Effect of daily azithromycin therapy and adherence on readmission risk in COPD

To the Editor:

Patients with chronic obstructive pulmonary disease (COPD) frequently experience unplanned hospital readmissions leading to increased morbidity [1]. The European COPD Audit found that 35% of patients admitted with acute exacerbation of COPD (AECOPD) were readmitted within 90 days [2]. In the USA, 22% of patients admitted with AECOPD experienced a 30-day readmission, motivating financial policies to incentivise readmission reduction [1]. Interventions to decrease the risk of readmissions have had mixed results [3]. In a previously published, double-blinded, placebo-controlled, randomised clinical trial (MACRO), azithromycin taken daily for 1 year reduced the risk of COPD exacerbations [4]. We hypothesised that patients taking long-term azithromycin in the MACRO study who experienced an index hospitalisation for an AECOPD would have a decreased risk of readmission when compared to the placebo arm.

Patients (n=1142) in the MACRO study had a clinical diagnosis of COPD and were randomised to receive 250 mg daily azithromycin or placebo for 1 year [4]. In this analysis, we focused on a subgroup who experienced an AECOPD hospitalisation after randomisation and survived their index hospitalisation; the outcome of interest was all-cause, unplanned readmission. Hospitalisation due to AECOPD was determined by the presence of at least two of the following symptoms: cough, shortness of breath, chest tightness, wheeze or increased sputum production and ⩾3 days of treatment with an antibiotic or steroid. To account for variable drug exposure, we calculated patient adherence to the assigned drug. This consisted of counting the number of pills taken during the study divided by the number of days within the follow up period [5]. Patient characteristics in the azithromycin *versus* placebo group were compared using Student's t-test for continuous variables and the χ^2-test for categorical variables. The association of azithromycin use and time to readmission was examined using a Cox proportional hazards regression models. The endpoint for the proportional hazards model was time to readmission after discharge from the index hospitalisation or in cases where there was no readmission, the data were censored at the end of the follow-up period.

Hospitalisations due to AECOPD occurred in 233 patients; 214 patients (116 in the placebo arm and 98 in the azithromycin arm) had time to readmission data and were included in our analysis. The average time to index hospitalisation in the placebo group was 158±105 days and 157±110 days in the azithromycin group; the p-value for the difference was 0.966. Patients in the placebo group and azithromycin group were generally well matched with regards to age, sex, post-bronchodilator forced expiratory volume in 1 s (FEV_1) % of predicted, smoking history, bronchodilator use and number of hospitalisations in the year prior to randomisation. Comorbid congestive heart failure was present in 16% (19 out of 116) patients in the placebo group *versus* 7% (seven out of 98) in the azithromycin group (p=0.04).

Readmissions occurred in 90 (42%) out of 214 patients, 35 (36%) out of 98 in the azithromycin arm and 55 (47%) out of 116 in the placebo arm. Respiratory-related readmissions occurred in 70 (77%) out of 90 patients. Our proportional hazards regression model (figure 1) demonstrates that patients receiving azithromycin did not have a significant increase in time to all-cause readmission (hazard ratio (HR) 0.70, p=0.10). Similarly, respiratory related readmission were nonsignificantly decreased in patients randomised to azithromycin (HR 0.70, p=0.14). Two patients were excluded from this analysis as respiratory-related

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Patients with COPD who were randomised to azithromycin did not experience prolonged time to hospital readmission. There was a trend toward decreased risk of readmission when adjusted for total exposure to azithromycin. http://ow.ly/NAzI30nb651

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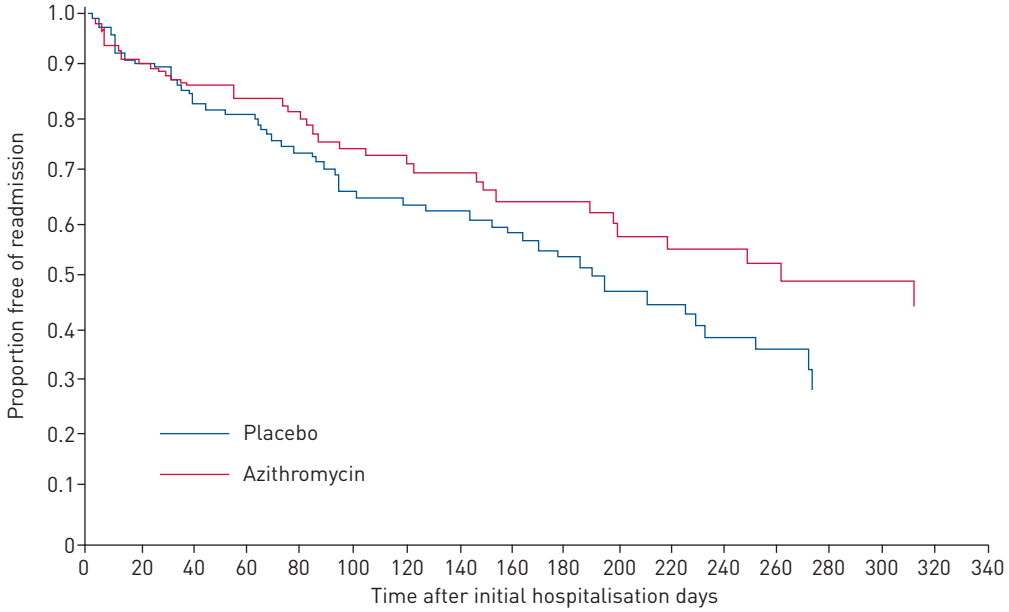

FIGURE 1 Time to readmission in the placebo arm *versus* the azithromycin arm using a Cox proportional hazards model. Patients who were randomised to azithromycin experienced a statistically nonsignificant increase in time to readmission (hazard ratio 0.70, p=0.10).

admission could not be determined from discharge summary review. We examined the association between intensity of exposure to azithromycin, with placebo patients having zero exposure intensity. Increased exposure to azithromycin was associated with a prolonged time to readmission (HR 0.82, p=0.038).

In a multivariate analysis, increased exposure to azithromycin (patients assigned to placebo had zero exposure intensity) was associated with a nonsignificant decrease in risk of readmission (HR 0.85, 95% CI 0.70–1.03; p=0.09). Female sex (HR 0.76, 95% CI 0.48–1.21; p=0.25), older age (HR 1.02, 95% CI 0.99–1.05; p=0.15), active smoking (HR 1.05, 95% CI 0.61–1.81; p=0.87), higher post bronchodilator FEV_1 % of predicted (HR 1.0, 95% CI 0.99–1.01; p=0.9) and history of congestive heart failure (HR 1.76, 95% CI 0.98–3.17; p=0.06) were not associated with risk of readmission. Previous hospitalisation in the past year, however, was associated with increased risk of readmission in our multivariate model (HR 1.81, 95% CI 1.06–3.09; p=0.03).

Two additional unadjusted Cox proportional hazards models examined whether increased adherence to the assigned drug, either azithromycin or placebo, was associated with better outcomes. In a univariate analysis restricted to the azithromycin group, time to readmission was nonsignificantly increased among patients with increased adherence (HR 0.45, p=0.16). When restricted to the placebo group, patients with increased adherence to placebo also experienced increased time to readmission (HR 0.41, p=0.039). We studied time to readmission in a single model adjusted for overall adherence as a behavioural indicator. In this model, randomisation to azithromycin demonstrated a trend to increased time to readmission (HR 0.66, p=0.05), with more adherent patients experiencing decreased readmission risk (HR 0.43, p=0.01).

To our knowledge, this is one of only a few studies designed to examine the effect of a pharmacological intervention on COPD readmissions. A systematic review examining five randomised clinical trials utilising nonpharmacological interventions demonstrated varied effects on readmission [6]. In our study, randomisation to azithromycin did not lead to a significant increase in time to readmission. However, increased exposure to azithromycin was associated with a trend to prolonged time to readmission, though this needs to be further explored in a larger sample.

We found that increased adherence to prescribed drug, either azithromycin or placebo, was also associated with increased time to readmission. This is consistent with a growing body of literature demonstrating that adherence to treatment is an important predictor of positive outcomes, regardless of whether the treatment is an active therapy or placebo. One possible explanation is the healthy adherer effect, which suggests that adherence is an indicator of overall healthy behaviour and therefore associated with improved outcomes in randomised trials [7, 8]. This has not been well explored in the COPD literature.

Limitations to our study include its *post hoc*, retrospective design and the possibility of Type II error. With only 214 patients included, there would need to be a substantial reduction in readmission rates to be able to detect an azithromycin effect in the subgroup of patients hospitalised for AECOPD. Our study may have underestimated the effect of azithromycin on readmission. Patients were already taking azithromycin when they experienced their index admission and therefore may be nonresponders to the medication for unknown reasons, resulting in a similar readmission rate as individuals taking placebo. Future studies should randomise patients to azithromycin after index hospitalisation to better estimate true effect on readmission rates.

In addition, we relied on pill pack counts to determine adherence, which do not always correlate with actual drug usage [9]. Finally, though patients in the placebo arm were not placed on long-term azithromycin therapy, some were likely prescribed infrequent short courses, which could have biased the results. The possibility of a protective effect of azithromycin in preventing COPD readmissions should be further explored in a larger sample that would decrease the possibility of Type II error. If shown to be effective in prolonging time to readmission, a targeted approach for azithromycin therapy could be developed in patients post-discharge. Future clinical trials in COPD should also consider the overall effect of adherence to medication on positive outcomes.

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