CHEST™

Biomarker Profiles in Asthma With High vs Low Airway Reversibility and Poor Disease Control

William W. Busse, MD; Stephen T. Holgate, MD, DSc; Sally W. Wenzel, MD, FCCP; Paul Klekotka, MD, PhD; Yun Chon, PhD; JingYuan Feng, MS; Edward P. Ingenito, MD, PhD; and Ajay Nirula, MD, PhD

BACKGROUND: High bronchodilator reversibility in adult asthma is associated with distinct clinical characteristics. This analysis compares lung function, biomarker profiles, and disease control in patients with high reversibility (HR) and low reversibility (LR) asthma.

METHODS: A retrospective analysis was performed with data from two completed clinical trials of similar design. Patients were divided into HR and LR subgroups based on their response to bronchodilators (HR = ΔFEV_1 postbronchodilator $\geq$ 20%). Blood eosinophil count, serum IgE level, and fraction of exhaled nitric oxide concentration, biomarkers commonly used to stratify patients into T-helper (Th)-2-high vs Th2-low phenotypes, were measured in patients with not well controlled (1.5 $\leq$ Asthma Control Questionnaire [ACQ] $\leq$ 2.143) and very poorly controlled (ACQ $>$ 2.143) disease.

RESULTS: The majority of patients in the HR and LR subgroups displayed Th2-low biomarker profiles and very poor disease control. HR was more frequently associated with Th2-high biomarker profiles (40.1% vs 29.4%, $P = .006$), lower lung function (FEV_1, 63.5 $\pm$ 7.7% predicted vs 67.9 $\pm$ 8.4% predicted; $P < .001$), and atopy (93.7% vs 86.5%, $P = .005$).

CONCLUSIONS: HR is a physiologic indicator of reduced lung function and is more often associated with elevations in Th2 biomarkers than LR in moderate to severe asthma. However, the majority of patients with HR and LR asthma in this analysis had a Th2-low biomarker profile. Moreover, a Th2-high biomarker profile was not associated with worse disease control.

CHEST 2015; 148(6):1489-1496

Manuscript received October 3, 2014; revision accepted July 1, 2015; originally published Online First July 30, 2015.

ABBREVIATIONS: ACQ = Asthma Control Questionnaire; CART = classification and regression tree; FENO = fraction of exhaled nitric oxide; GINA = Global Initiative for Asthma; HR = high reversibility; IPI = Immune Profile Index; LR = low reversibility; NWC = not well controlled; PPV = positive predictive value; SARP = Severe Asthma Research Program; Th = T-helper; VPC = very poorly controlled

AFFILIATIONS: From the University of Wisconsin (Dr Busse), Madison, WI; Clinical and Experimental Sciences (Dr Holgate), Facility of Medicine, University of Southhampton, Highfield, Southhampton, England; University of Pittsburgh Medical Center (Dr Wenzel), Pittsburgh, PA; and Amgen Inc (Drs Klekotka, Chon, Ingenito, and Nirula and Ms Feng), Thousand Oaks, CA.

FUNDING/SUPPORT: This study was supported by Amgen Inc, Thousand Oaks, CA.

CORRESPONDENCE TO: Edward P. Ingenito, MD, PhD, Clinical Development Team, Amgen Inc, 360 Binney St, Cambridge, MA 20141; e-mail: ingenito@amgen.com

DOI: 10.1378/chest.14-2457

Data from large patient registries have identified clusters of patients with asthma and severe airflow limitation and disease that is difficult to control with conventional therapy.[1-4] Characteristics differentiating these patients from the general asthma population include longer duration of disease, high reversibility (HR) of the airway following bronchodilator administration, sputum neutrophilia, increased oral corticosteroid use, and increased health-care resource utilization.[1,4] Indeed, HR is a distinctive physiologic characteristic of cluster 4 and 5 patients in the Severe Asthma Research Program (SARP), the two cohorts displaying the worst disease control and highest frequency of clinic and ED visits and hospitalizations. Serum and BAL fluid biomarkers have been analyzed to characterize the immune processes modulating disease severity.[2,5] However, limited information exists regarding how serum biomarkers define endotypes across the asthma population, correlate with disease control, and relate to distinctive physiologic features such as HR. The present study uses combined baseline datasets from two randomized controlled trials involving patients with moderate to severe asthma to examine the relationship between immune pathway biomarkers and disease control in those with HR and low reversibility (LR).

Materials and Methods

A retrospective exploratory analysis was performed using data from two phase 2 clinical trials involving patients with partly or poorly controlled moderate to severe asthma (GINA [Global Initiative for Asthma] steps 3 and 4). The first trial was initiated on December 21, 2009, to assess the efficacy of a dual inhibitor of the prostaglandin D2 and chemoattractant receptor homologous molecule expressed on T-helper (Th) 2 cells.[6] Full baseline datasets were available for 358 of 396 enrolled patients. The second trial was initiated October 4, 2010, to assess the efficacy of a monoclonal antibody against the IL-17 receptor A subunit in a similar cohort.[7] Full baseline datasets were available for 272 of 302 enrolled patients. Although both trials were interventional, treatment responses were not considered in this analysis. Data collected beyond the baseline time point were used solely to assess stability of phenotypic characteristics in patients who did not receive experimental therapy.

Inclusion and exclusion criteria for the two trials were identical: (1) age 18 to 65 years, (2) disease requiring inhaled corticosteroids with and without a long-acting β-agonist, (3) baseline Asthma Control Questionnaire (ACQ) score $\geq$ 1.5, (4) FEV_1 % predicted between 50% and 80%, (5) reversibility in $FEV_1 \geq 12\%$ (and at least 200 mL) following administration of a short-acting β-agonist, (6) no evidence of active infection, and (7) no medical conditions associated with immune suppression. Patients were excluded from study participation if they had COPD or asthma-COPD overlap syndrome,[8] were receiving maintenance oral corticosteroids or IgE antibody therapy, were current or recent smokers, had a history of intubation within 3 years of enrollment, or had OSA.

Subjects were classified into (1) an HR group of those with high airway reversibility defined as a $\geq$ 20% increase in FEV_1 following administration of a short-acting bronchodilator during screening and baseline pulmonary function testing and (2) an LR group of those with reversibility below this level.[1,4] Subgroups were further divided into subjects with not well controlled (NWC) (ACQ score $\geq$ 1.5 and $\leq$ 2.143) or very poorly controlled (VPC) (ACQ > 2.143) disease. The ACQ cut point defining VPC disease was derived from a linear extrapolation of ACQ scores of well controlled (five total ACQ points corresponding to an ACQ cut point of 0.75) and NWC (10 total ACQ points corresponding to an ACQ cut point of 1.5) disease.[9] VPC disease was defined as corresponding to an additional five-point increment in total ACQ score beyond the NWC cut point (ie, ACQ > 2.143). Disease control was summarized in terms of both ACQ6 and ACQ7 values. Biomarkers reflecting Th2 immune activation were assessed in each patient and included serum IgE level, circulating eosinophil count, and fraction of exhaled nitric oxide (Feno) concentration. For each biomarker, cut points used to define a high level were as follows: IgE $\geq$ 100 IU/mL, eosinophil count $\geq$ 300/μL, and Feno $\geq$ 30 parts per billion.[10,11] Patients were classified as having either a positive or a negative Th2 Immune Profile Index (IPI) (positive IPI indicates elevation in two or more Th2 biomarkers; negative IPI indicates elevation in one or no Th2 biomarkers).

Results are reported using descriptive statistics as mean ± SD, median, or quartiles as appropriate. Comparisons of baseline data between the two trials[6,7] and between the HR and LR subgroups were performed by either Student *t* or Wilcoxon rank sum test. Correlations between baseline and week 12 biomarker assessments were performed using the Pearson product-moment correlation method. Assessments of the significance of relationships between Th2 biomarker elevations and disease control were performed by χ^2 test (applying Yates correction as appropriate). A classification and regression tree (CART) analysis was included in the sensitivity analysis of cut points defining Th2 biomarker status. Statistically significant differences between groups were defined by $P < .05$.

Results

Demographics, biometrics, medical history, pulmonary function values, and medication use for all patients (N = 698) in both studies are summarized in Table 1. Patients studied in the first clinical trial[6] were more likely to be atopic (93% vs 83%, $P < .001$) and had a higher FEV_1 % predicted (66.9% ± 8.24% vs 65.2% ± 8.53%, $P = .0081$) than those in the second trial.[7] However, these differences were small and not clinically significant or substantial enough to affect interpretation of results when considered as a single combined cohort.

Two hundred thirty-seven patients (38%) in the combined study cohort met the HR criterion. Relative to those with LR (n = 385), patients with HR asthma tended to be younger; were more often atopic; and had a significantly lower BMI, lower baseline pulmonary function, higher mean Feno and IgE values, and higher ACQ7 scores (Table 2). One hundred thirty-six patients (63.6%) with HR asthma met the criterion for VPC