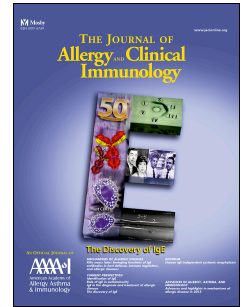


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Seasonal Variability of Severe Asthma Exacerbations and Clinical Benefit from Lebrikizumab

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Short Summary:

Post-hoc analyses of two Phase III studies of lebrikizumab in moderate to severe asthma suggest that IL-13 inhibition is effective at preventing seasonal exacerbations in subjects with high blood eosinophil counts. Further work is required to understand and treat exacerbations that are independent of seasonal and Type 2 pathway factors.

Key Words:

IL-13, asthma, Type 2, T_H2, rhinovirus, seasonal exacerbations

Abbreviations

ICS Inhaled Corticosteroids

IgE Immunoglobulin E

IL-13 Interleukin-13

RR rate reduction

RV rhinovirus

26 *To the Editor:*

27 Epidemiologic studies have implicated aeroallergens and respiratory infections
28 as triggers underlying the majority of asthma exacerbations¹. Spikes in asthma
29 exacerbation rates follow seasonal patterns of aeroallergen exposure and
30 respiratory viral infection prevalence, particularly rhinovirus (RV) infection in
31 children during the autumn (RV infections peak in September in the northern
32 hemisphere and March in the southern hemisphere)^{1, 2}. These seasonal
33 environmental factors may trigger or amplify airway inflammation in Type 2^{HIGH}
34 atopic asthma patients that precipitates acute worsening of symptoms³.
35 Seasonal increases in airborne allergens exacerbate allergic inflammation in
36 sensitized subjects via antigen mediated IgE/FcεRI crosslinking and
37 degranulation of airway mast cells and basophils leading to release of potent pro-
38 inflammatory mediators, e.g., Type 2 cytokines (interleukins-4/5/13) ³.
39 Respiratory viral infections, e.g., RV, initiate a cascade of host immune
40 responses. Multiple mechanisms have been described where viral respiratory
41 infections may augment Type 2 inflammation. Recently, much attention has
42 focused on the role of virus mediated release of epithelial cytokine alarmins, e.g.,
43 IL-25, IL-33, and TSLP, as key molecular triggers amplifying airway Type 2
44 inflammation that may underlie the loss of symptom control in patients with
45 asthma⁴. Additionally, viral components may directly activate eosinophils via
46 TLR-signaling⁵.
47 Biologic therapies targeting Type 2 cytokine pathways have demonstrated
48 efficacy in reducing the rate of severe asthma exacerbations, particularly in

patients selected on the basis of Type 2 biomarkers⁶. Anti-IgE therapy has been shown to prevent seasonal increases in asthma exacerbations, primarily in children^{7, 8}. In the present study, we conducted *post-hoc* analyses of the previously described LAVOLTA studies⁹ to assess the seasonal dependence of exacerbations and efficacy of lebrikizumab (anti-IL-13) in adults with moderate to severe asthma, who were uncontrolled despite inhaled corticosteroid (ICS) and a second controller therapy. The LAVOLTA studies enrolled and treated 2,148 patients from 28 countries in both the northern and southern hemispheres. The primary efficacy outcome of the LAVOLTA studies was the rate of severe asthma exacerbations over 52 weeks and patients were on study uniformly throughout all seasons for nearly a full year (median placebo controlled period participation was 11.95 months, *Online Repository* Figure 1). In this *post-hoc* analysis we hypothesized that the treatment effect of lebrikizumab would be maximal in the spring and autumn and conversely at a minimum in the summer.

We estimated annualized exacerbation rates by calendar month and accounted for hemispheric season by normalizing by study site location; herein we refer to a calendar month utilizing the northern hemisphere reference (see *Supplementary Methods*). By month exacerbation rates in placebo treated patients varied more than in lebrikizumab-treated patients. For example, exacerbation rates in February (0.95/year) and September (0.95/year) were more than double compared to the nadir in July (0.47/year) (Figure 1A). In contrast, exacerbation rates by month for lebrikizumab-treated patients were markedly less variable with a range of 0.40 to 0.61 exacerbations per year. Placebo-adjusted treatment

effect expressed as percent exacerbation rate reduction (RR) was assessed as a function of calendar month and peaked during the autumn and spring months (44.4[1.7,68.5]% for September and 49.3[5.9, 72.7]% for April); conversely the minimum treatment effect was observed in July (-2.0[-104.4,49.1]%) (Figure 1B).

We further explored the seasonal variability in exacerbation rate and treatment effect of lebrikizumab in patients whose baseline blood eosinophil count was < 300/ μ L (eosinophil-low) or $\geq$ 300/ μ L (eosinophil-high) (Figure 2A and B).

Exacerbation rates in placebo treated eosinophil-low patients were lower and less variable by month (0.34 to 0.72 per year) than in eosinophil-high patients; (0.63/year in August to 1.43/year in September). The by month treatment effect 95% confidence intervals overlapped with zero for eosinophil-low patients for all calendar months. In addition, the exacerbation rates for eosinophil-low patients receiving placebo or lebrikizumab were highly overlapping, suggesting that the exacerbations observed in eosinophil-low patients were not as dependent on IL-13 activity as eosinophil-high patients. The maximal per month treatment effects for eosinophil-high patients were observed during the autumn and spring months (62.7[10.1,84.5]% for September and 65.1[8.6,86.7]% for May). The minimal per month treatment effects were observed in the summer months (11.3[-148.7,68.4]% for July and 6.6[-166.0,67.2]% for August).

Further linking seasonal factors with a measure of Type 2 biology, i.e. blood eosinophil counts, we observed a distinct temporal association which mirrored the seasonal increases in asthma exacerbations (*Online Repository* Figure 2).

We assessed the levels of blood eosinophils during the study on a per month basis. As previously reported, blood eosinophil counts were modestly elevated in subjects treated with lebrikizumab presumably through inhibition of IL-13 dependent migration from blood vessels⁹. In both lebrikizumab and placebo-treated subjects, the geometric mean of blood eosinophil counts were at a minimum during the summer months and increased modestly to a maximum during the winter months (210 and 270 eosinophils per μL respectively for placebo treated subjects; 250 and 310 eosinophils per μL respectively for lebrikizumab treated subjects).

There are several limitations of this study which may be caveats or the basis for further investigation in future studies. Despite the relatively large size of the LAVOLTA studies, these analyses were *post-hoc* in nature and were partially limited by statistical power when considering per month exacerbation rates within patient subsets, as well as by the relatively low, albeit expected⁹ exacerbation rates observed overall in the placebo arms as compared to other asthma studies. Furthermore, while our observations in placebo treated subjects have robustly replicated previous epidemiology studies describing spring and autumn spikes in asthma exacerbations, we did not assess regional aeroallergen exposures or confirm viral infection in subjects at time of exacerbation.

Taking together 1) the previously published reports that anti-IgE therapy may prevent fall exacerbations^{7, 8}, 2) our observations that lebrikizumab is maximally effective at preventing asthma exacerbations in the spring and autumn months, and 3) that seasonal exacerbations are more prominent in asthma patients with

117 elevated blood eosinophil counts, a biomarker of Type 2^{HIGH} asthma, we
118 conclude that lebrikizumab has the potential to reduce seasonal asthma
119 exacerbations, especially in subjects with high blood eosinophil count. However,
120 these findings need to be replicated in a study adequately powered to
121 demonstrate this particular end-point.

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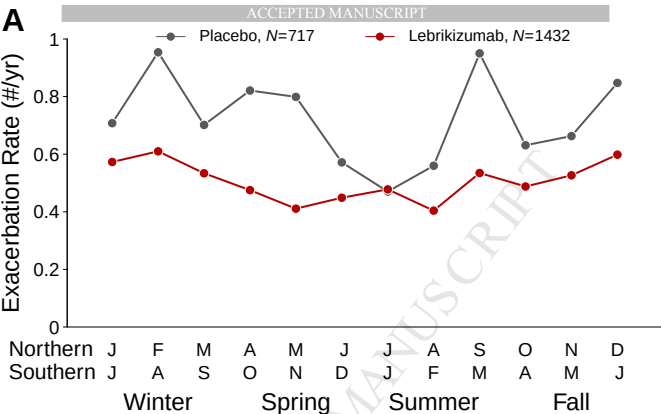
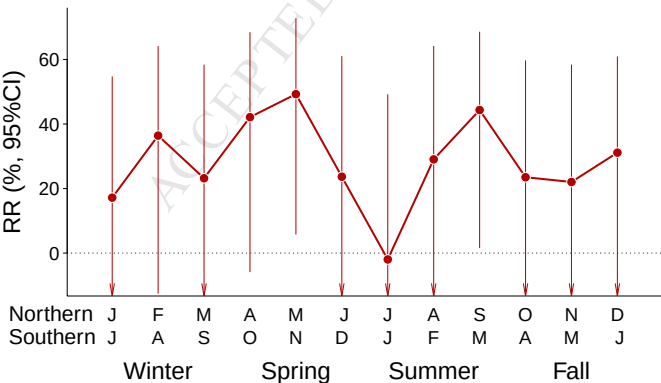
FIGURE LEGENDS

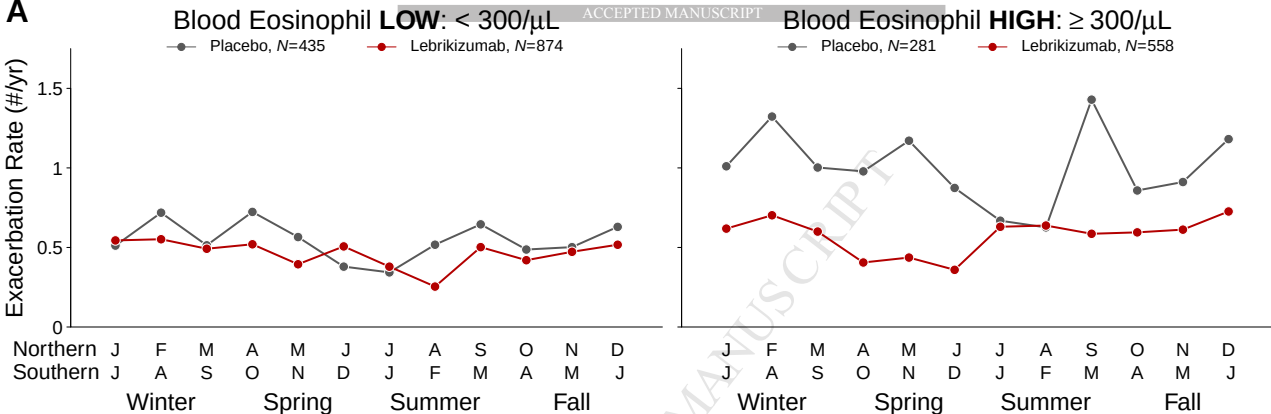
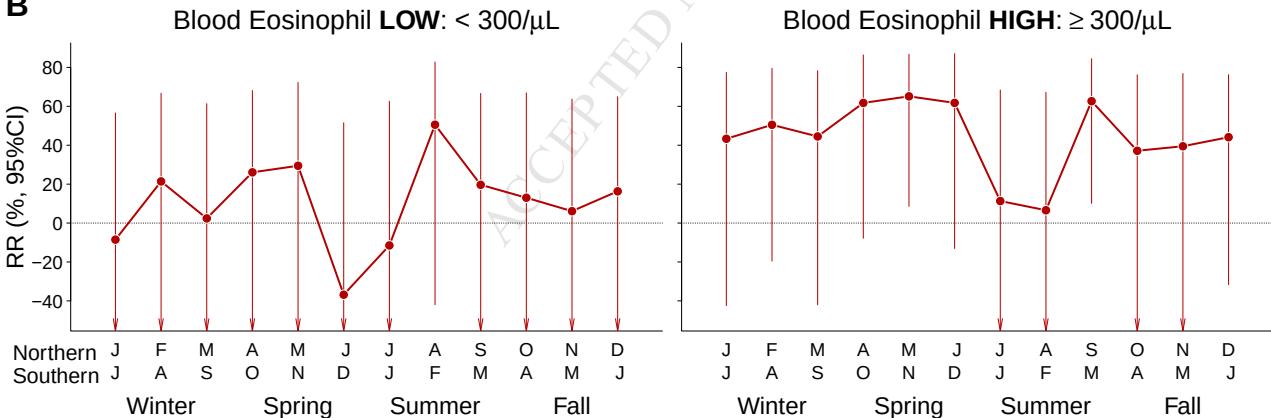
Figure 1. Seasonal analysis of exacerbations in all subjects. **A**, Unadjusted exacerbation rates and **B**, treatment effect expressed as percent exacerbation rate reduction (RR) are plotted as a function of normalized hemisphere month. The months for corresponding hemispheric season is annotated in plot margins. Confidence interval (CI) segments terminated by arrowheads indicate censored values; CI extends past plot limit.

Figure 2. Seasonal analysis of exacerbations in subjects defined by baseline blood eosinophil counts. **A**, Unadjusted exacerbation rates and **B**, treatment effect expressed as percent exacerbation rate reduction (RR) are plotted as a function of normalized hemisphere month (northern hemisphere reference). Analyses for subjects with baseline blood eosinophils $< 300/\mu\text{L}$ or $\geq 300/\mu\text{L}$ are plotted on left and right panels respectively. The months for corresponding hemispheric season is annotated in plot margins. Confidence interval (CI) segments terminated by arrowheads indicate censored values; CI extends past plot limit.

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A**B**

A**B**

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SUPPLEMENTARY METHODS

Clinical Cohort

The LAVOLTA I and II studies were replicate Phase III asthma studies of lebrikizumab and were previously described¹. Adult patients with uncontrolled asthma, pre-bronchodilator FEV1 40–80% predicted, and stable background therapy were randomly assigned (1:1:1) to receive lebrikizumab 37.5 mg or 125 mg, or placebo subcutaneously, once every 4 weeks. The primary efficacy endpoint was the rate of asthma exacerbations over 52 weeks in biomarker-high patients (periostin ≥ 50 ng/mL or blood eosinophils ≥ 300 cells per μ L). Both trials are registered at ClinicalTrials.gov, LAVOLTA I, number NCT01867125, and LAVOLTA II, number NCT01868061.

Statistics

R software² was used for plotting and analysis. All analyses constituted pooled data from LAVOLTA I and II studies. Separate lebrikizumab dose arms were pooled. Seasonal analyses were normalized by hemispheric season, based on subjects' study site location. Annualized (#/year) exacerbation rates by calendar month were estimated by Poisson regression, accounting for each subject's time at risk. Treatment effect (lebrikizumab versus placebo) by calendar month was estimated by linear contrasts from a Poisson regression Mixed-effect Model with Repeated Measures (MMRM), adjusted by the following covariates: 1) number of asthma exacerbations in 12 months prior to study entry (0, 1, ≥ 2), 2) baseline asthma medication - ICS total daily dose ≥ 1000 μ g fluticasone propionate, or

33 equivalent, plus LABA (Y, N), and 3) geographic region (North America, Central
34 and Eastern Europe, rest of the world). Exacerbation rate reduction and 95%
35 confidence intervals were calculated as the one minus the exponentiated
36 adjusted treatment effect coefficient.

SUPPLEMENTARY FIGURE LEGENDS

Figure 1. Histogram of placebo controlled period. The counts (y-axis) of subjects by duration of their placebo controlled period (x-axis) is plotted. The placebo controlled period for the LAVOLTA study subjects is nearly completely uniform at 12 months.

Figure 2. Seasonal variability of blood eosinophil counts. Geometric means plus and minus geometric standard errors for blood eosinophil counts ($\#/\mu\text{L}$) by calendar month are plotted. The months for corresponding hemispheric season are annotated in plot margins.

47 **SUPPLEMENTARY REFERENCES**

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Counts

