Novel AMG 157 Improved Inflammation and Bronchoconstriction in Allergic Asthma

Written by Mary Mosley

AMG 157 is a human antithymic stromal lymphopoietin (TSLP) monoclonal immunoglobulin-2γ molecule that blocks the interaction between TSLP and its receptor, a process that is thought to be important in initiating allergic inflammation. Gail M. Gauvreau, PhD, McMaster University, Hamilton, Ontario, Canada, presented data from the Double-Blind, Multiple Dose Study in Subjects With Mild Atopic Asthma study [NCT01405963; Gauvreau GM et al. *Am J Crit Care Med* 2014] evaluating whether the AMG 157 monoclonal antibody reduced baseline airway inflammation and allergen-induced bronchoconstriction as measured by early (6-week) and late (12-week) asthmatic responses (EAR and LAR, respectively) to allergen challenge in subjects with mild allergic asthma.

Eligible patients had mild asthma and responded to an inhaled allergen challenge with EAR and LAR during screening, which determined the concentration of the allergen challenge. Subjects were randomized in a 1:1 ratio to AMG 157 (n=16) or placebo (n=15). Patients were treated on Days 1, 29, and 57 (700-mg intravenous infusion) and were given an allergen challenge on Days 42 and 84. Induced sputum was collected 1 day before and 7 and 24 hours after each allergen challenge, and methacholine airway responsiveness was measured 1 day before and 1 day after each allergen challenge.

The baseline characteristics are detailed in Table 1.

Table 1. Baseline Characteristics in Study Patients[a]

Characteristic	Placebo (n=15)	AMG 157 (n=16)
Age, years	31.5 ± 2.9	30.8 ± 2.7
Female gender, Number (%)	11 (73)	10 (63)
White race, Number (%)	13 (87)	14 (88)
Body mass index, kg/m^2	26.5 ± 1.1	234.9 ± 0.7
FEV_1, L	3.35 ± 0.19	3.37 ± 0.20
FEV_1, % predicted	97.6 ± 3.9	95.4 ± 3.3
Methacholine PC_{20}, mg/mL[b]	1.87 (0.97–3.61)	1.31 (0.48–3.64)
F_ENO, ppb	58.9 ± 14.3	42.3 ± 4.3
Sputum eosinophils, %	4.7 ± 2.2	4.1 ± 2.3
Blood eosinophils, ×10^6/L	281.1 ± 57.2	296.5 ± 40.2

F_ENO=fractional exhaled nitric oxide; FEV_1=forced expiratory volume in 1 second; PC_{20}=provocative concentration causing 20% decrease in FEV_1.

[a]Data are expressed as mean ± SEM except as indicated.

[b]Geometric mean (95% CI).

There was a trend toward improvement in the primary end point, LAR between 3 and 7 hours after the allergen challenge as measured by maximum percentage decrease in forced expiratory volume in 1 second at 6 weeks for AMG 157 compared with placebo (14.9% vs 22.5%; treatment

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difference, 7.65; 95% CI, –1.30 to 16.60; p=0.09) and a significant improvement at 12 weeks (11.7% vs 21.6%, p=0.02). There was a trend toward improvement in a secondary end point, EAR between 0 and 2 hours after the allergen challenge using the same measure at 6 weeks (23.3% vs 31.8%; treatment difference, 8.57; 95% CI, 0.01 to 17.13; p=0.05) and 12 weeks (22.7% vs 32.9%; treatment difference, 10.27; 95% CI, –0.46 to 21; p=0.06) for AMG 157 compared with placebo.

Exploratory analyses revealed that the increases in blood eosinophil (p=0.004) and sputum eosinophil (p=0.015) levels were less with AMG 157 compared with placebo. Also, fractional exhaled nitric oxide, a surrogate marker of inflammation, was significantly reduced with AMG 157 treatment versus placebo (p=0.002). The number of adverse events was similar between treatments (15 in the AMG 157 group and 12 in the placebo group).

Prof. Gauvreau highlighted the unexpected reductions in inflammatory markers (blood and sputum eosinophil counts and fractional exhaled nitric oxide) with AMG 157 versus placebo before the allergen challenge, suggesting that TSLP is constitutively expressed in the airway in the setting of asthma, even in the absence of allergen exposure. She suggested that the findings support a role for targeting TSLP to control both persisting airway inflammation and allergen-induced airway responses in individuals with allergic asthma.

Gene Expression Test Boosts Sensitivity of Bronchoscopy in Lung Cancer Diagnosis

Written by Emma Hitt Nichols, PhD

The addition of gene expression analysis of 17 cancer genes increases sensitivity of bronchoscopy for the diagnosis of lung cancer, regardless of lesion size, location, and histology. Duncan Whitney, PhD, Allegro Diagnostics Corporation, Maynard, Maryland, USA, presented data from the Airway Epithelium Gene Expression in the Diagnosis of Lung Cancer trial [AEGIS; NCT01309087; Whitney D et al. *Am J Respir Care Med* 2014].

Bronchoscopy is the standard method of lung cancer diagnosis. Although it is a safe procedure associated with few complications, it is unable to rule out cancer because of a relatively high false-negative rate [Ost DE et al. *Chest* 2011; Ernst A et al. *Chest* 2010; Wilson DO et al. *Am J Respir Crit Care Med* 2008]. Gene expression profiles are able to detect damage to lung epithelium from smoking and may be a technique to differentiate cancer from benign disease [Beane J et al. *Genome Biol* 2007; Spira A et al. *Nat Med* 2007]. The purpose of this study was to determine if a gene expression–based classifier would increase the sensitivity of the bronchoscopic diagnosis of lung cancer.

In AEGIS, a prospective multicenter cohort trial, mainstem bronchus epithelial cells were collected from patients scheduled for bronchoscopy and then followed for 12 months. All patients were suspected to have lung cancer, were current or former smokers, and did not have any other malignancies or history of lung cancer.

In the study, 597 samples were evaluated, with half assigned to the training set and half to the validation set. The training set was used for gene selection and model fitting. A total of 232 differentially expressed genes were identified, and the selected cancer genes were from residuals of clinical covariates, such as age, smoking, pack-years, and sex. The final algorithm included 17 cancer prediction genes. The independent validation set was used to validate the gene expression biomarkers identified in the training set.

Seventy-four percent of subjects were diagnosed with lung cancer by pathology as the gold standard. The remainder was followed for 12 months to confirm cancer-free status if no malignancy was initially diagnosed. The addition of genomics to bronchoscopy (BronchoGen; Allegro) increased the sensitivity from 74% to 96% but decreased the specificity from 100% to 47%, which is not expected to lead to a high false-positive rate when the genomic test is used to rule out cancer. The increased sensitivity of BronchoGen was not affected by lesion size, location, stage, or histology. The diagnostic yield was most improved in small peripheral lesions. As a result, the combination technique resulted in a negative likelihood ratio of 0.077, compared with 0.260 from bronchoscopy alone, thereby improving the ability to rule out lung cancer and avoid unnecessary invasive follow-up procedures.

In the AEGIS study, 43% of bronchoscopies were negative for cancer, and 34% of surgeries were performed in patients with benign lesions. Therefore, 42% of patients could avoid invasive procedures if BronchoGen were used instead of bronchoscopy alone to diagnose lung cancer.

In conclusion, Dr. Whitney stated that, in his opinion, the results of the AEGIS study suggest that adding a genomic classifier to bronchoscopy increases clinical sensitivity of bronchoscopy, which is independent of lesion size, location, and histology. This increased sensitivity was at the expense of decreased specificity and a higher false-positive rate. BronchoGen is currently under development to be released as a Clinical Laboratory Improvement Amendments laboratory service.