CORRESPONDENCE

Thorax editorial by Jenkins and Beasley related to tiotropium respimat

We thank Drs Jenkins and Beasley for their comments in the recent editorial regarding tiotropium (SPIRIVA)[1]. Preceding the Singh *et al*[2] analysis cited by the authors, Boehringer Ingelheim (BI) had analysed both the tiotropium HandiHaler and Respimat pooled datasets using patient-level data on-treatment as well as including vital status. The results showed a nominally statistically significant reduction for tiotropium HandiHaler and a numerical increase with tiotropium Respimat compared with the respective placebo group for all-cause mortality.

These results are adequately reflected in the local SPIRIVA product information (http://www.medicines.org.uk/EMC/search results.aspx?term=spiriva&searchtype=QuickSearch).

Recently published analyses on tiotropium Respimat data (including the analyses of Dong *et al*[3]) were conducted on the same set of clinical data; therefore, they cannot be considered independent evidence, and are all limited by not using patient-level data.

The tiotropium Respimat dose (5 μg once daily) was chosen to match the efficacy and safety of the well-established tiotropium HandiHaler 18 μg. Three pharmacokinetics (PK) studies compared the PK of tiotropium after inhalation from both devices. One study[4] found 22% and 35% higher exposures (area under the curve from 0 to 6 h (AUC_{0-6}) and maximum plasma concentration (C_{max})) for Respimat 5 μg versus HandiHaler 18 μg. A second study[5] in Japanese patients showed virtually identical plasma levels. A newly available third study,[6] with optimised procedures for PK analysis, reported 24% and 19% lower exposures (AUC_{0-6} and C_{max}) for tiotropium Respimat 5 μg versus tiotropium HandiHaler 18 μg. This study also demonstrated similar PK variability for the two tiotropium formulations. Therefore, available data suggest similar systemic exposure for both devices and any apparent difference between formulations remains unexplained and implausible. In order to confirm the hypothesis of no difference between matching formulations, BI is conducting the TIOSPIR study in over 17 000 patients comparing once-daily tiotropium Respimat 5 μg and tiotropium HandiHaler 18 μg with all-cause mortality and COPD exacerbations as co-primary endpoints. A further arm with tiotropium Respimat 2.5 μg is included in order to inform dose selection for future combination products. The study is supervised by an independent Data Safety Monitoring Board (DSMB) with access to fully unblinded data. The DSMB evaluates the most current database every 4 months and has, up to now, recommended to 'continue as planned'. The study is approaching finalisation in 2013 and has exceeded three-quarters of the number of events used in the power calculation for the primary analysis.

Finally, the patients enrolled in the tiotropium trial programme had a comorbidity profile comparable with the general COPD population (see online supplement).

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