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Early View

Research letter

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Anti-IL5 and anti-IL5Rα therapy for clinically significant bronchiectasis with eosinophilic endotype: a case series

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To the Editor:

Bronchiectasis is a chronic and often progressive disease, which frequently is associated with significant symptom burden requiring intensive treatment. Regardless of the multiple potentially underlying etiologies the vicious cycle of airway inflammation, structural airway damage, impaired mucus clearance and airway pathogen acquisition is the crucial pathogenic pathway for the progression of disease (1).

Although inflammation in bronchiectasis has been classically regarded as neutrophilic, it is increasingly recognized that eosinophils may play a role in the disease. Allergic bronchopulmonary aspergillosis is an example of a common cause of bronchiectasis which is primarily eosinophilic. Small studies suggest a significant number of patients have airway eosinophilia even after exclusion of patients with underlying ABPA and asthma. Tsikiras et al found that among 40 patients with bronchiectasis excluding asthma and ABPA, 30% in total had sputum eosinophilia defined as >3% cells. This supports the possibility that there may be an eosinophilic endotype of bronchiectasis although published data on the prevalence and clinical significance of airway and systemic eosinophilia in bronchiectasis remains limited. (2,3).

Mepolizumab, a humanized monoclonal antibody, reduces eosinophil counts in blood and tissues by blocking interleukin-(IL)-5, a key eosinophil cytokine, and preventing its binding to eosinophil surface receptors (4). In patients with severe eosinophilic asthma, add-on mepolizumab treatment resulted in a decrease of exacerbation frequency, reduced symptom burden, improved of quality of life (QoL) and, moreover, had an oral corticosteroid-(OCS)-sparing effect (4–7).

The use of mepolizumab for eosinophilic chronic obstructive pulmonary disease (COPD) was associated with a lower annual rate of moderate or severe exacerbations (9,10). Benralizumab is a biological drug blocking the alpha-chain of the IL-5 receptor, which leads to an antibody-dependent cell-mediated cytotoxicity. The use of benralizumab resulted in a reduction in exacerbations and OCS use in patients with severe eosinophilic asthma (5,11), but add-on benralizumab was not associated with a lower annualized rate of COPD exacerbations (12). Overall, there is a considerable overlap between different eosinophilic diseases (allergic and eosinophilic asthma, eosinophilic granulomatosis with polyangiitis (EGPA) and allergic bronchopulmonary aspergillosis/mycosis (ABPA/M)) as well as conditions that may be associated with significant peripheral eosinophilia (asthma-COPD overlap syndrome (ACOS), eosinophilic COPD). It has been recognized that not only the clinical phenotype of severe asthma may have different underlying endotypes (13), Recently, one pilot study of four patients with severe uncontrolled asthma and concomitant bronchiectasis showed the efficacy of mepolizumab in terms of exacerbations, FEV1, blood as well as sputum and nasal eosinophilis (14). The aim of the present retrospective case

series was to study the effect of anti-eosinophilic therapy using anti-IL5 and anti-IL5α monoclonal antibodies in patients with the primary diagnosis of bronchiectasis and a consistent eosinophil endotype defined by a reproducible peripheral eosinophila ≥300 cells·μL^{-1} at baseline or before initiation of long-term OCS therapy.

Overall, 450 patients, accounting for 1392 consultations, had been in regular follow up at the Adult Bronchiectasis Clinic of the Hannover Medical School between January 2016 and October 2018. Of those, 11% had blood eosinophils ≥300 cells·μL^{-1} during stable state. In 21 patients of this subgroup we decided to initiate therapy with an anti-IL5 or anti-ILRα antibody due to refractory disease despite optimized maintenance therapy, including recommended vaccinations, pulmonary rehabilitation, daily chest physiotherapy with adjunct nebulized mucolytics and triple inhaled therapy consisting of high-dose ICS and long-acting dual bronchodilator therapy. All patients were over 18 years of age, had characteristic symptoms of clinically significant bronchiectasis, including cough and sputum production on most days of the week as well as a history of exacerbations, CT-confirmed bronchiectasis and were referred to our Adult Bronchiectasis Clinic by chest physicians due to the diagnosis of bronchiectasis. In addition, all subjects had frequent or severe pulmonary exacerbations requiring OCS in the previous year, chronic airflow limitation, reduced QoL and persistent as well as reproducible peripheral eosinophilia ≥300 cells·μL^{-1} at baseline or before initiation of long-term OCS therapy, respectively.

Overall, 12 bronchiectasis patients receiving mepolizumab and 9 patients receiving benralizumab had complete follow up data available after 3 and 6 months of therapy, including the number of exacerbations in the previous 12 months, lung function tests, eosinophil blood count, modified Medical Research Council (mMRC) dyspnea scale, 24-hour sputum volume and overall QoL measured with a visual analog scale (VAS; score 0-10). Of those, 10 were female (48%); median (interquartile range, IQR) age was 55 (51-58) years; median (IQR) time of chronic respiratory symptoms was 18.6 (5.8-38.1) years; and median (IQR) duration of known bronchiectasis was 2.8 (1.1-13.1) years. Fourteen patients (67%) were on long-term OCS treatment, three patients received anti-inflammatory azithromycin maintenance therapy and four patients had obtained omalizumab for allergic asthma and/or ABPA before treatment. The most common pathogens in sputum culture were *Aspergillus fumigatus* (n=4), followed by *Staphylococcus aureus*, *Haemophilus influenzae* (n=3, each) and Pseudomonas aeruginosa (n=2). Eight subjects were former smokers, while there were no active smokers in the study group. After comprehensive and thorough diagnostic work-up according to current guidelines (15,16), including bronchodilator reversibility testing, exhaled nitric oxide (FeNO), measurement of nasal NO, sweat test and panel genetics for *CFTR* and primary ciliary dyskinesia (PCD) pathogenic genetic variants if indicated, the aetiology of bronchiectasis was severe and refractory eosinophilic asthma, severe allergic and

eosinophilic asthma, ABPA/M (n=4, each), idiopathic (n=2), asthma-COPD overlap syndrome, EGPA and PCD (n=1, each) as determined by the treating physician. In the remaining four subjects no distinction could be made between severe and refractory eosinophilic asthma and EGPA according to established EGPA criteria as disease manifestations were limited to the upper and lower airways (with no antineutrophil cytoplasmic antibodies detectable; history of asthma, ≥10% eosinophils on differential leukocyte count, paranasal sinus abnormalities and radiographical detection of transient pulmonary opacities or (transbronchial or sinonasal) biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas) (17). We refrained from performing bronchial challenge testing as all patients showed mild to very severe chronic airflow limitation at baseline, with 19 of 21 subjects (90%) already showing at least moderate chronic airflow limitation.

Mepolizumab 100 mg (every 4 weeks) and benralizumab 30mg (every 4 weeks for the first three doses, then every 8 weeks) were administered subcutaneously, as licensed for use in severe eosinophilic asthma. As all subjects had refractory disease despite optimized maintenance therapy both drugs were used as part of a targeted and individualized treatment attempt, with no ethical consultation required. IBM SPSS Statistics (version 25.0, IBM Corp., Armonk, New York) and STATA (version 13.0, StataCorp, College Station, Texas) statistical software programs were used to analyze the data. Comparisons between different time points were performed using the non-parametric Wilcoxon signed-rank test. A two-tailed *P* value of <0.05 was considered statistically significant.

After 6 months of treatment with anti-IL5 and anti-IL-5Rα therapy the median (IQR) forced expiratory volume in one second (FEV_1) increased from 53 (40-69) to 68 (38-94) percent predicted (figure 1A; p=0.033). In the same period, the median (IQR) annualized exacerbation rate improved from 3 (1-6) exacerbations at baseline to 1 (0-3) (figure 1B; p=0.059). Similar results were observed for the median (IQR) score on the mMRC dyspnea scale, which decreased from 2 (1-3) to 0 (0-1) (figure 1C; p=0.008). As a patient-reported outcome the median (IQR) QoL (VAS) improved significantly from 4 (3-6) to 7 (5-8) (figure 1D; p=0.002), while the median (IQR) eosinophil count decreased significantly from 800 (550-1240) to 100 (0-100) cells·μL^{-1} (figure 1E; p<0.001) and the median 24-hour sputum volume (IQR) decreased from 10 (8-25) ml to 8 (0-14) ml (figure 1F; p=0.009). In all 14 patients on long-term OCS therapy an OCS-sparing effect was observed with therapy. Nine out of 14 patients were able to cease OCS therapy, while five patients were able to reduce the OCS dose (prednisone aquivalent median (IQR) 6.5 (4.3-7.8) mg at baseline vs. 3.8 (1.8-5) mg after 6 months; p=0.042). Using improvement of FEV_1, decrease of blood eosinophils and improvement of any subjective measure (mMRD or QoL) as response criteria 13 out of

21 patients (62%) were classified as responders to anti-eosinophilic therapy (18).

Overall, mepolizumab and benralizumab were well tolerated. One patient with underlying OCS-dependent eosinophilic asthma experienced bilateral pneumonia requiring hospitalization 10 days after first application of mepolizumab. Another patient with EGPA developed chronic parotitis after being treated with mepolizumab for several months. However, in both subjects these events were rated unrelated to treatment with mepolizumab, but rather related to the underlying condition by the treating physician.

Overall, patients with clinically significant bronchiectasis featuring an eosinophilic inflammatory endotype, who did not respond to standard bronchiectasis treatments and were treated with add-on mepolizumab or benralizumab, showed a significant reduction of blood eosinophils as well as a significant improvement of FEV_1, symptom burden and QoL. Moreover, we observed a trend towards a reduced annualized exacerbation frequency. Our results suggest that monoclonal anti-IL5 or anti-IL5Rα antibodies may be promising add-on anti-eosinophilic treatment options for this extensively pretreated patient population.

Our results are in line with earlier studies showing a reduction of exacerbations with the use of mepolizumab or benralizumab in patients with eosinophilic asthma and eosinophilic COPD (5,8,10,11,19). In addition, Chupp and colleagues described an increase in QoL and a decrease in symptom burden, similar to our findings (4). Our study has several limitations. First, the sample size was small and the observation period was comparatively short so that exacerbation frequency had to be annualized. However, one may expect that our results would have been even more impressive after 12 months of treatment. Second, the measurement of QoL by a VAS is not validated for patients with bronchiectasis. Nevertheless, a similar VAS has previously been used to quantify symptoms for lower respiratory tract infections in bronchiectasis (LRTI-VAS) and showed excellent validity, reliability and responsiveness in assessment of overall symptom burden (20). All of the patients in this study had a primary diagnosis of bronchiectasis, but there was clearly evidence of overlap with other eosinophil diseases including asthma, ABPA and EGPA. This is not surprising as overlap between bronchiectasis and other airway diseases is common and we nevertheless demonstrated effectiveness of anti-IL-5 therapy in a cohort including patients with idiopathic and PCD related bronchiectasis without evident overlap. Finally, the findings of our case study are preliminary and it remains to be determined whether the effects are sustained over time.

Nevertheless, our findings emphasize the importance of recognizing the underlying inflammatory endotype as a prerequisite for successful treatment in line with the concept of treatable traits (21). Bronchiectasis has ever been perceived as a purely neutrophilic disease. In this regard, our findings challenge traditional definitions of airway diseases. However, as inflammation persists, disease progresses and tissue damage as well as further

complications like chronic infections arise the origin of bronchiectasis often is impossible to establish beyond any doubt. Given the fact that the majority of recent clinical trials in bronchiectasis, which mainly addressed neutrophilic inflammation and infection, were unsuccessful we propose that there are shared biological mechanisms between bronchiectasis and several eosinophilic diseases in many patients (22–24).

In conclusion, a randomized controlled trial evaluating the use of a monoclonal anti-eosinophilic antibody as an anti-inflammatory add-on therapy in subjects with clinically significant bronchiectasis and eosinophilic endotype is warranted.

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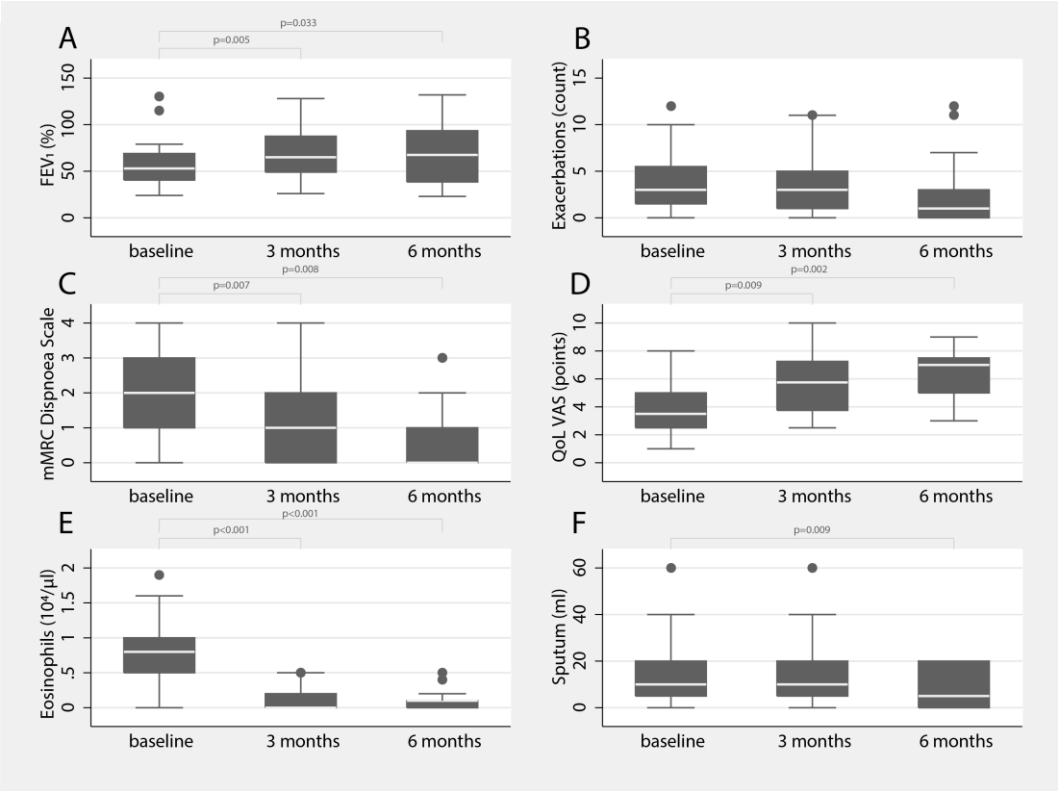

FEV1 (% predicted), annualized exacerbation frequency, mMRC dyspnoea scale, Quality of life, eosinophiles and 24-hour sputum volume at baseline and after three and six months of treatment