The Medical Xchange

NOT FOR DISTRIBUTION

MEETING REPORT

San Francisco, California | May 15-18, 2016

American Thoracic Society (ATS) 2016 International Conference

Biomarkers of Severe Asthma May Help Better Direct Emerging Therapies

San Francisco - In asthma patients with frequent and difficult-to-control exacerbations, data from the Severe Asthma Research Program (SARP) promises to guide the newest targeted therapies to the underlying pathophysiology. Data presented at this year's ATS from the SARP program suggest that highly-specific biomarkers are likely to allow expensive but effective emerging therapies to be used to reduce both the risk of life-threatening events and excess consumption of healthcare resources.

Latest Analysis from SARP

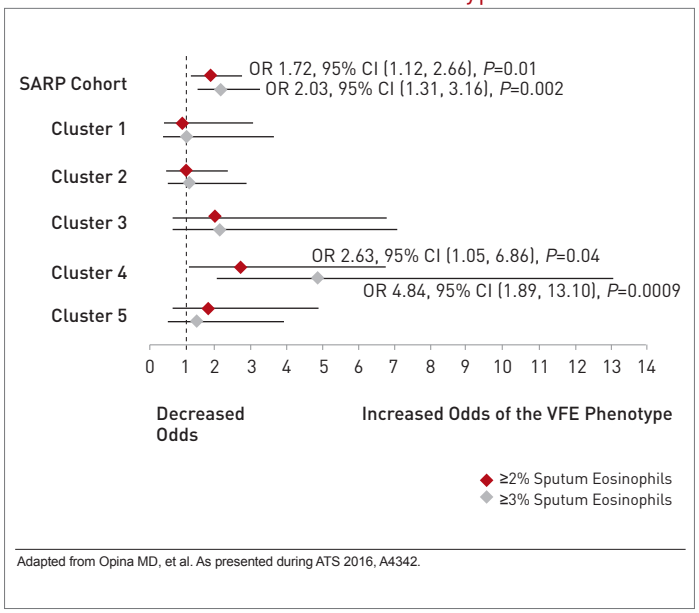
"Elevated blood eosinophils, sputum eosinophils, sputum neutrophils, and exhaled nitric oxide are all among biomarkers that have been associated with very frequent severe exacerbations, but our data suggest that these are not equally predictive of severe asthma in the phenotypes identified in the SARP cluster analysis," reported Dr. Maria Theresa D. Opina, a researcher for the National Heart, Lung, and Blood Institute's SARP program at Wake Forest University, Winston-Salem, North Carolina.

In the previously-published SARP cluster analysis (Moore WC et al. *Am J Respir Crit Care Med*. 2010;181:315-23), five distinct phenotypes were identified on the basis of 34 core variables. Severe airflow obstruction was most common in clusters 4 and 5. In specifically subtyping very frequent exacerbators (VFE), defined as having at least 3 courses of oral corticosteroids for asthma in the last 3 years, this new analysis provided even greater detail about the role of inflammatory mediators.

"Across the SARP [severe asthma] cohort, sputum eosinophils ≥2% were significantly associated with the very frequent exacerbator phenotype."

"Across the SARP cohort, sputum eosinophils ≥2% were significantly associated with the VFE phenotype but when clusters were assessed individually, the association was significant only in cluster 4," according to Dr. Opina (Figure 1). Elevated sputum neutrophils, although associated with "exacerbator prone" asthma, were not a predictor of VFE across the SARP cohort or in any of the individual clusters regardless of cut-off employed. Elevated exhaled nitric oxide, defined as ≥35ppb, was significantly associated with the VFE phenotype in clusters 4 and 5 with a higher predictive value in cluster 5.

FIGURE 1 I Sputum Eosinophils ≥2% Significantly Associated with VFE Phenotype in Cluster 4



Adapted from Opina MD, et al. As presented during ATS 2016, A4342.

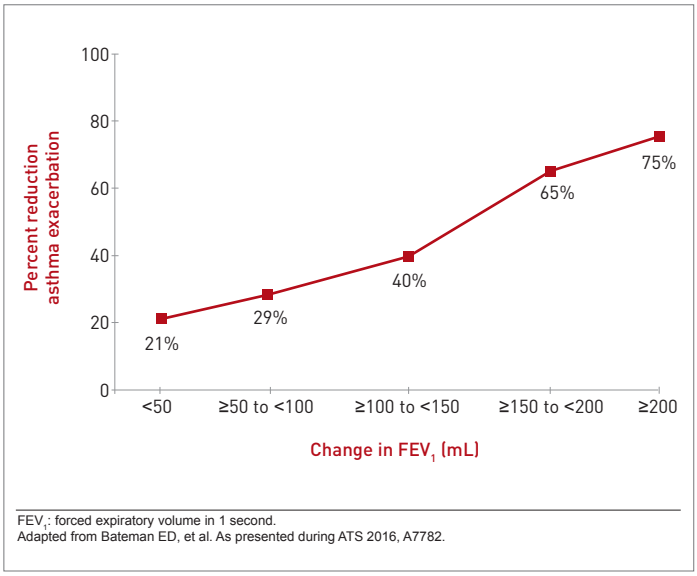
The variability in inflammatory mediator expression across the SARP clusters is consistent with the principle expressed in the joint ATS and European Respiratory Society (ERS) guidelines that there are multiple causes of severe asthma (Chung KF et al. *Eur Respir J*. 2014;43:343-73). In those guidelines, severe asthma, distinguished from "difficult" asthma, is defined as uncontrolled symptoms despite high-dose inhaled corticosteroids (ICS) and a second controller. The guidelines estimate that up to 10% of patients with asthma have a severe phenotype that places them at exceptional risk of life-threatening events.

Newer Targeted Therapies in Severe Asthma

Progress in defining severe asthma subtypes will be valuable for ensuring that newer targeted therapies, such as the anti-interleukin-5 (IL-5) monoclonal antibodies (mAb), are employed cost effectively. Several studies presented at the ATS reinforced the activity of these agents in severe asthma while also suggesting that some subgroups may derive particular benefit.

In efficacy data pooled from two phase 3 studies with reslizumab, for example, there was a 50% reduction in adjudicated exacerbations for those randomized to the mAb relative to placebo (0.84 vs. 1.81 events/year; rate ratio of 0.46; *P*<0.0001). However, the authors of the study, led by Dr. Eric Bateman, National Research Foundation of South Africa, Cape Town, reported that an early improvement in lung function and symptom control was an additional predictor of long-term benefit (Figure 2).

FIGURE 2 | Reduction in Annual Rate of Asthma Exacerbations



FEV_1: forced expiratory volume in 1 second.
Adapted from Bateman ED, et al. As presented during ATS 2016, A7782.

"The reduction in the annual exacerbation rate was associated in a stepwise fashion with relative improvement in FEV_1 at week 16," Dr. Bateman reported. He also reported that a similar association with benefit was made with early improvement on the 6-item Asthma Control Questionnaire (ACQ-6).

In this pooled analysis of 953 patients randomized to 3.0 mg/kg reslizumab or placebo administered every four weeks, a baseline eosinophil count ≥400 µL was an entry criterion. By week 16, 58% of reslizumab patients had a FEV_1 response defined as ≥100 mL increase, 71% had an ACQ-6 response, defined as ≥0.5 unit improvement, and 83% had either response. While an early response predicted greater protection against exacerbations, Dr. Bateman also reported that responders had a higher baseline blood eosinophil count, and a slightly lower prevalence of allergic disease than non-responders.

In most trials with the anti-IL5 agents, including reslizumab and mepolizumab, some degree of eosinophilia has been an entry criterion, but other biomarkers or patient characteristics may also be useful in selecting patients for this type of therapy. In a post-hoc analysis presented at the 2016 ATS of baseline characteristics among patients randomized in the placebo-controlled DREAM and MENSA trials with mepolizumab, serious events, such as hospitalization or near fatal events, did not differ when comparing patients who entered the study with eosinophil counts <300 µL or ≥300 µL.

"The reduction in the annual exacerbation rate was associated in a stepwise fashion with relative improvement in FEV_1 at week 16."

However, these data, presented by Dr. Eric Bradford, a researcher with GlaxoSmithKline, Research Triangle Park, North Carolina, were contradicted by a study evaluating asthma exacerbations over a median of 4 years in 4,838 patients stratified into tertiles by baseline eosinophil levels. Relative to patients in the lowest tertile, those in the highest had about a 65% increased risk of severe asthma exacerbations, defined as a hospitalization, and 56% increased risk of a moderate exacerbation, defined as a short course of oral steroids.

"We also saw a surprisingly high risk of moderate exacerbations in patients with low blood eosinophil levels, but this was explained by high levels of blood neutrophils," reported Dr. Signe Vedel-Krogh, Copenhagen University Hospital, Herlev, Denmark.

Conclusion

The growing focus on inflammatory mediators of severe asthma has major implications for directing novel therapies such as anti-IL5 mAbs to those patients likely to derive the most benefit.●