Efficacy was assessed on the basis of lung function parameters, including mean forced expiratory volume in 1 second (FEV_1), as well as mean change in forced expiratory flow from 25% to 75% of vital capacity, which (FEF_{25-75}) that the authors noted is a fairly reliable surrogate marker of small airway function. These lung function parameters were recorded during each patient visit for 2 weeks.

Overall, the study revealed that the dose of long-term oral corticosteroids was reduced in all treatment arms. For patients who received add-on therapy, lung function parameters improved significantly at Week 18 from baseline, whereas no significant improvements were seen in patients in the placebo and conventional nebulizer arms. The mean FEV_1 were 239 mL ($p<0.001$) and 126 mL ($p=0.01$) for AICS-BUD (1 mg) and AICS-BUD (0.5 mg), respectively, and 93 mL ($p=0.36$) and 137 mL ($p=0.18$) for placebo and CN-BUD, respectively. Regarding small airway function, the study revealed that patients treated with AICS-BUD (1 mg) had significant improvement in mean FEF_{25-75} from baseline to Week 18 compared with patients in the AICS-placebo arm. The study also indicated that patients treated with AICS-BUD (1 mg), compared with those treated by CN-BUD, had fewer asthma exacerbations (7.5% vs 22.5%), a longer mean time to first exacerbation (96.5 vs 50.1 days), and a smaller subsample of patients who experienced asthma instability (15.0% vs 25.0%).

These findings show an improvement in lung function 12 weeks after initiation of consistent dosing of BUD via a novel delivery system. Without controlling for differences among treatment groups, there appears to be greater benefit of consistent delivery of BUD (1 mg) over similar dosing with a conventional nebulizer.

CYT003-QbG10 Not Effective in Uncontrolled Allergic Asthma

Written by Emma Hitt Nichols, PhD

Treatment with the A-type CpG oligodeoxynucleotide CYT003-QbG10 did not improve asthma control or lung function in patients with allergic asthma not adequately controlled with inhaled corticosteroids. Thomas Casale, MD, University of South Florida, Tampa, Florida, USA, presented data from the Randomized, Placebo-Controlled, Phase IIb Dose-Finding Study of CYT003-QbG10, a TLR9-Agonist, for Treatment of Uncontrolled Moderate to Severe Allergic Asthma [NCT01673672; Casale T et al. *Am J Respir Care Med* 2014].

CYT003-QbG10 is an A-type CpG oligodeoxynucleotide that activates toll-like receptor 9 to inhibit T-cell mediated airway inflammation. A previous study demonstrated that CYT003-QbG10 maintained or improved symptom control in patients with allergic asthma that was controlled with an inhaled corticosteroid [Beeh KM et al. *J Allergy Clin Immunol* 2013]. The purpose of this trial was to determine if treatment with CYT003-QbG10 would achieve similar results in patients with allergenic asthma that was not controlled by inhaled corticosteroids.

In this Phase 2 trial, 365 adults with moderate to severe allergic asthma were randomly assigned to receive 3 different dose levels of CYT003-QbG10 or placebo for 12 weeks. CYT003-QbG10 was administered by subcutaneous injection weekly for the first 4 weeks, then every other week up to 12 weeks. Patients aged 18 to 65 years were eligible if their asthma (Global Initiative Against Asthma steps 3 and 4) was not controlled with standard therapy. The primary outcome was asthma control after 12 weeks, and secondary outcomes included lung function, asthma symptoms, medication score, exacerbation, and quality of life.

Treatment with any dose of CYT003-QbG10 did not significantly change asthma control from baseline compared with placebo, as determined by the Asthma Control Questionnaire (ACQ) score. In addition, there were no significant changes from baseline in lung function or Mini Asthma Quality of Life Questionnaire scores.

Dr. Casale discussed the potential reasons that CYT003-QbG10 failed in this trial, focusing on the differences in study populations between the initial and current study. He noted that the ACQ score and eosinophil count were lower, and lung function was higher, in the patients in the initial study compared with the present study [Beeh KM et al. *J Allergy Clin Immunol* 2013]. He hypothesized that immune modulators such as CYT003-QbG10 may only benefit certain subpopulations. For example, the initial study demonstrated that CYT003-QbG10 treatment resulted in better outcomes in patients with the Th2-hi phenotype, which encompasses patients with higher eosinophil counts [Beeh KM et al. *J Allergy Clin Immunol* 2013]. Dr. Casale further differentiated the 2 study populations by pointing out that in the initial study, the improvement in ACQ score occurred when the corticosteroid dose was tapered to a lower dose and then discontinued. In the current study, no additional benefit was seen with the addition of CYT003-QbG10 to inhaled corticosteroids. Therefore, he suggested that CYT003-QbG10 may be most effective in patients who are not being treated for their asthma and that those with uncontrolled asthma represent the wrong patient population for this therapy.

In conclusion, Dr. Casale stated that although CYT003-QbG10 is not effective in patients with uncontrolled allergic asthma on inhaled corticosteroids, it may be effective

in patients with allergic asthma who are steroid naive with the Th2-hi phenotype. However, development of this drug for use in asthma has been discontinued.

Short-Term Treatment With Rosuvastatin Reduces Systemic Inflammation in Stable COPD Patients

Written by Mary Beth Nierengarten

The use of short-term rosuvastatin to treat patients with stable chronic obstructive pulmonary disease (COPD) reduces systemic inflammation but has no effect on pulmonary function and improves endothelial function only in patients with baseline C-reactive protein (CRP) levels >1.7 mg/L.

Anke Neukamm, MD, Cardiothoracic Research Group, Akershus University Hospital, Lørenskog, Norway, presented results of the Effect of Rosuvastatin Treatment in Stable COPD study [RODEO; NCT00929734; Neukamm A et al. *Am J Respir Crit Care Med* 2014], a randomized, double-blind clinical trial conducted to test the hypothesis that the use of statin therapy in patients with stable COPD would be associated with improved endothelial and pulmonary function and reduced systemic inflammation.

The study included 99 patients with stable COPD who were randomly assigned to once-daily treatment with rosuvastatin 10 mg (n=49) or placebo (n=50) for 12 weeks. Patients were excluded from the study if they had histories of or active coronary artery diseases, other lung diseases except asthma bronchiale, uncontrolled arterial hypertension, histories of diabetes or hypercholesterolemia, or statin use within the 4 weeks prior to the onset of the study.

Of the 99 patients, 94 patients completed the study (47 in each treatment arm). Baseline characteristics were similar between the 2 groups for age (mean, 65 years), sex (48% women), history of hypertension (25%), and smoking habit (mean, 37 pack-years).

To evaluate the effect of rosuvastatin on endothelial and pulmonary function and systemic inflammation, the primary endpoint was the change in peripheral vasodilator function measured by peripheral arterial tonometry and expressed as the reactive hyperemia ratio (RHI). The study also included a prespecified subgroup analysis of the effect of rosuvastatin in patients with elevated CRP levels.

Secondary endpoints included change in change in pulmonary function as assessed by forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced volume capacity ratio (FVC), as well as change in the circulating proinflammatory markers CRP, interleukin-6 (IL 6), and high-sensitivity CRP (hsCRP).

In an intention-to-treat analysis, the study found no difference between rosuvastatin and placebo in the primary end point of the study, vasodilator function.

However, there was a significant difference in vasodilator function, as determined by the change in RHI, with rosuvastatin compared with placebo in the subgroup of patients with elevated baseline CRP levels (median >1.7 mg/L, p=0.026).

In terms of secondary endpoints, rosuvastatin was associated with a significant reduction in hsCRP and attenuated the rise in IL6 compared with placebo (Table 1). No significant differences were seen in pulmonary function in FEV_1 or FEV_1/FVC.

Based on these results, the investigators emphasize the need for long-term randomized trials with large cohorts to more accurately assess the benefits of statin therapy in patients with stable COPD.

Table 1. Results of Secondary Endpoints

	Rosuvastatin (n=47)		Placebo (n=47)		
Variable	**Baseline**	**Follow-Up**	**Baseline**	**Follow-Up**	**p[a]**
FEV_1, L[b]	1.34 ± 0.09	1.35 ± 0.08	1.47 ± 0.10	1.45 ± 0.94	.462
FEV_1/FVC, %[b]	46.9 ± 2.01	47.3 ± 1.72	48.8 ± 1.72	47.9 ± 1.79	.292
hsCRP, mg/L[c]	1.4 (0.8, 3.7)	1.2 (0.7, 2.6)	1.8 (1.0, 4.4)	2.2 (1.3, 3.6)[d]	.017
IL-6, pg/mL[c]	4.1 (2.9, 5.2)	4.1 (3.4, 5.5)	3.4 (2.7, 4.7)	4.4 (3.0, 6.7)[e]	.028

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; hsCRP=high-sensitivity C-reactive protein; IL-6=interleukin-6.
[a]Analysis of covariance.
[b]Mean ± SEM.
[c]Median (25th percentile, 75th percentile).
[d]p<0.05, paired *t* test.
[e]p<0.05, Student *t* test.