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LETTER TO THE EDITOR

Tiotropium safety in 'real-world' populations

Response to Schmiedl, *et al*. in the *British Journal of Clinical Pharmacology*

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We read with interest the publication of Schmiedl *et al*. [1] describing the characteristics of patients treated with tiotropium HandiHaler® or Respimat® in the Tiotropium Safety and Performance in Respimat (TIOSPIR®) study compared with their 'real-world' database [2]. The authors noted that patients starting either treatment had similar characteristics but suggest that we may have included a selected population with chronic obstructive pulmonary disease (COPD), who might react differently to treatment (and be at lower risk of cardiac adverse effects) than a 'real-world' population.

The baseline characteristics of the patients with COPD enrolled in placebo-controlled tiotropium studies using HandiHaler® or Respimat® were recently compared with those from a range of epidemiological studies. Patients included in tiotropium studies were found to be widely representative of the overall COPD population [3]. While 'real-world' observational studies may be useful in generating relevant clinical questions, randomized controlled trials, such as TIOSPIR®, use robust methodologies designed and powered to answer these.

As Schmiedl *et al*. [1] note, one of the main reasons for their 'real-world' patients not meeting the inclusion/exclusion criteria of TIOSPIR® was a diagnosis of asthma. Indeed, a concomitant diagnosis of asthma was an exclusion criterion in most studies of tiotropium in COPD. On the other hand, tiotropium was investigated in a large clinical programme of patients with asthma (including severe asthma, excluding COPD); a higher risk of adverse cardiac effects in these patients was not identified [4].

Another criterion for exclusion from TIOSPIR® was milder COPD [forced expiratory volume in 1 s (FEV_1) >70% predicted]. While Schmiedl *et al*. [1] were right to highlight differences in their 'real-world' population from those meeting more stringent criteria in clinical trials, there is no reason to believe that patients with milder disease would be at any additional specific risk for adverse cardiac effects with tiotropium treatment beyond the assessments performed in TIOSPIR®. On the contrary, as TIOSPIR® was a safety study, and therefore focused on patients with more severe respiratory disease, it would be expected that any safety signal would be more evident than in an overall 'real-world' population, which was not the case.

Owing to the specific exclusion criteria of tiotropium trials, some differences in characteristics compared with patients in clinical practice do remain. For example, TIOSPIR® [2] [and also the 4-year Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT®) trial of tiotropium HandiHaler®] [5] excluded patients with moderate-to-severe renal impairment. However, a pooled analysis of 22 blinded, placebo-controlled studies of tiotropium HandiHaler® and Respimat® in which baseline serum creatinine was collected did not indicate an increased risk for all-cause or cardiac mortality, or serious adverse events, in patients with COPD and existing mild-to-moderate renal impairment [3, 6–8].

Patients with recent severe cardiac events [myocardial infarction within ≤6 months, unstable/life-threatening arrhythmia requiring intervention or change in treatment, or hospitalization with severe (New York Heart Association class III/IV) cardiac failure within ≤1 year] were also excluded from tiotropium trials [9]. To investigate the safety of tiotropium in patients with a recent history of cardiac events, patients in UPLIFT® and TIOSPIR® were followed up for mortality and cardiac adverse events occurring after an initial on-treatment cardiac event, while continuing on therapy. Neither the results for tiotropium HandiHaler® *vs*. placebo (UPLIFT®) [10], nor for tiotropium Respimat® *vs*. HandiHaler® (TIOSPIR®) [11], indicated a specific risk for subsequent mortality or cardiac events in this high-risk group.

Another possible confounder could be the selection of patients with high tolerability for anticholinergic agents (i.e. pretreated with this class of drug). While this could explain the variation in results between TIOSPIR® and some epidemiological studies, the analysis of a large group of patients from TIOSPIR® who were anticholinergic-naïve at baseline did not indicate any differential effects *vs*. the total study population, or between the tiotropium HandiHaler® and Respimat® groups [12].

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To conclude, while it is true that certain groups of patients may be under-represented in individual studies of tiotropium, the very large clinical trial database [9] (including long-term studies of up to 4 years' duration) allows for comprehensive subgroup analyses of patients potentially at risk and, in our opinion, supports the safety of tiotropium in these patients.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work and no other relationships or activities that could appear to have influenced the submitted work. Outside of the submitted work and within the previous 3 years, RW received consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Mylan, Novartis, Pfizer, Pulmonx, Roche, Spiration, Sunovion, Teva and Theravance and grant support from Boehringer Ingelheim, GlaxoSmithKline and Pearl Therapeutics; AA received consulting fees, lecture fees and travel support from AstraZeneca, Boehringer Ingelheim, Forest Laboratories, GlaxoSmithKline and Novartis and grant support from GlaxoSmithKline; RD received personal fees for advisory board participation and lectures/educational activities from ALK-Abello, AstraZeneca, Boehringer Ingelheim, CIPLA, GlaxoSmithKline, Meda and Novartis; DD received consulting fees, lecture fees, and payment for the development of educational activities from Boehringer Ingelheim, Chiesi, Dey Pharma, Novartis, Nycomed and Pfizer; and PC received research grants from GlaxoSmithKline and Takeda, personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis and Takeda and nonfinancial support from Boehringer Ingelheim.

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