Should we give long-term macrolide therapy for COPD?

We would like to take this opportunity to respond to the invitation from the editors of *Thorax* to engage in a debate over the current place of macrolide therapy in patients with chronic obstructive pulmonary disease (COPD). We believe that the optimism imparted by Albert *et al*[1] may hide harmful effects that outweigh the currently perceived benefits. In this placebo-controlled, parallel group (but not double-blind) randomised trial, one-quarter of screened patients were excluded from study entry. The main reason for exclusion was the presence of 'cardiac issues' related to the known potential of macrolides to prolong the electrocardiographic QT interval and, thus, the propensity for the development of the potentially malignant arrhythmia 'Torsades de Pointes'; an effect that could be further potentiated by the many other QT interval-prolonging drugs commonly taken by older patients. The study reassuringly found no significant difference in mortality between the two study groups. However, mortality was not the study's primary endpoint, and a mortality difference that could be significant at a population level may not have been detected. In a recent retrospective cohort study, an excess of deaths in those treated with azithromycin was noted, albeit mainly in those with cardiovascular disease.[2]

Macrolides are recommended by all international guidelines for the treatment of community-acquired pneumonia, especially in the management of severe disease, and are consistently associated with reduced mortality.[3] Azithromycin is a very potent inducer of antimicrobial resistance[4]—a topic recently highlighted by the UK chief medical officer as posing a major threat. In the study by Albert *et al*,[1] the incidence of macrolide resistance, as measured in nasopharyngeal flora, was significantly higher in those treated with azithromycin (81% vs 41%). The impact of widespread use of macrolides to prevent COPD exacerbations on the wider community bacterial flora is hard to quantify. There has to be concern that more widespread use of azithromycin in the context of COPD could increase pneumonia mortality through the promotion of bacterial macrolide resistance. So while the potential for exacerbation frequency reduction is tantalising, there is a potential and currently unquantifiable risk of increased respiratory mortality from more widespread use of low-dose macrolides. We agree with Vestbo and Rodriguez-Roisin[5] that the time is not yet right, and that until such risk is more robustly quantified, low-dose macrolides for exacerbation prevention, should not be recommended in the management of COPD.

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