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Early View

Research letter

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Steroid-sparing effects of benralizumab in patients with eosinophilic granulomatosis with polyangiitis

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Take Home Message

Benralizumab reduces oral corticosteroid requirements in patients with EGPA and leads to improved patient reported outcome measures.

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare, ANCA associated vasculitis characterised by asthma, chronic rhinosinusitis and blood eosinophilia which may be accompanied by neurological, cardiac, cutaneous and renal involvement [1]. Oral corticosteroids (OCS) are the most frequently used drugs to control eosinophilic inflammation and symptoms. Persistent symptoms or relapses are common, however, and many patients are at risk of developing long-term complications from systemic steroid therapy [2]. The ability of other immunosuppressant agents to achieve consistent disease control or to reduce maintenance OCS (mOCS) requirements appears to be limited [3].

Interleukin-5 (IL-5) is a key cytokine implicated in the proliferation, maturation and differentiation of eosinophils and clinical trials have reported a beneficial and steroid sparing effect of the subcutaneous anti-IL-5 monoclonal antibody (mAb) mepolizumab in patients with EGPA [4]. We have previously reported on the effect of the intravenous anti-IL-5 mAb reslizumab in EGPA [5]. Here we present our experience with benralizumab, which mediates eosinophil apoptosis via binding to the IL-5 receptor alpha (IL-5Rα), and its effect on patient-reported outcomes and OCS requirements in patients with EGPA.

Patients with established EGPA based on the American College of Rheumatology 1990 criteria [6] and on mOCS therapy were commenced on benralizumab 30mg administered by subcutaneous injections every 8 weeks, with the first 3 doses given every 4 weeks. All patients attended a dedicated EGPA clinic run jointly between respiratory and rheumatology physicians and all patients gave written informed consent. Ethical approval was gained from the London Bloomsbury Researcg ethics Committee 915/LO/0886). Patient reported outcomes were assessed by the Birmingham Vasculitis Activity Score (BVAS), the Asthma Control Questionnaire (ACQ), the Asthma Quality of Life Questionnaire (AQLQ) and the Sino-Nasal Outcome test (SNOT)-22. Lung function, blood eosinophils, white blood count, CRP, Troponin T, renal function, fractional exhaled nitric oxide (F_{ENO}), mOCS dose and exacerbation rate were recorded at baseline, 24 weeks and 48 weeks of treatment. All patients had confirmed adherence to prednisolone via paired blood prednisolone/cortisol levels.

Eleven patients (6 female) with a mean age of 50±14 years had completed 24 weeks of treatment by the time of this analysis; nine had completed 48 weeks of treatment.

All eleven patients had severe eosinophilic asthma and paranasal sinus involvement. Two (18%) had cardiac, one (9%) dermatological, and one (9%) neurological involvement. Anti-neutrophil cytoplasmic antibodies were positive in four (36%); three (27%) had histopathological evidence of eosinophilic vasculitis. Five (46%) patients had received treatment with other immunosuppressive drugs (mycophenolate mofetil, methotrexate, azathioprine); three (36%) had previously failed treatment with mepolizumab, whilst one patient had failed both mepolizumab and reslizumab, based on ongoing OCS requirements and high symptom score and assessed by a mutli-disciplinary team review.

At the start of benralizumab therapy, patients were taking a median dose of 15mg (IQR 10-20) mOCS daily and had evidence of poor symptom control (ACQ 2.13 (±0.98); AQLQ 4.15 (±1.41); BVAS 7.91±3.27) and persistent airways inflammation with a F_{ENO} of 38 (IQR 25-77) ppb and mean blood eosinophil count of 0.2 (IQR 0.1-0.7) cells x 10^9/L. Following 24 weeks of treatment, there was a median reduction in mOCS of 50% and 8/11 (73%) patients were able to reduce their dose by ≥ 50%. Amongst the nine patients who had completed 48 weeks of treatment, the median reduction in mOCS was 65% and 8 (89%) were able to reduce their dose by ≥ 50%. The median prednisolone dose was reduced from 15 (IQR 10-20) mg to 5 (IQR 5-10) mg at 24 weeks and 5 (IQR 1-6.5) mg at 48 weeks (p = 0.0018) (Figure 1a). Blood eosinophil counts were totally depleted after 24 and 48 weeks of treatment. There was no significant difference and no change from baseline to 24 and 48 weeks in white blood count (9.75 (±2.39), 7.71 (±2.94), 7.16 (±2.34) x10^9/L), CRP (5 (1-7), 7.71 (±2.94), 7.16 (±2.34) mg/L), Troponin T (8 (5-11), 7 (5-10), 6 (5-7) ng/L) or creatinine (78.8 (±16), 77.9 (±18.8), 76.6 (±19.4) µmol/L).

A significant improvement in BVAS from baseline 7.91 (±3.27) to 3.45 (±2.52) at 24 weeks (p=0.0001) and 3.44 (±2.88) at 48 weeks (p=0.0007) was recorded. The ACQ changed from baseline 2.13 (±0.98) to 1.73 (±1.57) at 24 weeks (p = 0.47) and 1.03 (±0.71) at 48 weeks (p=0.012) (Figure 1 b,c). AQLQ scores changed from baseline 4.15 (±1.41) to 4.96 (±1.63) at 24 weeks (p = 0.13) and 5.5 (±1.27) at 48 weeks (p=0.013). We recorded an improvement in the SNOT-22 Questionnaire from baseline 55.7 (±20.8) to 35 (±20.7) at 24 weeks (p = 0.005) and 20.9 (±12.5) at 48 weeks (p = 0.004).

No significant changes were observed in absolute forced expiratory volume in 1 second (FEV_1) (Δ 0.2±0.3 $L{\cdot}s^{-1}$ at 24 weeks; Δ 0.3±0.4 $L{\cdot}s^{-1}$ at 48 weeks). F_{ENO} did not significantly change from baseline at 24 weeks (Δ 6.5±48ppb) or at 48 weeks (Δ -22±40ppb). No increase in frequency of exacerbations was seen. Benralizumab was well tolerated and no treatment-limiting adverse effects were recorded.

EGPA is a rare but severe systemic illness for which few therapeutic options exist. Hitherto patients have been treated with high dose glucocorticosteroids and other immunosuppressants, drugs with considerable side effect profiles [7]. Inhibiting eosinophilic inflammation in a more targeted manner via blockade of the IL-5/5R pathway has been a focus of novel therapeutic options in both severe asthma and EGPA. To date, mepolizumab remains the only FDA approved therapy for EGPA after it was found to be safe and effective in reducing corticosteroid dose and disease relapse [4]. However persistent tissue eosinophilia despite mepolizumab has been reported and 47% of subjects in the mepolizumab group of the phase 3 trial did not achieve remission [8]. There is sound rationale that benralizumab, with its unique eosinophil depleting properties, may offer improved outcomes in EGPA in which multi-organ eosinophilic infiltration is believed to drive morbidity and mortality. Our data demonstrate that EGPA patients treated with benralizumab have substantially reduced mOCS requirements, and significant improvements in patient related outcome measures as early as 24 weeks and maintained up to 48 weeks of treatment. It is noteworthy that our EGPA patient cohort is of the asthma phenotype with foremost airways and dominant sino-nasal disease and a lower prevalence of ANCA positivity and vasculitic features.

Our results are in line with other recently published findings [9] as well as our earlier experience with reslizumab [5]. Important limitations of our data include the relatively small cohort described, and the absence of a control arm inherent in any open label observational report.

In summary we report significant reductions in mOCS requirements and improved measures of disease control following benralizumab therapy in patients with EGPA. Further research exploring the mechanism(s) of residual disease in eosinopaenic patients treated with benralizumab is needed and must compliment upcoming prospective controlled trials of this therapy in EGPA.

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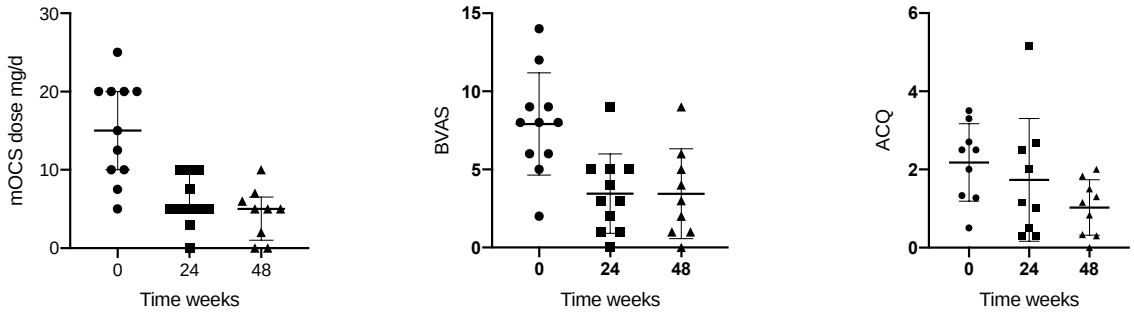

FIGURE 1 Reduction from baseline to 48 weeks in a) maintenance oral corticosteroid (mOCS) dose (p = 0.0018); b) Birmingham Vasculitis Activity Score (BVAS) (p=0.0007); c) seven item Asthma Control Questionnaire score (ACQ) (p=0.012). Data are presented as median (IQR) (a), mean (SD) (b and c).