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EDITORIAL

Effects of LAMA/LABA Alone and in Combination on Cardiac Safety

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Chronic obstructive pulmonary disease (COPD) is a multidimensional, progressive condition characterized by airflow obstruction, worsening dyspnea and respiratory failure.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report suggests that long-acting β_2-agonists (LABAs) or long-acting muscarinic antagonists (LAMAs) are the preferred initial pharmacologic therapy option in the majority of patients with COPD, with escalation to dual therapy as required.[1]

Extensive clinical data show that the LAMA tiotropium (SPIRIVA®; Boehringer Ingelheim Pharma GmbH, Ingelheim, Germany) delivered as a dry powder formulation by HandiHaler® (DPI; 18 µg nominal dose) or as an aqueous solution via the Respimat® Soft Mist™ inhaler (SMI; 5 µg nominal dose) can improve lung function, symptoms and outcomes, such as dyspnea and quality of life, and reduce exacerbations in patients with COPD.[2] Olodaterol (Striverdi®; Boehringer Ingelheim Pharma GmbH & Co K.G., Ingelheim, Germany) is a LABA that provides 24-hr bronchodilation, and has been shown to improve lung function and reduce symptoms in patients with COPD.[3] When given in a fixed-dose combination with tiotropium via the SMI (Spiolto®; Boehringer Ingelheim Pharma GmbH & Co K.G., Ingelheim, Germany), further improvements in lung function and health-related quality of life have been reported.[4]

Patients with COPD often have comorbidities that can impact disease management, including choice of treatment. The most serious and prevalent comorbidities are cardiovascular (CV) diseases,[5–8] which are known to be leading causes of hospitalization and death.[6,9] In a study by Fuhrman et al in patients for whom COPD was an associated cause of death, 32.0% of patients had an underlying CV disease, and 13.6% of the total population had ischemic heart disease.[6] As such, initial concerns were raised regarding the cardiac safety of LAMAs and LABAs, particularly among patients with CV comorbidities.[10,11] For LABAs, for example, there are theoretical concerns over increases in heart rate and blood pressure resulting from their interaction with β_2-adrenoceptors in the atria, ventricles and peripheral vasculature via the baroreflex mechanism.[12] However, since these concerns were raised, there have been many reassuring analyses from safety databases of LABA and LAMA.[13–17] For tiotropium and olodaterol, in particular, there is a large volume of published safety data on the long-term general and specific CV adverse events (AEs) of these agents. These data show that tiotropium and olodaterol given as monotherapy have similar, or lower, AE rates than placebo,[18,19] and in combination can be safely administered

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to patients with moderate-to-very-severe COPD, including patients with CV comorbidities.[20]

Since the early debate about the CV safety of LABAs and LAMAs, and the reassurance provided by extensive clinical and real-world experience with these agents, attention has focused on the wider implications of bronchodilation therapy on the CV system of individuals with COPD. In this context, real-time measurement of physiologic data such as heart rate, heart rhythm and blood pressure are of interest. Two papers investigating the cardiac safety of tiotropium and olodaterol treatment in COPD have previously been published.[21,22] The first investigated the long-term effects of tiotropium maintenance therapy on cardiac parameters using a combined analysis of Holter-ECG data from four randomized clinical trials.[21] This paper concluded that tiotropium maintenance therapy administered using the SMI (1.25–10 µg) or DPI (18 µg) once daily for up to 48 weeks was well tolerated, with no increased risk of supraventricular or ventricular arrhythmia in patients with COPD. The second paper investigated the effect of olodaterol (5 or 10 µg) and formoterol (12 µg) on heart rate and blood pressure in moderate-to-severe COPD, demonstrating that heart rate and blood pressure are not adversely affected following long-term administration.[22]

In the current series, we conducted detailed analyses of heart rate, 24-hr Holter electrocardiogram data and blood pressure from large clinical cohorts of patients with moderate-to-severe COPD receiving tiotropium and/or olodaterol as mono- or combination therapy.

In the first article, we report a post hoc analysis of the effects of dual bronchodilation with tiotropium/olodaterol 5/5 µg versus tiotropium 5 µg or olodaterol 5 µg on heart rate and blood pressure in patients included in the two large, 52-week TONADO® studies. This analysis included 3100 patients with moderate-to-very-severe COPD, and was the first study to comprehensively investigate heart rate and blood pressure in a large Phase III study of dual bronchodilation.[23]

In the second article, we report a sub-analysis of the extensive Holter ECG data from four 48-week, Phase III studies that assessed olodaterol 5 µg versus placebo to investigate whether olodaterol monotherapy increases the risk of cardiac arrhythmia in patients with COPD. Two of the studies also included formoterol (12 µg). Holter ECG records were evaluated for 24-hr mean heart rate as well as the number of supraventricular premature beats and ventricular premature beats.[24]

The final paper in this series reports the results of Holter ECG examinations from two large, long-term, controlled clinical COPD trials (TONADO® 1 and 2) to investigate whether tiotropium/olodaterol 5/5 µg increases the risk of cardiac arrhythmia compared with tiotropium 5 µg or olodaterol 5 µg. Holter ECG records from 506 patients were evaluated for 24-hr mean heart rate as well as the number of supraventricular premature beats and ventricular premature beats.[25]

Overall, this series of analyses showed that long-term administration of dual bronchodilation therapy was not associated with changes in heart rate or blood pressure and did not present any medically relevant effects on arrhythmias compared with monotherapies.[23,25] Additionally, treatment with olodaterol or formoterol was not associated with arrhythmias or persistent increases in heart rate in patients with COPD.[24] The conclusions from these extensive analyses of our clinical database support the findings of the previously published monotherapy evaluations.[21,22] We now have an extensive body of published evidence supporting the CV safety of tiotropium and olodaterol administered either alone or as a fixed-dose combination in patients with moderate-to-very-severe COPD.

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Disclosure

Professor Stefan Andreas reports personal fees from Boehringer Ingelheim and GlaxoSmithKline as part of advisory boards, and held presentations for AstraZeneca, Berlin Chemie, Chiesi, and Novartis, outside the submitted work. The author reports no other conflicts of interest in this work.

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