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Benralizumab After Sub-optimal Response to Mepolizumab in Severe Eosinophilic Asthma

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COI:

Dr. Kavanagh has nothing to disclose.

Dr Hearn has nothing to disclose.

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Ms Roxas has nothing to disclose.

Ms Green has nothing to disclose.

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To the Editor,

Mepolizumab and benralizumab are monoclonal antibodies (mAb) directed against anti-IL-5 and anti-IL5R respectively and their use reduces exacerbation rate and maintenance oral corticosteroid (mOCS) requirements in severe eosinophilic asthma (SEA) (1-4). We recently reported that a minority of patients

treated with mepolizumab experience a suboptimal response including those with a higher baseline ACQ and mOCS requirement (1). It remains unclear if such patients may improve following a switch to benralizumab which provides a more complete depletion of airway eosinophils (5,6).

We retrospectively assessed patients with SEA treated at our specialist centre, who were switched from mepolizumab to benralizumab following a sub-optimal response defined as failing to achieve either: $\geq 50\%$ reduction in mOCS dose; $\geq 50\%$ reduction in annualised exacerbation rate (AER); an ongoing requirement of $\geq 7.5\text{mg}$ prednisolone/day or an AER of ≥ 3 . Ethical approval to report on the outcomes of our routine clinical care using benralizumab without written consent was gained from the local Research Ethics Committee (15/LO/0886).

Thirty-three patients were included in the analysis (mean age 52 ± 11 , 55% female, BMI 32.1 ± 7.3 , see table S1). Values are mean (standard deviation) when normally distributed, or median (interquartile range) when non-parametric. Overall, AER fell by 58% from $3.89 (\pm 2.17)$ on mepolizumab to $1.64 (\pm 1.57)$ on benralizumab ($p < 0.001$, Fig 1a and Table 1). Twenty-six patients were on mOCS at the end of mepolizumab treatment, and by 48 weeks benralizumab 11/26 (42%) were able to discontinue, with 18/26 (69%) achieving $\geq 50\%$ dose reduction (Fig 1b-c and Table 1 and S2). There were statistically and clinically significant improvements in ACQ and AQLQ on benralizumab (Fig 1d-e). FEV1 improved from the end of mepolizumab to 48 weeks benralizumab, however, there was no improvement from pre-mepolizumab levels (a fall in FEV1 was observed on mepolizumab in this cohort, Fig 1f). Three (9%) patients deteriorated on benralizumab, with an increase in mOCS dose of $\geq 5\text{mg}$ od. A further 5 (15%) patients had no clear benefit (i.e. they had $< 50\%$ reduction in annualised exacerbation rate or $< 50\%$ reduction in mOCS dose compared to that at the end of mepolizumab treatment). There were no statistically significant differences in baseline characteristics between responders and those without a clear response (table S3).

Mepolizumab is known to reduce bone marrow and airway eosinophils by approximately 50% (7) and the phase 2b DREAM study highlighted a dose-related response in sputum eosinophil counts on mepolizumab (2). A sub-study of the OCS-sparing SIRIUS trial demonstrated the ongoing presence of sputum eosinophils and eosinophil progenitor (EoP) cells despite mepolizumab treatment, which was associated with a lower prednisolone sparing effect (8). Benralizumab has been shown to effectively deplete both blood and sputum eosinophil and EoP counts(6). It is therefore conceivable that a minority of patients may have a poor response to mepolizumab due to insufficient airway eosinophil depletion with the 100mg dose of

mepolizumab. In essence this notion is no different from the reality that within severe eosinophilic asthma some patients require low dose maintenance oral steroids whilst others require a higher dose to adequately suppress their airways inflammation. Our results appear to support this possibility and suggest that a more profound depletion in airway eosinophilia as occurs with benralizumab may offer additional clinical benefit in patients with particularly severe eosinophilic asthma.

To our knowledge this is the largest case series examining the clinical effectiveness of benralizumab in patients previously treated with mepolizumab. Our data suggests that SEA patients with a suboptimal response to mepolizumab may benefit from switching to benralizumab. Indeed, some have a dramatic response becoming exacerbation-free and off all mOCS for asthma (table S4). We report substantial and clinically meaningful improvements in exacerbation rate, oral corticosteroid use, asthma control and quality of life scores. Of note, a minority of patients had no clear benefit from switching to benralizumab and the mechanisms of this lack of response requires further research but may include unidentified airway infection or an IL-13 dominant type-2 pathway (9,10). The major limitation of our data is that it is uncontrolled and retrospective but nonetheless represents real world experience at a specialised asthma centre. Unfortunately, induced sputum was not routinely performed which would have added valuable insights into the mechanisms of poor response. Interestingly, the recently reported MEX study (11) highlighted that approximately 50% of exacerbations in a large mepolizumab treated asthmatic cohort were associated with persistent eosinophilic inflammation in sputum. This may in part explain the improved response with benralizumab.

Aside from indirect treatment comparisons, no prospective data comparing the efficacy of mepolizumab and benralizumab exists but it is hoped that such head-to-head trials are conducted to aid clinicians in choosing between biologic therapies for SEA.

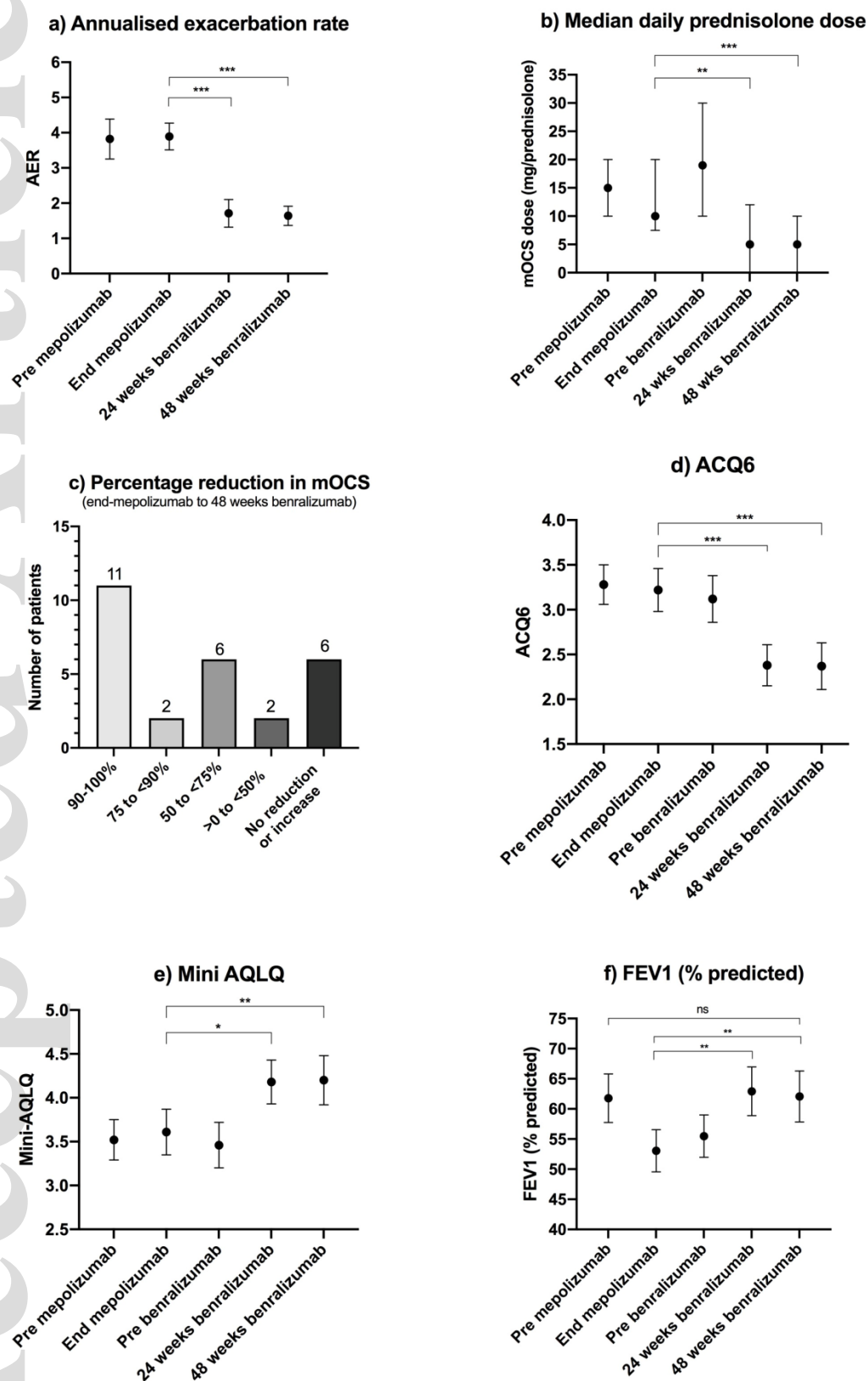
Table 1: Clinical outcome measures over time

	Baseline mepolizumab	End of mepolizumab	Baseline benralizumab	48 weeks benralizumab	Change	P value	P value
	A	B	C	D	B to D	A vs D	B vs D
Annualised exacerbation rate	3.82 (3.28)	3.89 (2.17)		1.64 (1.57)	-2.18	0.004	<0.001
On mOCS (number on ≥5mg/day prednisolone)	26	26	26	14*	-12	0.120	0.090
Median mOCS dose (prednisolone, mg/day)	15.0 (10.0-20.0)	10 (7.5-20)	19.0 (10.0-30.0)	5.0 (0.0-10.0)	-5	0.001	<0.001
FEV1 (L)	1.72 (0.70)	1.51 (0.64)	1.58 (0.67)	1.78 (0.79)	0.27	0.474	0.008
FEV1 (% predicted)	61.78 (22.02)	53.05 (20.08)	55.48 (20.14)	62.06 (24.22)	9.01	0.747	0.007
Blood eosinophil count (x10 ⁹)	0.20 (0.05-0.35)	0.00 (0.00-0.10)	0.10 (0.00-0.10)	0.00 (0.00-0.00)	0	<0.001	0.019
FeNO (ppb)	45 (30-84)	57 (33-81)	56 (27-77)	48 (29-83)	-9	0.636	0.221
ACQ-6	3.28 (1.24)	3.22 (1.36)	3.12 (1.52)	2.37 (1.51)	-0.85	<0.001	0.001
Mini-AQLQ	3.52 (1.28)	3.61 (1.48)	3.46 (1.44)	4.20 (1.59)	0.59	0.005	0.008

ABBREVIATIONS: ACQ6 =Asthma Control Questionnaire 6; FEV1 = Forced Expiratory Volume in 1 second; mOCS = maintenance Oral Corticosteroid; Mini-AQLQ = Mini Asthma Quality of Life Questionnaire; ppb = parts per billion

Values are mean when normally distributed data (± standard distribution) or median when data is non-parametric (interquartile range). *One patient started mOCS on benralizumab

Figure 1: Clinical Outcome Measures



*** = $p \leq 0.001$; ** = $p \leq 0.01$; * = $p \leq 0.05$; ns = non-significant

Fig 1 a, c, d, e and f: data points are the mean and error bars denote standard error of the mean. Fig 1b data are non-parametric and presented as median with error bars representing the interquartile range.

ABBREVIATIONS: ACQ6 = Asthma Control Questionnaire 6; FEV1 = Forced Expiratory Volume in 1 second; mOCS = maintenance Oral Corticosteroid; Mini-AQLQ = Mini Asthma Quality of Life Questionnaire

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Online Supplementary: Benralizumab After Sub-optimal Response to Mepolizumab in Severe Eosinophilic Asthma

Supplemental methods:

All patients when commenced on mepolizumab had blood eosinophils of $\geq 0.3 \text{ cells} \times 10^9$ in the previous year and either ≥ 4 asthma exacerbations requiring oral prednisolone in the prior year, or mOCS ($\geq 5 \text{ mg}$ prednisolone/day) for at least 6 months. Adherence was assessed prior to commencing mepolizumab by prescription pick-up rates of inhaled therapy and/or paired blood prednisolone and cortisol levels if on mOCS. All patients had received a minimum of 24 weeks of mepolizumab therapy to be included, and all had a washout period of 8-10 weeks between the last mepolizumab dose and the first benralizumab dose. At each visit we documented exacerbations since the previous visit, current asthma treatment, asthma control questionnaire (ACQ6), asthma quality of life score (mini-AQLQ), fractionated exhaled nitric oxide (FeNO) and forced expiratory volume in 1 second (FEV1).

Statistical methods:

Data was analysed using SPSS (version 24) (IBM SPSS, Chicago, IL). Figures were generated using Graphpad Prism (version 8) (GraphPad Software, La Jolla, CA). Data are given as mean (standard deviation [SD]) if normally distributed or median (interquartile range [IQR]) if nonparametric. Parametric variables were compared using T tests (paired or independent) and non-parametric variables using Mann-Whitney U test (unrelated) or Wilcoxon Signed Rank (related). Categorical variables were analysed by Chi-Square test, or Fisher's exact when required. Differences were considered significant at $P < 0.05$. All P values are two-sided.

Supplemental results:

119 patients treated with mepolizumab were screened to identify 33 patients who met the inclusion criteria. Two patients did not complete the full 48 weeks of benralizumab treatment; 1 stopped at 24 weeks due to lack of response and 1 was lost to follow up after the 40-week appointment. Both were included in the analysis with data carried forward.

Table S1: Baseline characteristics

Characteristic	n=33
Age (years)	51.9 (±11.3)
Female subjects	18 (54.5%)
BMI (kg/m ²)	32.14 (±7.31)
Atopy [†]	24 (72.7%)
Previous Omalizumab treatment	8 (24.3%)
Adult onset disease (≥ 18 years)	16 (48.5%)
Nasal polyposis	11 (33.3%)
Smoking history	
Never smoker	21 (63.6)
Ex-smoker	11 (33.3)
Current smoker	1 (3.0)
Co-morbid COPD	3 (9.4%)
Peak blood eosinophil count in the year preceding mepolizumab (x10 ⁹) [‡]	0.6 (0.5-0.75)
Median weeks of mepolizumab completed	48 (40-48)

Table S2: Prednisolone dose reduction from end of mepolizumab treatment

mOCS dose reduction n=27	Benralizumab 48 weeks
90 to 100%	11 (40.7%)
75 to <90%	1 (3.7%)
50 to <75%	6 (22.2%)
>0 to <50%	3 (11.1%)
No decrease, increase or early discontinuation due to lack of efficacy	6 (22.2%)
100% reduction	11 (40.7%)
≥ 50% reduction	18 (66.7%)
Off mOCS for asthma*	16 (59.3%)
Median % reduction from end-mepo dose	-53 (-100 to -20)

N=27, as one patient commenced prednisolone on benralizumab; they are therefore included here despite not being on mOCS at end of mepolizumab treatment.

*In total, 7 patients were still on prednisolone but at a dose of ≤5mg at 48 weeks. This was for adrenal insufficiency in 6 out of 7.

Table S3: Responder analysis

	Responder to Benralizumab n = 25	No clear response to Benralizumab n = 8	P value
Age (years)	52.32 ± 12.42	50.63 ± 7.41	0.719
Female subjects, n (%)	13 (52%)	5 (63%)	0.699
BMI (kg/m ²)	33.34 ± 7.72	28.36 ± 4.29	0.093
Atopy [†] , n (%)	18 (72%)	6 (75%)	1.000
Adult-onset disease (≥ 18 years), n (%)	11 (44%)	5 (63%)	0.438
Nasal polyposis, n (%)	9 (36%)	2 (25%)	0.687
Smoking history			
Never smoker	15 (60%)	6 (75%)	0.686
Ex-smoker	9 (36%)	2 (25%)	
Current smoker	1 (4%)	0 (0%)	
Co-existent COPD	1 (4%)	2 (25%)	0.147
Peak blood eosinophil count in the year preceding mepolizumab (cells x 10 ⁹)	0.60 (0.5-0.8)	0.50 (0.3-0.7)	0.127
Baseline blood eosinophil count (pre-mepolizumab, cells x 10 ⁹)	0.20 (0.0 – 0.4)	0.15 (0.1-0.3)	0.918
FeNO (ppb)	62 ± 28	44 ± 31	0.109
Exacerbation rate in year prior to anti-IL5/IL5R	4.44 ± 3.27	1.88 ± 2.64	0.053
Previous Omalizumab treatment, n (%)	5 (20%)	3 (38%)	0.366
High-dose ICS/LABA treatment, n (%)	25 (100%)	8 (100%)	1.000
Number on mOCS pre-mepo	19 (76%)	7 (88%)	0.652
Number on mOCS baseline benra	18 (72%)	8 (100%)	0.154
Median mOCS dose pre-mepo (prednisolone, mg/day)	13.5 (10-20)	17.5 (11.3-27.5)	0.539
Median mOCS dose baseline benra (prednisolone, mg/day)	15 (10-25)	25 (5-37.5)	0.397
FEV1 (L) at end mepolizumab	1.61 ± 0.50	1.22 ± 0.95	0.148
FEV1 (% predicted) at end mepolizumab	56.67 ± 17.15	43.46 ± 26.71	0.123
ACQ-6 at end mepolizumab	3.12 ± 1.51	3.62 ± 0.85	0.220
Mini-AQLQ at end mepolizumab	3.74 ± 1.48	3.22 ± 1.51	0.392

NOTE: Responder defined here as achieving ≥ 50% reduction in prednisolone dose from end of mepolizumab treatment if on mOCS, or as ≥50% reduction in AER compared to the AER on mepolizumab treatment if not on mOCS.

Table S4: Exploring ‘super’ response

	Number (%)
Zero exacerbations on benralizumab	10 (33.3%)
ACQ improved by ≥1 from end-mepolizumab to end-benralizumab	15 (45.5%)
Off mOCS for asthma (n=27)	16 (59.3%)
Achieve all 3 criteria (for n=27 on mOCS)	2 (7.4%)
Achieve top 2 criteria (for n=6 not on mOCS)	2 (33.3%)