The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia

To the Editor:

Atopy is a common finding in asthma, but at least one third of severe asthmatics have no evidence of atopy (so-called “intrinsic” asthma) [1–4]. Despite the uncertainty of the mechanisms leading to nonatopic asthma, these patients have no history of allergic respiratory disease, no detectable specific IgE to common aeroallergens, and no positive skin-prick test. One hypothesis suggests that differences in the phenotypes might be driven by the local, and not by the systemic, production of IgE [5]. Eosinophils are involved in diverse inflammatory responses irrespective of atopy. Eosinophilic inflammation and IgE production are promoted by T-helper cell (Th2) cytokines, such as interleukin (IL)-5, IL-4 and IL-13. IL-4/IL-13 are major factors involved in Th2 differentiation and IgE class switching [6], while IL-5 is involved primarily in eosinophil growth, survival, activation, and in mediating inflammation.

Recurrent asthma exacerbations are a major problem in some patients and can predominate in a subgroup of asthmatics with elevated eosinophils, irrespective of their atopic status [2, 7]. Mepolizumab, a humanised monoclonal antibody against IL-5, selectively inhibits eosinophilic airway inflammation and has been shown to be associated with a significant reduction in severe asthma exacerbations irrespective of the baseline IgE levels or radioallergosorbent test (RAST) status in the Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) trial [7]. In this post hoc analysis of the DREAM trial, we aimed to: examine and discuss the effect of treatment with mepolizumab on the frequency of exacerbations in the atopic and nonatopic subgroups; to present the analyses of seasonal patterns of response by subgroup; and to evaluate changes in lung function and exhaled nitric oxide fraction (FeNO) according to subgroup. Specific details on the study methods have been published previously [7]. In brief, subjects were required to have evidence of two or more exacerbations requiring treatment with high-dose inhaled corticosteroids in the previous 12 months, despite current therapy, and had evidence of eosinophilic inflammation (blood eosinophils, sputum eosinophils, FeNO or changes in asthma control following reduction in steroids). Atopy was defined as a positive RAST test to any of the following allergens: house dust mite, dog, cat, seasonal pollen (i.e., Bermuda, wild rye, western ragweed, elm, oak white, olive tree and thistle) or Alternaria, (tests were performed by Quest Diagnostics-Nichols Institute; San Juan Capistrano, CA, USA). All participants provided written informed consent. The study protocol was approved by the local ethics committees. Exacerbations were defined as worsening of asthma requiring use of oral corticosteroids for 3 days and/or hospitalisation and/or an emergency department visit. Standard spirometry was performed in accordance with the American Thoracic Society (ATS) criteria, FeNO was measured using a NIOX MINO (Aerocrine AB, Stockholm, Sweden) in the majority of the centres; as specified by the ATS guidelines. Safety and immunogenicity data were collected from screening to end of treatment follow-up visit. Exacerbations were analysed using a negative binomial log-link model. The analysis by IgE subgroup was performed by quartile rather than the previously defined thresholds. The effect of season on exacerbation rates was examined with a generalised estimating equation (GEE). All analyses were performed using SAS version 9 (SAS Institute, Cary, NC, USA).

Overall, at baseline the nonatopic, when compared to the atopic subjects, were older (52 versus 46 years), had a shorter duration of the disease (12 versus 20 years), greater percentage use of maintenance oral corticosteroids (37% versus 24%), lower FEV1 (1.72 versus 1.92 L), and greater percentage of nasal polyposis (38% versus 24%). In our reanalysis of the data at baseline IgE level quartiles, the rate ratios (95% CI) of exacerbations for mepolizumab versus placebo showed: 0.49 (0.31–0.76) for ≤70 KU·L⁻¹; 0.77 (0.49–1.21) for >70 ≤170 KU·L⁻¹; 0.48 (0.30–0.77) for >170 ≤430 KU·L⁻¹; 0.49 (0.31–0.77) for >430 KU·L⁻¹.

FeNO geometric means at baseline in the nonatopic and atopic subgroups group were 32 ppb and 31 ppb, respectively. At the end of the treatment period (week 52), the ratio of the geometric mean (95% CI) of FeNO in mepolizumab to placebo was 0.86 (0.71–1.04) in the atopic subgroup, while in the nonatopic subgroup the ratio was 1.05 (0.87–1.28). Lung function at the end of the treatment period showed nonsignificant improvements in the mepolizumab group compared with placebo (atopic 33 mL (-83–149 mL), nonatopic 117 mL (3–231 mL)). Initially we fit a GEE model to the exacerbations with an interaction term for season by treatment; however, this term was not statistically significant (p =0.1077) so we concluded that treatment...
effect did not depend on season and removed the covariate from the model. The exacerbations in the atopic subgroup (fig. 1a) occurred with a peak in the winter (rate 3.02 (2.32–3.93) for placebo and 1.74 (1.37–2.21) for mepolizumab), and nadir in summer. Exacerbations in the nonatopic subgroup (fig. 1b) occurred with a peak in winter (rate 2.84 (2.18–3.71) for placebo and 1.41 (1.10–1.79) for mepolizumab); however the spring, summer and autumn had similarly low exacerbation rates. There were no major differences in safety or immunogenicity when the population was analysed by atopy.

In particular patients with uncontrolled severe asthma at a high risk since they experience frequent exacerbations, though some patients experience stable periods punctuated by significant exacerbations during “seasonal” times of the year [8]. There are many triggers that lead to an increase in symptoms or exacerbations including respiratory infections, allergens, irritants, and occupational exposures among others. Although it is thought that allergen sensitisation acts in synergy with other pro-inflammatory environmental cofactors, such as respiratory viral infections [9], the current study indicates that this may also apply to nonatopic asthma. The annual exacerbation rate in patients treated with placebo plus standard of care was similar in the atopic and nonatopic patients, 2.41 and 2.33 exacerbations per year, respectively. Consistent with previous reports, we observed more exacerbations during the winter months in both groups [8, 10]. This seasonal pattern further supports the role that viral infections play as a common trigger for asthma exacerbations in adults [11]. Treatment with mepolizumab resulted in a consistent reduction in eosinophils and reductions in exacerbation frequency in both atopic and nonatopic asthma patients (42% and 51%, respectively). Baseline IgE was the only predictor of efficacy in the omalizumab INNOVATE trial in severe atopic asthmatics [12, 13]. In contrast, treatment response was similar when subjects, studied in the DREAM trial, were divided into subgroups on the basis of IgE quartile at baseline; significant reduction in exacerbations with mepolizumab were observed irrespective of IgE levels (e.g. ≤70 or >430 KU·L⁻¹ showed a 51% reduction in exacerbations). In the quartile >70 ≤170 KU·L⁻¹ a not statistically significant reduction in exacerbations of 23% was observed. This is likely to have been a random anomaly; however further research is needed to aid the understanding.

A cross-sectional analysis in an asthmatic cohort showed an interaction between environmental allergen exposure and allergic sensitisation, with the highest FeNO levels in sensitised asthmatic patients exposed to increased allergens [14]. Although elevated FeNO was observed at baseline independent of atopy in the current study, the specific mechanism associated with the lack of effect in the reduction of FeNO levels following mepolizumab treatment is still unclear. A limitation to be considered is the lack of viral exposure characterisation, which precludes conclusions to be established regarding viral exposure as a trigger. Additionally, we used a limited panel of common allergens to characterise the atopic status.

Overall, reduction in exacerbations with mepolizumab were observed irrespective of IgE levels or atopy and were more frequent in winter months but treatment response was unaffected by season or atopy. This suggests that a trial with mepolizumab of <1-year duration might be acceptable to evaluate

**FIGURE 1** Seasonal variation of exacerbations over a 1-year treatment period by atopic status. The three doses of mepolizumab (750, 250 and 75 mg) were combined. The exacerbation rate per year for the a) atopic subgroup, and b) the nonatopic subgroup are presented. The season of an exacerbation was defined using the start date of the exacerbation. For subjects from a northern hemisphere country exacerbations were classified as follows. Winter: December, January or February; spring: March, April or May; summer: June, July or August; and autumn: September October or November. For subjects from the southern hemisphere, 6 months were added to the exacerbation start date to make the classification.
exacerbations. The use of mepolizumab to neutralize IL-5 and reduce eosinophils is a promising intervention for managing patients with severe eosinophilic asthma.

Mepolizumab is effective in reducing exacerbations in both atopic and nonatopic severe patients with asthma http://ow.ly/tyaIm

Hector Ortega1, Geoffrey Chupp2, Philip Bardin3, Arnaud Bourdin4, Gilles Garcia5,6, Benjamin Hartley7, Steve Yancey1 and Marc Humbert5,6,8

1GlaxoSmithKline, Respiratory Medicine Development Center, Research Triangle Park, NC, USA. 2Dept of Pulmonary and Critical Care, Yale University Medical School, Winchester Chest Clinic, 20 York Street, New Haven, CT, USA. 3Monash University and Medical Centre, Lung and Sleep, Melbourne, Australia. 4Dept of Allergy, Hospital Arnaud de Villeneuve, Montpellier, France. 5University Paris-Sud, Faculté de Médecine, Le Kremlin-Bicêtre, France. 6AP-HP, Service de Pneumologie, DHU Thorax Innovation, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. 7GlaxoSmithKline, Research and Development, Stockley Park, Middlesex, UK. 8Inserm U999, LabEx LERMIT, Le Plessis Robinson, France.

Correspondence: H. Ortega, GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, North Carolina, USA. E-mail: hector.g.ortega@gsk.com

Received: Dec 16 2013 | Accepted after revision: Jan 29 2014

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

References
5 Humbert M, Durham SR, Ying S, et al. IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and nonatopic asthma: evidence against “intrinsic” asthma being a distinct immunopathologic entity. Am J Respir Crit Care Med 1996; 154: 1497–1504.