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Once-Daily QVA149 Improves Breathlessness in COPD Patients

Written by **Wayne Kuznar**

A once-daily inhaled dual bronchodilator consisting of a long-acting β2-agonist and a long-acting muscarinic antagonist (QVA149) significantly improved self-reported shortness of breath and lung function compared with placebo and tiotropium in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Donald A. Mahler, MD, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA, presented results of the Effect of QVA149 on Dyspnea in Patients With Chronic Obstructive Pulmonary Disease study [BLAZE; NCT01490125], a multicenter, randomized, blinded, double-dummy, placebo-controlled, 3-period, crossover trial.

Dyspnea in COPD is not always controlled adequately by bronchodilator monotherapy, providing the rationale for combining two bronchodilators with different mechanisms of action [Rabe KF et al. *Am J Respir Crit Care Med* 2007; Vestbo J et al. *Am J Respir Crit Care Med* 2013]. QVA149 is an investigational fixed-dose combination of indacaterol maleate 110 µg and glycopyrronium bromide 50 µg. QVA149 had previously demonstrated improvements in dyspnea versus its individual components, tiotropium, and salmeterol/fluticasone using the interviewer-based Transition Dyspnea Index (TDI) [Bateman ED et al. *Eur Respir J* 2013; Vogelmeier C et al. *Respir Med* 2013].

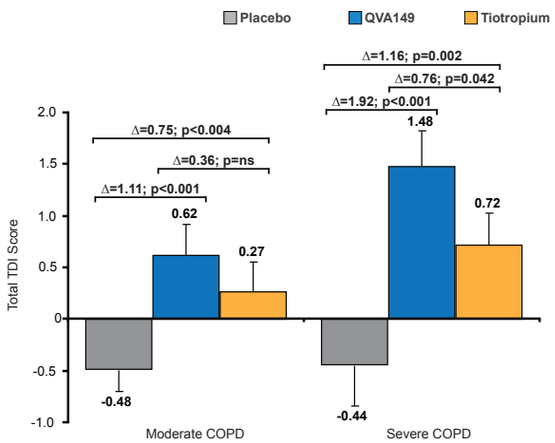
In BLAZE, patients with moderate to severe COPD (n=246) were randomized to once-daily QVA149, tiotropium 18 µg, or placebo. Patients were current or former smokers, had a Modified Medical Research Council scale of >2 at screening, a postbronchodilator forced expiratory volume in 1 second (FEV_1) ≥30 and <80% predicted, and FEV_1/forced vital capacity <0.7. There was a 2-week washout between crossover periods.

The primary objective was superiority of QVA149 versus placebo on the improvement in patient-reported levels of breathlessness during daily activities using the Self-Administered Computerized (SAC) version of the Baseline Dyspnea Index (BDI)/TDI after 6 weeks. The SAC version of the BDI/TDI was developed as a tool to provide direct patient-reported ratings of dyspnea and to provide a standard method to reduce the potential bias with an interviewer [Mahler DA et al. *COPD* 2004]. The secondary objective was superiority of QVA149 versus tiotropium on the same endpoint.

Other secondary objectives included evaluation for lung function by FEV_1 area under the curve from 0 to 4 hours ($AUC_{0–4h}$) and rescue medication use over 6 weeks.

After 6 weeks of treatment, QVA149 significantly improved patient self-reported shortness of breath during daily activities versus placebo (Δ=1.37; p<0.001) and versus tiotropium (Δ=0.49; p=0.021). Significantly more moderate COPD patients achieved ≥1 point TDI total score improvement on QVA149 (35.9%) versus placebo (18.1%; p<0.001) and tiotropium (24.4%; p=0.012). Subgroup analysis showed that the improvement in the SAC TDI with QVA149 was more pronounced in patients with severe COPD (Figure 1).

Figure 1. Subgroup Analysis by COPD Severity



COPD=chronic obstructive pulmonary disease; LS=least squares; NS=nonsignificant; SE=standard error; TDI=Transition Dyspnea Index.

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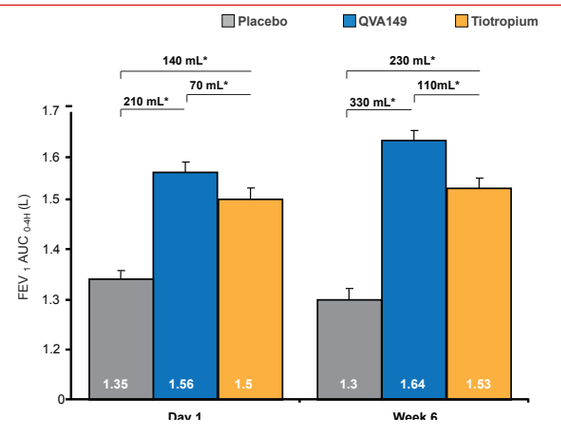
QVA149 produced significant and clinically meaningful improvements in FEV_1 $AUC_{0–4h}$ versus placebo and versus tiotropium on Day 1 and Week 6 (p<0.001 for both comparisons; Figure 2).

Figure 2. FEV_1 Area Under the Curve



$AUC_{0–4h}$=area under the curve from 0 to 4 hours; FEV_1=forced expiratory volume in 1 second; LS=least squares; SE=standard error.

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Rescue medication use over 6 weeks was significantly lower with QVA149 versus placebo (–1.43 puffs/day; p<0.001) and tiotropium (–0.45 puffs/day; p=0.002).

QVA149 was well tolerated. The most frequent adverse events (COPD, nasopharyngitis, cough, and dyspnea) occurred with similar frequency to that of placebo and tiotropium.

Results from BLAZE add to the evidence that improved lung function with once-daily QVA149 translates into greater relief of breathlessness and improved patient-reported outcomes, concluded Dr. Mahler.

CPAP in CVD and OSA Does Not Significantly Improve Cardiovascular Biomarkers

Written by **Emma Hitt, PhD**

Patients with cardiovascular disease (CVD) and moderate to severe obstructive sleep apnea (OSA) treated with continuous positive airway pressure (CPAP) and standard CV care demonstrated a small, nonsignificant decrease in fasting blood glucose and HbA1C levels, compared with patients that were randomized to standard care only. Emma Heeley, PhD, The George Institute, Sydney, Australia, presented data from a substudy within the Sleep Apnea Cardiovascular Endpoints Study [SAVE].

Evidence from observational studies suggests that there is an association between CVD and OSA [Loke YK et al. *Circ Cardiovasc Qual Outcomes* 2012]. OSA can lead to oxidative stress, sympathetic hyperactivity, and nocturnal episodic hypertension, causing endothelial dysfunction, hypertension, and altered glucose and lipid metabolism. These factors can lead to coronary artery or cerebrovascular disease and other CV events. The substudy (n=500) tested the hypothesis that 6 months of CPAP treatment would improve biomarkers of CVD risk, such as blood glucose, HbA1C, blood lipid level, C-reactive protein (CRP), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in patients with CVD and OSA, who were participating in the substudy of the SAVE trial.

SAVE is an ongoing, international, prospective, multi-center, open-label, randomized controlled trial. Patients with CVD and diagnosed with moderate to severe OSA (n=2500) received a 1-week sham CPAP treatment and were then randomized to receive standard CV care only, or CPAP treatment plus standard care. Patients received follow-up care at 1, 3, and 6 months thereafter. When the main trial completes in 2016 patients will have an average follow up of 4.5 years.

Prior to the study, patients were screened with overnight oximetry and nasal pressure tests. Patients were excluded from the study if they did not have CVD, or if they had an oxygen desaturation index (ODI) <12, an Epworth sleepiness scale score (ESS) >15, or Cheyne-Stokes respiration. Patients were also excluded if their average adherence to the 1-week CPAP sham was <3 hours per night.

The main SAVE trial has currently recruited 90% of the required sample size, the average adherence to treatment in the CPAP arm is currently about 4 hours/night at 6 and 36 months post randomization. The primary endpoint of the main SAVE study is a composite of CV events, including CV death, myocardial infarction, stroke, and hospitalization for CV-associated events. Secondary endpoints included revascularization procedures, types of CV events, blood pressure, new onset atrial fibrillation, new onset diabetes, daytime sleepiness, and quality of life. Dr. Heeley also presented data from the SAVE substudy, which evaluated CV biomarkers at 6 months.

Patients treated with CPAP experienced a small decrease in blood glucose levels and HbA1C from baseline, as compared with patients that received standard care alone. This effect was more pronounced in individuals with an average nightly CPAP adherence of ≥4 hours. In addition, patients treated with CPAP demonstrated a small decrease in total cholesterol and LDL cholesterol from baseline, as compared with the control arm. There was no apparent difference in CRP, or NT-proBNP levels in either study arm.

Dr. Heeley pointed out that in the intention-to-treat analysis of the substudy none of the changes in CV biomarkers at 6 months between the active and control groups were statistically significant; however, a regression analysis of the change in fasting blood glucose levels, showed a significant CPAP treatment effect with increasing severity of OSA in participants who used the therapy ≥4 hours/night. This finding suggests that CPAP treatment has, at best, only small effects on the traditional biochemical markers of CV risk in OSA, however multiple pathways may be involved in the genesis of CV events in OSA, and even small gains in traditional risk markers may be important and have an additive effect. The SAVE trial is still ongoing to determine if CPAP treatment may play a role in reducing heart attack and stroke in CVD patients.

CPAP Reduces BP in Patients With Resistant Hypertension and Obstructive Sleep Apnea

Written by **Phil Vinall**

In a randomized clinical trial conducted in Spain, blood pressure (BP) in patients with resistant hypertension (RH) and obstructive sleep apnea (OSA) was significantly and