nasal polyposis (37% vs 20%; $P = .015$). Baseline lung function was better in super responders than responders when measured in absolute terms (FEV_1, 1.92 ± 0.64 L vs 1.62 ± 0.74 L; $P = .028$) and trended toward significance when measured as FEV_1 percent

TABLE 2] One-Year Outcomes (N = 130)

Outcome	Baseline	48 Weeks	*P* Value
Annual exacerbation rate	4.92 ± 3.35	1.34 ± 1.71	< .001
OCS dose, prednisolone, n = 74, mg/d	10 (5-20)	0 (0-5)	< .001
ACQ6 score	2.90 ± 1.39	2.15 ± 1.41	< .001
mAQLQ score	3.46 ± 1.49	4.35 ± 1.51	< .001
FEV_1 after bronchodilator, L	1.76 ± 0.69	1.90 ± 0.70	< .001
FEV_1 after bronchodilator, % predicted	63.8 ± 20.6	69.4 ± 21.9	< .001
Blood eosinophil count, cells × 10^9/L	0.2 (0.1-0.4)	0.0 (0.0-0.0)	< .001
FENO, ppb	45 (26-78)	38 (23-71)	.135
Responder rate[a]	N/A	112 ± 86.2	N/A
Super-responder rate[b]	N/A	51 ± 39.2	N/A

Data are presented as mean ± SD or median (interquartile range). N/A = not applicable; OCS = oral corticosteroid. See Table 1 legend for expansion of other abbreviations.
[a]Fifty percent or more reduction in mOCS dose or, if not receiving mOCS therapy, ≥ 50% reduction in annual exacerbation rate.
[b]Not receiving maintenance oral corticosteroid therapy for asthma and zero exacerbations with benralizumab treatment.

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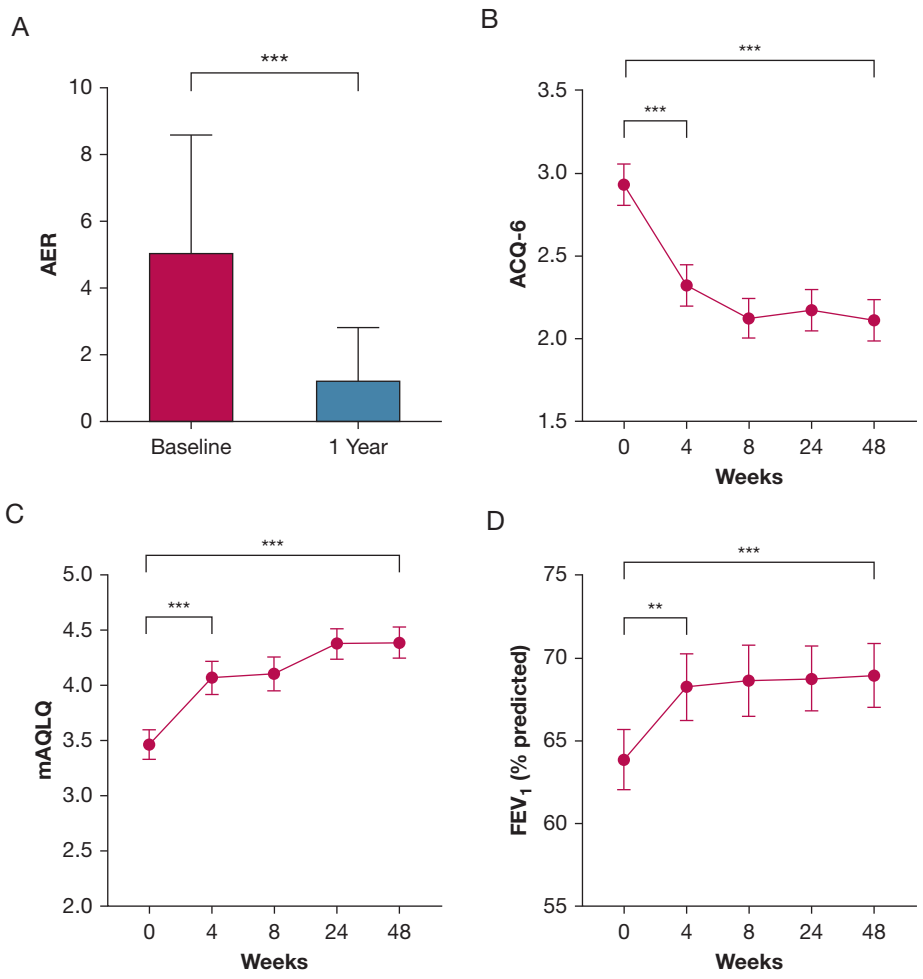

Figure 1 – *Graphs showing clinically significant outcome measures with benralizumab treatment. ACQ6 = Asthma Control Questionnaire 6; AER = annualized exacerbation rate; mAQLQ = Mini Asthma Quality of Life Questionnaire. **P ≤ .01. ***P ≤ .001.*

predicted (66.7 ± 16.4% predicted in super responders vs 60.03 ± 22.7% predicted in responders; $P = .055$). At baseline, super responders on average showed better levels of asthma control: ACQ6 score, 2.66 ± 1.37 vs 3.13 ± 1.44 ($P = .018$), and quality-of-life scores, mAQLQ score, 3.77 ± 1.45 vs 3.16 ± 1.42 ($P = .006$) (Table 5).

A multivariate analysis was conducted, and the optimal model after variable selection included the following panel of predictors that were associated strongly with super responders: number of patients receiving mOCS therapy, peak blood eosinophil count, presence of nasal polyposis, adult-onset disease, and FEV_1 (liters) (e-Table 1). The resulting accuracy of this model using the area under the receiver operating characteristic curve was 76% (95% CI, 67%-85%). However, because of the small sample size of nonresponders (n = 18), the optimal model for responders vs nonresponders was inconclusive.

A number of patients showed particularly marked improvements with benralizumab treatment (Table 6). Among those not requiring mOCS therapy at baseline, 46.4% were exacerbation-free after 48 weeks of treatment, 50.0% showed an ACQ6 score of ≤ 1 or an improvement in ACQ6 score of ≥ 1 (representing twice the minimal clinically important difference), and 26.8% showed both zero exacerbations and significant improvements in ACQ6 score (Fig 3A). Similarly, 41.9% of patients receiving mOCS therapy were exacerbation-free at 48 weeks, 70.3% no longer required mOCS therapy for asthma control, and 45.9% showed an ACQ6 score of ≤ 1 or an improvement in ACQ6 score of ≥ 1, with all three of these outcomes occurring in 18.9% of mOCS patients (Fig 3B).

Among the nonresponder cohort, we observed chronic or recurrent bacterial infection (defined as more than one positive sputum culture or bronchial lavage culture result) in six patients (33.3%) and the sudden

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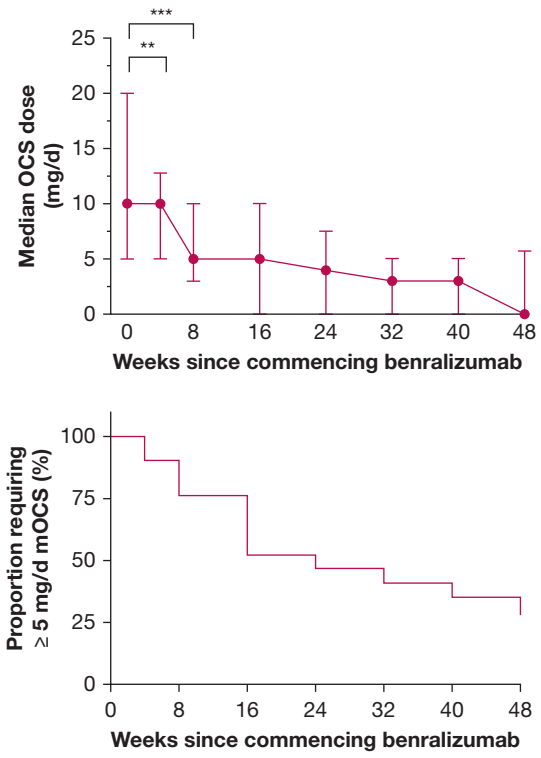

Figure 2 – *Graphs showing changes in maintenance oral corticosteroid (mOCS) requirements with benralizumab treatment. Dosages referred to are prednisolone (or prednisolone equivalent dose). OCS = oral corticosteroid. **P ≤ .01. ***P ≤ .001.*

development of detectable blood eosinophil counts in keeping with the presumed development of ADAs in 5 patients (27.8%) (e-Table 2).

Discussion

We report real-world experience of using the anti-IL5-receptor monoclonal antibody benralizumab in a large cohort of patients with SEA. We observed that benralizumab leads to clinically and statistically significant reductions in asthma exacerbations, with more than 40% of patients remaining exacerbation-free at 1 year. This was achieved despite a median reduction in mOCS dose of 100%, with 70% of patients able to stop mOCS therapy for asthma. Marked improvements in the patient-reported outcome measures ACQ6 and mAQLQ scores also were seen, with increases of at least twice the minimal clinically important difference (≥ 1.0) observed in approximately 40% of patients. Additionally, benralizumab led to significant improvements in lung function.

Benralizumab results in the rapid, almost complete, depletion of circulating and tissue eosinophils via the mechanism of antibody-mediated cytotoxicity, and therefore it is noteworthy that the observed improvements in ACQ6 score, mAQLQ score, and FEV_1 already largely were evident by the time of the second dose at week 4. Our clinical experience with benralizumab reaffirms the central role of eosinophilic inflammation in the immunopathologic and exacerbation pathogenesis of severe asthma.[10,11] In particular, the observation that some patients previously reliant on mOCS therapy became exacerbation-free and were able to discontinue systemic steroid therapy supports the notion that other aspects of type 2 inflammation, including IL-13 pathways, allergen-driven IL-4 pathways, or both, may be of questionable relevance for a proportion of high type 2 inflammation patients with severe asthma. Indeed, the absence of any clinical deterioration in those able fully to discontinue daily mOCS therapy raises the hope that such patients additionally may be able to reduce their inhaled steroid exposure without loss of control; the randomized controlled SHAMAL study currently is underway with the specific aim of exploring this possibility (ClinicalTrials.gov Identifier: NCT04159519).

Conversely, benralizumab is not a universal panacea: 30% of patients reliant on mOCS therapy at baseline continued to require at least 5 mg/d prednisolone to maintain asthma control, despite 1 year of treatment with benralizumab. Overall, using a responder definition as either a 50% reduction in exacerbations or a 50% reduction in mOCS dose for oral corticosteroid-dependent patients, we identified 18 of 130 patients (13.8%) in our cohort who seemed to show a suboptimal response to benralizumab. This is despite what seemed to be an appropriate eosinophilic phenotype, with a median blood eosinophil count of 0.65 cells × 10^9 in the year before biologic treatment. Of note, this group did demonstrated a lower median FENO at baseline than the responder group, and one-third of the nonresponders showed objective evidence

TABLE 3] mOCS Reduction at 48 Weeks (n=74)

Variable	Data
Reduction from baseline (%)	…
100	38 (51.4)
≥75	44 (59.5)
≥50	58 (78.4)
>0	65 (87.8)
Any increase or no change in dose	9 (12.2)
Reduction from baseline dose	100.0 (100 to 50)
Receiving < 5 mg/d prednisolone	48 (64.9)

Data are presented as No. (%) or median (interquartile range). See Table 1 legend for expansion of abbreviation.

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TABLE 4] Analysis of Responders vs Nonresponders (N = 130)

Variable	Responders[a] (n = 112)	Nonresponders (n = 18)	*P* Value
Age, y	53.8 ± 14.2	47.0 ± 11.7	.057
Female sex	65 (58.0)	15 (83.3)	.041
BMI, kg/m^2	30.9 ± 7.0	32.3 (7.8)	.414
Atopy[b]	82 (73.2)	14 (77.8)	.683
Previous omalizumab treatment	14 (12.5)	2 (11.1)	.907
Previous anti-IL5 treatment	41 (36.6)	7 (38.9)	.852
Receiving mOCS therapy	63 (56.3)	11 (61.1)	.699
Baseline mOCS dose,[c] prednisolone, mg/d	10 (5-19)	10 (5-20)	.792
Adult-onset disease, ≥ 18 y	59 (52.7)	10 (55.6)	.820
Nasal polyposis	33 (29.5)	6 (33.3)	.757
Smoking history (n = 110)	…	…	.277
Never smoker	75 (67.0)	13 (72.2)	…
Former smoker	34 (30.4)	4 (22.2)	…
Current smoker	1 (0.9)	1 (5.6)	…
Comorbid COPD	7 (6.3)	2 (11.1)	.465
FVC < 65% predicted before treatment	22 (19.6)	4 (22.2)	.828
Peak blood eosinophil count in the year preceding anti-IL5 or IL5-receptor mAb, cells × 10^9	0.60 (0.43-0.90)	0.65 (0.42-0.95)	.911
Baseline blood eosinophil count, cells × 10^9/L	0.15 (0.10-0.40)	0.20 (0.05-0.35)	.965
Baseline F_{ENO}, ppb	48 (26-82)	29 (19-48)	.048
Annual exacerbation rate in the year preceding anti-IL5 or IL5-receptor mAb therapy	4.90 ± 3.02	5.06 ± 5.03	.857
Baseline FEV_1 after bronchodilator, L	1.75 ± 0.70	1.81 ± 0.67	.748
Baseline FEV_1 after bronchodilator, % predicted	63.4 ± 20.2	66.3 ± 23.1	.583
Baseline ACQ6 score	2.85 ± 1.40	3.25 ± 1.35	.259
Baseline mAQLQ score	3.50 ± 1.42	3.25 ± 1.90	.521

Data are presented as No. (%), mean ± SD, or median (interquartile range). mAb = monoclonal antibody. Categorical variables were compared using the χ^2 or Fisher exact tests, where appropriate. Parametric continuous variables were compared using the independent t test. Nonparametric continuous variables were compared using the Mann-Whitney U test. See Table 1 legend for expansion of abbreviations.

[a]Fifty percent or more reduction in mOCS dose or, if not receiving mOCS therapy, ≥ 50% reduction in annual exacerbation rate.

[b]Raised specific IgE to ≥ 1 common aero-allergen or a clinical history of eczema.

[c]Calculated from the subgroup receiving mOCS, not the entire cohort.

of repeated or chronic lower respiratory bacterial infection. Taken together, these results suggest additional activation of non-type 2 pathways that would be unresponsive to eosinophil depletion. Phase 3 clinical trials of benralizumab reported the development of neutralizing ADAs in approximately 10% of patients, although this did not seem to be associated with a differential treatment response in these studies. Because of the unavailability of a commercial ADA assay, we were not able to measure ADAs directly in patients; however, the emergence of blood eosinophils in a benralizumab-treated eosinopenic patient can be considered a marker of ADA development. Evidence of possible ADAs was apparent in more than one-quarter of the nonresponders in our cohort, offering a further potential explanation for their suboptimal response. However, this requires objective confirmation in future studies. Two additional patients demonstrated evidence of eosinophilic granulomatosis with polyangiitis, resulting in an increase in their systemic steroid exposure. Overall, no reason for nonresponse could be identified in 5 of 18 patients (e-Table 2). The only other clinical characteristic found to be of significance in comparing responders and nonresponders was female sex, with 83% of nonresponders to benralizumab being female compared with 58% of responders. This did not remain statistically significant in the multivariate analysis; however, the higher proportions of women seen across severe asthma clinical trials and large international severe asthma registries[18] highlights the

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TABLE 5] Analysis of Super Responders vs Responders Not Meeting Super-Responder Definition (N = 130)

Variable	Super Responders[a] (n = 61)	Responders[b] (Excluding Super Responders; n = 51)	*P* Value
Age, y	53.6 ± 15.2	52.9 ± 13.7	.482
Female sex	29 (57)	37 (60.7)	.539
BMI, kg/m^2	29.5 ± 5.4	31.86 ± 8.1	.098
Atopy[c]	36 (70.6)	46 (75.4)	.566
Previous omalizumab treatment	4 (7.8)	10 (16.4)	.247
Previous anti-IL5 treatment	12 (23.5)	28 (45.9)	.026
Receiving mOCS therapy	24 (47.1)	39 (63.9)	.073
Baseline mOCS dose, prednisolone, mg/d[d]	10 (5-11.9)	10 (7.5-25)	.032
Adult-onset disease, ≥ 18 y	33 (64.7)	25 (41.0)	.015
Nasal polyposis	19 (37.3)	12 (19.7)	.015
Smoking history	(n = 50)	(N = 60)	.527
Never smoker	35 (68.6)	39 (63.9)	…
Former smoker	15 (29.4)	20 (32.8)	…
Current smoker	0 (0.0)	1 (1.7)	…
Comorbid COPD	2 (3.9)	5 (8.2)	.329
FVC < 65% predicted before treatment	8 (15.7)	14 (23.7)	.293
Peak blood eosinophil count in the year preceding anti-IL5 or IL5-receptor mAb, cells × 10^9	0.70 (0.50-1.10)	0.50 (0.45-0.70)	.010
Baseline blood eosinophil count, cells × 10^9/L	0.30 (0.1-0.5)	0.10 (0.0—0.4)	.035
Baseline FENO, ppb	45 (25-83)	54 (29-86)	.259
Annual exacerbation rate in the year before anti-IL5 or IL5-receptor mAb therapy	5.59 ± 3.38	4.44 ± 2.96	.079
Baseline FEV_1 after bronchodilator, L	1.92 ± 0.64	1.62 ± 22.7	.028
Baseline FEV_1 after bronchodilator, % predicted	66.7 ± 16.4	60.0 ± 22.7	.055
Baseline ACQ6 score	2.66 ± 1.37	3.13 ± 1.44	.018
Baseline mAQLQ score	3.77 ± 1.45	3.16 ± 1.42	.006

Data are presented as No. (%), mean ± SD, or median (interquartile range). Categorical variables were compared using the χ^2 or Fisher exact tests, where appropriate. Parametric continuous variables were compared using the independent t test. Nonparametric continuous variables were compared using the Mann-Whitney U test. See Table 1 and 4 legends for expansion of abbreviations.

[a]Not receiving maintenance oral corticosteroid therapy for asthma and zero exacerbations with benralizumab treatment.

[b]Fifty percent or more reduction in mOCS dose or, if not receiving mOCS therapy, ≥ 50% reduction in annual exacerbation rate.

[c]Defined as raised specific IgE to ≥ 1 common aero-allergens.

[d]Calculated from the subgroup receiving mOCS therapy, not the entire cohort.

need for research into sex-specific differences in the immunologic characteristics of T2 high asthma.

The small number of nonresponders to benralizumab that we have observed limits firm conclusions being drawn regarding any associated baseline clinical characteristics. However, comparing the two larger super-responder and responder groups (with 51 and 61 patients, respectively) highlighted several characteristics associated with a superior response to treatment, including higher baseline eosinophil counts, nasal polyposis, and adult-onset asthma. These findings are in keeping with the results of the pooled analysis of the SIROCCO and CALIMA studies[19] and identify patients with a strongly eosinophilic phenotype. This analysis also highlighted that the super responders demonstrated less severe disease at baseline when compared with other responders, with better patient-reported scores (ACQ6 and mAQLQ), better lung function, and less mOCS use. This is unsurprising, because the patients with the most severe disease require a more dramatic improvement to meet the super-responder definition than the general cohort of SEA patients. Our observation that atopic status does not influence benralizumab effectiveness was consistent with a post hoc analysis assessing the influence of atopy on benralizumab efficacy.[20]

FLA 5.6.0 DTD ■ CHEST3567_proof ■ 24 December 2020 ■ 2:38 am ■ EO: CHEST-20-2764

TABLE 6] Super-Responder Outcomes at 48 Weeks

Outcome	Data
Exacerbation-free	57 (43.8)
ACQ6 score ≤ 1	32 (24.6)
ACQ6 score improved by ≥ 1 from baseline	56 (43.1)
ACQ6 score ≤ 1 and improved by ≥ 1 from baseline	25 (19.2)
mAQLQ score improved by ≥ 1 from baseline (n = 120[a])	47 (36.2)
100% reduction in mOCS (n = 74)	38 (51.4)
Receiving < 5 mg/d prednisolone[b]	48 (64.9)
Discontinued mOCS therapy for asthma (receiving ≤ 5 mg/d prednisolone for adrenal insufficiency)[c]	52 (70.3)

Data are presented as No. (%). See Table 1 legend for expansion of other abbreviations.
[a]Missing data at baseline or 48 weeks in 10 patients.
[b]Ten patients continued mOCS therapy at a dose of < 5 mg for adrenal insufficiency.
[c]Four patients continued 5 mg prednisolone therapy for adrenal insufficiency, not for asthma, at 48 weeks.

There is no universally agreed consensus on what defines a super responder to a severe asthma therapy. We have attempted to provide sufficient information to satisfy a range of views in this regard, because individual clinicians may place exacerbation frequency, oral corticosteroid requirements, or patient-reported outcome measures in opposing hierarchies of importance. We hope our results additionally may facilitate shared decision-making with the patient, who may value one of these outcome measures above all

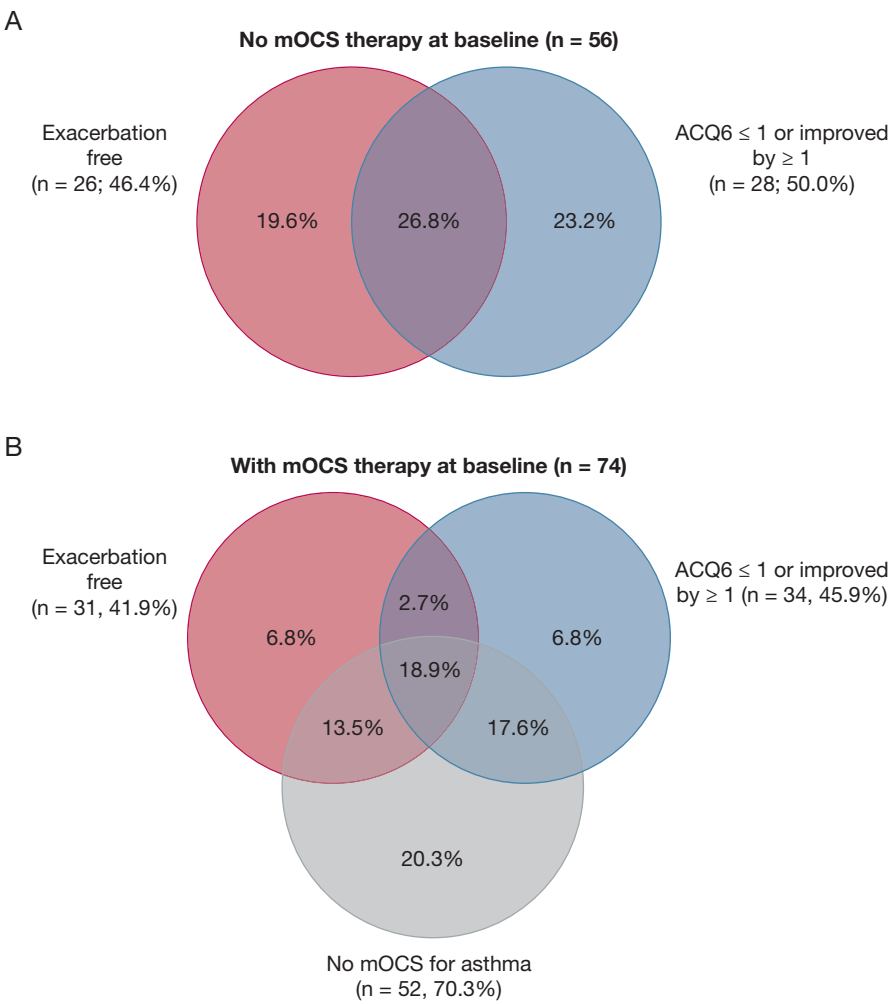

Figure 3 – *Venn diagrams exploring a super response to benralizumab. See Figure 1 and 2 legends for expansion of abbreviations.*

FLA 5.6.0 DTD ■ CHEST3567_proof ■ 24 December 2020 ■ 2:38 am ■ EO: CHEST-20-2764

others. What is apparent from our analysis is that most patients achieve at least one of the outcome measures used to define a super responder, but significant variability exists as to the degree of overlap among the outcome measures.

The notable placebo responses observed across all phase 3 trials of biologic agents in severe asthma suggest that despite the best intentions of study sponsors, a less than severe cohort of patients usually are recruited to these trials. For example, the mean exacerbation rate after randomization to the placebo arm of CALIMA was less than 1/year,[9] whereas 59% of the patients given placebo in the phase 3b mepolizumab MUSCA [Mepolizumab Adjunctive Therapy in Subjects With Severe Eosinophilic Asthma] trial showed no exacerbations at all during the study period.[21] This most likely represents resolving T2 inflammation subsequent to improved ICS use after study entry. The main limitation of all real-world observational studies therefore is the absence of a control arm. However, our cohort of 130 patients with poorly controlled, eosinophilic asthma all underwent extensive systematic assessment by a multidisciplinary team—including objective confirmation of adherence to treatment—before initiation of benralizumab. All patients either depended on daily oral corticosteroid therapy or had experienced at least three exacerbations in the year before commencing biologic therapy; therefore, we feel confident that these patients had genuine severe asthma and that the clinical improvements reflect the effectiveness of benralizumab, rather than any optimization of background therapy, which was rectified previously when necessary.

n summary, we describe the first real-world experience of benralizumab treatment in a large cohort of patients with severe asthma and report marked improvements in all the key clinical measures traditionally used to characterize this population, thus highlighting the pre-eminence of the eosinophil count in asthma pathobiologic analysis in a high proportion of SEA patients. In this regard, future research into asthma and other eosinophilic diseases should use the unique eosinophil-depleting opportunity that benralizumab presents to the scientific community. It is highly likely that such a course will promote a revised understanding of T2 high vs eosinophilic asthma.

Acknowledgments

Author contributions: J. E. K. takes responsibility for the integrity of the data and analysis. G. d'A., C. R., M. F., L. G., and L. T. contributed to data collection. J. E. F., A. P. H., A. D., J. D., A. M. N., B. D. K., and D. J. J. contributed to the study design, data analysis and interpretation, and the writing of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: D. J., B. K., and G. d'A. report advisory board and speaker fees and congress travel support from GSK, AstraZeneca, Chiesi, Napp, and Teva Pharmaceuticals. J. K. reports travel support from Teva. A. N. reports speaker fees and congress travel support from AstraZeneca. None declared (J. D., A. D., C. R., M. F., L. G., L. T., A. M. N.).

Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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