HR), with ROC values (areas in the ROC curves ranging from 0.79 to 1.0) in the excellent range as predictors (4 patients were considered successful, 6 unsuccessful; for further detail, see this article's Online Repository at www.jacionline.org). As a further measure of success, 3 of the 4 successfully treated patients chose to continue treatment.

The mobile diary provided a rich data source of time-stamped information that suggests that the kinetics of effects were, in general, relatively rapid, occurring in the first 8 weeks. The diary included a question about upper respiratory tract infections (URTIs), and it was apparent that daily symptom scores tracked closely with days with URTI reporting, but only during treatment. There were 6 reported URTIs in the run-in period but only 1 of these appeared to coincide with increased symptom scores. In contrast, there were 7 URTIs reported in the treatment period, 6 of which coincided with increased symptoms and 1 for which the increase in symptoms lagged the URTI by several days. The chi-square for this pattern being associated with treatment was 9.5 ($P = .002$). Fig E4 in this article's Online Repository at www.jacionline.org shows an example of the association during the treatment period.

A previous food allergy study suggested that the specific-to-total IgE ratio might be an important consideration for predicting successful treatment.[5] For a study of asthma, it is not immediately obvious which allergen-specific IgE should be considered in such a predictive analysis. Three approaches to examining this issue are to (1) sum the specific-to-total ratios for all perennial allergens or (2) consider only the largest specific-to-total ratio and (3) consider the overall number of perennial and seasonal allergens for which the patient shows positive skin test results. For this study, none of the 3 metrics was found to alter the predictions based on basophil metrics. No other patient metrics were found to relate to the outcomes.

At the inception of this study, it was the change in syk expression (ratio of syk, treatment/baseline) that was predicted to associate with the success of being treated with omalizumab. This was found to be true, but all 4 predictors produced excellent discrimination. The number of subjects is small and the study would need to be extended to a larger population to verify these findings. If the results are an indication that basophils could act as a biomarker, a simple pretreatment test examining basophil HR or CD63 expression (as a surrogate marker of HR) could be used to predict the success of omalizumab in a population with more severe asthma. It should be noted that these results suggest that basophil characteristics may be a biomarker of successful clinical response but do not necessarily indicate a causal relationship between basophil behavior and disease treatment. There are many factors that may contribute to this relationship. A practical observation is that if the basophil test suggests an ability to treat, treatment effects tend to occur rapidly.

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Seasonal variability of severe asthma exacerbations and clinical benefit from lebrikizumab

To the Editor:

Epidemiologic studies have implicated aeroallergens and respiratory infections as triggers underlying most asthma exacerbations.[1] Spikes in asthma exacerbation rates follow seasonal patterns of aeroallergen exposure and respiratory viral infection prevalence, particularly rhinovirus (RV) infection in children during the autumn (RV infections peak in September in the northern hemisphere and March in the southern hemisphere).[1,2] These seasonal environmental factors may trigger or amplify airway inflammation in patients with type 2^{HIGH} atopic asthma that precipitates acute worsening of symptoms.[3] Seasonal increases in airborne allergens exacerbate allergic inflammation in sensitized subjects via antigen-mediated IgE/FcεRI crosslinking and degranulation of airway mast cells and basophils leading to release of potent proinflammatory mediators, for example, type 2 cytokines (IL-4/5/13).[3] Respiratory viral infections, for example, RV, initiate a cascade of host immune responses. Multiple mechanisms have been described where viral respiratory infections may augment type 2 inflammation. Recently, much attention has focused on the role of virus-mediated release of epithelial cytokine alarmins, for example, IL-25, IL-33, and TSLP, as key molecular triggers amplifying airway type 2 inflammation that may underlie the loss of symptom control in patients with asthma.[4] In addition, viral components may directly activate eosinophils via TLR-signaling.[5]

Biologic therapies targeting type 2 cytokine pathways have demonstrated efficacy in reducing the rate of severe asthma exacerbations, particularly in patients selected on the basis of type 2 biomarkers.[6] 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 studies[9] 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 and a second controller therapy. The LAVOLTA studies enrolled

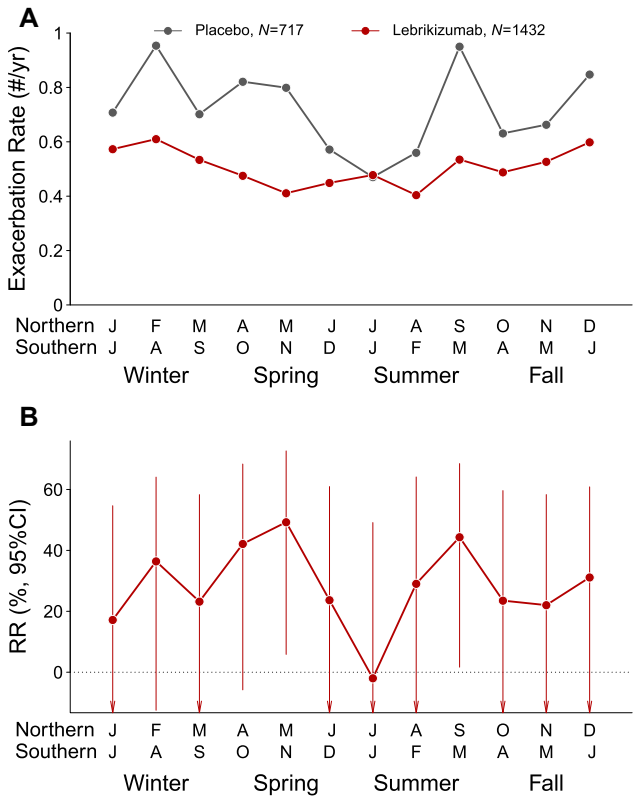

FIG 1. Seasonal analysis of exacerbations in all subjects. Unadjusted exacerbation rates **(A)** and treatment effect **(B)** expressed as percent exacerbation rate reduction (RR) are plotted as a function of normalized hemisphere month. The months for corresponding hemispheric season are annotated in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

and treated 2148 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; see Fig E1 in this article's Online Repository at www.jacionline.org). 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 using the northern hemisphere reference (see this article's Methods section in the Online Repository at www.jacionline.org). By month exacerbation rates in placebo-treated patients varied more than in lebrikizumab-treated patients. For example, exacerbation rates in February (0.95/y) and September (0.95/y) were more than double compared with the nadir in July (0.47/y) (Fig 1, *A*). 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 was assessed as a function of calendar month and peaked during the autumn and spring months (44.4 [95% CI, 1.7, 68.5]% for September and 49.3 [95% CI, 5.9, 72.7]% for April); conversely, the minimum treatment effect was observed in July (−2.0 [95% CI, −104.4, 49.1]%) (Fig 1, *B*).

We further explored the seasonal variability in exacerbation rate and treatment effect of lebrikizumab in patients whose baseline blood eosinophil count was less than 300/μL (eosinophil-low) or 300/μL or more (eosinophil-high) (Fig 2, *A* and *B*). Exacerbation rates in placebo-treated eosinophil-low patients were lower and less variable by month (0.34-0.72 per year) than in eosinophil-high patients (0.63/y in August to 1.43/y in September). The by month treatment effect 95% CIs 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 in eosinophil-high patients. The maximal per-month treatment effects for eosinophil-high patients were observed during the autumn and spring months (62.7 [95% CI, 10.1, 84.5]% for September and 65.1 [95% CI, 8.6, 86.7]% for May). The minimal per month treatment effects were observed in the summer months (11.3 [95% CI, −148.7, 68.4]% for July and 6.6 [95% CI, −166.0, 67.2]% for August).

Further linking seasonal factors with a measure of type 2 biology, that is, blood eosinophil counts, we observed a distinct temporal association that mirrored the seasonal increases in asthma exacerbations (see Fig E2 in this article's Online Repository at www.jacionline.org). 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 vessels.[9] In both lebrikizumab- and placebo-treated subjects, the geometric mean of blood eosinophil counts was at a minimum during the summer months and increased modestly to a maximum during the winter months (210 and 270 eosinophils/μL, respectively, for placebo-treated subjects; 250 and 310 eosinophils/μL, respectively, for lebrikizumab-treated subjects).

There are several limitations of this study that 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 expected[9] exacerbation rates observed overall in the placebo arms as compared with other asthma studies. Furthermore, although 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 the 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 patients with asthma with elevated blood eosinophil counts, a biomarker of type 2^{HIGH} asthma, we conclude that lebrikizumab has the potential to reduce seasonal asthma exacerbations, especially in subjects with high blood eosinophil count. However, these findings need to be replicated in a study adequately powered to demonstrate this particular end point.