British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 564–565 564

LETTER TO THE EDITOR

Response to Wise *et al.* (Tiotropium safety in real life populations)

Correspondence Dr Sven Schmiedl, Philipp Klee-Institute for Clinical Pharmacology, HELIOS Clinic Wuppertal, Wuppertal, Germany. Tel.: +49 (0) 202 896 1854; Fax: +49 (0) 202 896 1852; E-mail: sven.schmiedl@helios-kliniken.de

Received 23 March 2016; **revised** 8 April 2016; **accepted** 9 April 2016

Sven Schmiedl[1,2], Petra Thürmann[1,2], Rainald Fischer[3], Dominik Rottenkolber[4,5] and Marietta Rottenkolber[6,7]

[1]Department of Clinical Pharmacology, School of Medicine, Faculty of Health, Witten/Herdecke University, Witten, [2]Philipp Klee-Institute for Clinical Pharmacology, HELIOS Clinic Wuppertal, Wuppertal, [3]Pneumologische Praxis Muenchen – Pasing, Munich, [4]Institute of Health Economics and Management, Ludwig-Maximilians-Universitaet Muenchen, Munich, [5]Helmholtz Zentrum Muenchen – German Research Center for Environmental Health, Member of the German Center for Lung Research, Neuherberg, [6]Institute for Medical Information Sciences, Biometry, and Epidemiology, Ludwig-Maximilians-Universitaet Muenchen, Munich and [7]Diabetes Research Group, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ludwig-Maximilians-Universität München, Munich, Germany

We appreciate the comments made by Wise *et al.* [1] regarding the limited generalizability of the Tiotropium Safety and Performance in Respimat (TIOSPIR) trial [2] found in our study [3]. As Wise *et al.* [1] pointed out, Miravitlles *et al.* [4] compared baseline characteristics and comorbidities of patients included in tiotropium treatment examining randomized controlled trials (RCTs) *vs.* observational studies including chronic obstructive pulmonary disease (COPD) patients (irrespective of treatment). Summing up these comparisons as only 'similar' is, at least to some extent, a simplification. For example, the pooled prevalence estimates for hypertension were 39.4% (n = 28 HandiHaler® trials) and 40.0% (n = 7 Respimat® trials), whereas for five large observational studies, prevalence estimates were between 40.1% and 60.6% [4]. Of course, comparing pooled and non-pooled prevalence results [4] should be interpreted with caution and methodological differences between observational studies should be taken into account.

We agree with Wise *et al.* [1] mentioning that there is no reason to believe that patients with milder COPD would be at any additional specific risk of adverse cardiac effects. However, one of our main concerns regarding the generalizability of the TIOSPIR trial [2] was the exclusion of patients on account of relevant comorbidities, which might be more relevant in elderly, multimorbid patients suffering from severe COPD [3]. By excluding those patients, safety signals might have been overlooked to a relevant extent. Verhamme *et al.* [5] found a 27% increased risk of deaths among patients using Respimat® compared with HandiHaler®. Interestingly, no significant association was found for patients with normal renal function, whereas for patients with GFR <60 ml min^{-1} 1.73 m^{-2} BSA, the use of Respimat® was associated with increased mortality (aHR=1.52, 95% CI 1.02, 2.28) [6]. In contrast, no clear trend was found when comparing (S)AE incidence rate ratios of placebo-controlled studies examining HandiHaler® or Respimat® in patients with normal renal function, mild or moderate renal impairment [7]. For severe renal impairment, results were limited because of the low number of patients. However, only renal function at baseline was taken into account but a time-dependent analysis might be more appropriate.

Regarding cardiovascular risk factors, Loke *et al.* found, in a *post hoc* analysis of the TIOSPIR trial [8], an increased risk of myocardial infarctions comparing Respimat® (combined analysis of the two treatment groups) with HandiHaler® users. Recently, some data were published regarding cardiac adverse events occurring after an initial on-treatment cardiac event in the UPLIFT trial and the TIOSPIR trial [9, 10]. Wise *et al.* [1] mentioned that no increase in risk was found for subsequent mortality or cardiac events in patients receiving tiotropium *vs.* placebo (UPLIFT [9]) or tiotropium Respimat® *vs.* tiotropium HandiHaler® (TIOSPIR [10]). We agree that these data are relevant but, unfortunately, they do not fully cover our concerns. Underlining the assumption that initiating an antimuscarinic treatment might be the period with the highest risk of developing (S)AEs [11], Lee *et al.* [12] found an increased risk of tachyarrhythmias in patients starting a long acting β_2-adrenoceptor agonist (LABA) or antimuscarinic (LAMA) treatment. On the other hand, in a *post hoc* analysis of the TIOSPIR trial, no differential effects of anticholinergic-naïve patients at baseline *vs.* the total study population were reported [13]. However, excluding high risk patients due to major cardiovascular events, as conducted in the TIOPSPIR trial [2], limits the generalizability of these results too.

Antimuscarinic and β_2-adrenergic co-medication is of particular interest with regard to cardiovascular side effects.

DOI:10.1111/bcp.12970

In the protocol of the TIOSPIR trial [2], the concurrent use of short acting muscarinic antagonists was not explicitly stated as an exclusion criterion (and, henceforth, was not included in our generalizability analysis). However, the intake of antimuscarinic compounds was 'not allowed during the randomization period' [2]. Taking into account the cumulative anticholinergic drug burden, not allowing ipratropium intake may have decreased the risk of cardiovascular (and other) side effects, and it should be taken into account that ipratropium intake was present in approximately 5% of our 'real life' population [3]. With regard to β_2-adrenergic co-medication (which is frequently prescribed to asthma patients), there is some evidence showing a trend towards an increased risk of cardiovascular and cerebrovascular side effects from a combination of LABA and LAMA compared with LABA or LAMA alone [14], but the data are conflicting [11].

We totally agree that 'real world' observational studies are useful to generate questions, whereas RCTs are necessary to answer these questions [1]. However, there are far too many possible combinations of comorbidities and co-medications to be answered by RCTs, underlining the need for well-conducted observational studies. According to the evidence currently available, tiotropium Respimat® seems to have an overall safety profile comparable with tiotropium HandiHaler®, whereas an increased risk of cardiovascular (S)AEs in certain vulnerable patients receiving tiotropium Respimat® cannot be excluded [5, 11].

Competing Interests

All authors have completed the Unified Competing Interest form at ww.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. SS reports personal fees from Rottapharm Madaus (Cologne, Germany) and travel costs for an investigator meeting were reimbursed by Bayer HealthCare AG (Leverkusen, Germany) outside the submitted work. PT reports personal fees from Rottapharm Madaus (Cologne, Germany) outside the submitted work.

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