



Early View

Research letter

The Potential Impact of Azithromycin in Idiopathic Pulmonary Fibrosis

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Title: The Potential Impact of Azithromycin in Idiopathic Pulmonary Fibrosis

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To the Editor.

There is growing evidence of the role of infection in the pathogenesis and progression of idiopathic pulmonary fibrosis (IPF)¹⁻⁴. Over a third of patients with IPF will be hospitalised, at least once, during the course of their disease⁵. These events not only carry a significant morbidity and mortality, but also a health care cost and burden⁶. Indeed, there is a growing recognition of these events as a potential marker for disease progression, reflected in the growing consensus to include such events as outcomes in future clinical trials⁷. Therefore, treatments that reduce the risk of hospitalization could have a major impact. While recent evidence suggests that macrolide antibiotics may improve survival in acute exacerbations of IPF⁸, to date there has been no study examining the potential role of prophylactic macrolides on reducing these emergency admissions or disease progression. This retrospective, observational study aimed to evaluate the impact of long-term azithromycin treatment in reducing hospitalization rates in IPF patients.

We retrospectively identified all IPF patients receiving a prophylactic prescription of azithromycin 250 mg three times a week (Monday, Wednesday and Friday) between 2013 and 2016. The primary end point was reduction in hospitalizations, with secondary endpoints use of rescue antibiotics, tolerability and side effects profiles. Prophylactic azithromycin was instigated by the treating clinician when patients reported 3 or more lower respiratory tract infections (or courses of antibiotics) in the preceding 12 months. The number of all-cause non-elective hospitalization events and prescribed antibiotic courses were recorded for a period of 12 months before and after the commencement of therapy. A diagnosis of IPF was made following multidisciplinary discussion according to current international guidelines⁹. Patients with extensive radiological emphysema, an immunodeficiency, those receiving immunosuppressive therapy or using other prophylactic antibiotics were excluded. Approval for this study was obtained from the Institutional Ethics Committee of the Royal Brompton Hospital. Continuous variables were assessed for normality and are presented as means (\pm Standard Deviation [SD]), and categorical variables as proportions. Pulmonary function trends are expressed as percentage change from start of therapy, and changes were analysed using a paired T-Test or Wilcoxon signed-rank test.

One hundred and twenty-six patients with IPF receiving prophylactic azithromycin were identified. Thirteen patients on concomitant immunosuppressive therapy and 5 receiving other prophylactic antibiotics were excluded. The remaining 108 IPF subjects had a mean age of 68.3 ± 10.9 years, were predominantly male (61%) with moderately severe disease (DLco $33.2 \pm 13.8\%$ predicted; FVC $70.0 \pm 20\%$ predicted) (Table 1). The median survival in the cohort was 29 months.

The majority of IPF patients tolerated azithromycin (93%) while only 8 discontinued therapy due to side effects (tinnitus ($n=1$) and gastrointestinal intolerance ($n=7$)) in the first 12 months. One patient stopped following lung transplant and 4 had therapy discontinued at the discretion of the prescribing clinician who felt there had been no subjective improvement (although these individuals were not excluded from the analysis). The cohort of patients on azithromycin tended to be younger (OR -0.96, $P=0.006$) and have a lower DLco (OR -0.91, $P=0.01$) when compared to patients with IPF not prescribed prophylactic antibiotics. The strongest predictor, however, was previous number of antibiotics prescriptions (OR 3.2, $P=1.77e-06$).

In the pre-treatment twelve month period a total of 31 hospital admissions (0.29 ± 0.62 per patient years) and 176 courses of antibiotics (1.65 ± 1.70 per patient years) were recorded. In the same cohort a year after commencing prophylactic azithromycin, there were only 7 hospital admissions (0.08 ± 0.3 per patient years) and 40 therapeutic antibiotic courses prescribed (0.44 ± 0.8 per patient years) (Fig 1). This conferred a relative risk reduction in all cause non-elective hospitalisation rates of 0.72 (0.67-0.88; $P<0.001$). The mortality in the 12 months following instigation of therapy was 16% (18/108). Ten patients died on a palliative pathway. A sensitivity analysis was performed reclassifying these deaths as either an admission or antibiotic course. This did not alter the relationship between azithromycin use and outcome. In the 12 months prior to azithromycin prophylaxis treatment there was a median decline in FVC of -4.6% (-11.6 to 0.2%) and DLco of -7.4% (-13.0 to 4.1%). The introduction of therapy did not have any significant impact on rate of decline in lung function, with a median decline in FVC of -2.5% (-13.2 to 4.4%) and DLco of -8.4% (-18.75 to 5.5%) in the following 12 months on therapy.

This study is the first to report that prophylactic antibiotics may be of benefit in reducing the burden of non-planned hospitalisations in patients with IPF. Whether these events act as a surrogate for acute exacerbations of IPF or are clinically important in their own right remains unclear. However, they appear fundamentally important to the natural history of IPF from the perspective of morbidity and mortality^{7,10}. The introduction of prophylactic antibiotics was well tolerated, associated with minimal side effects and reduced the unplanned hospitalisation rate by over two thirds in this cohort. This reduction in admissions was achieved without impacting upon other well established markers of disease progression including lung function. Whilst it is tempting to conclude that it is the antibacterial properties of azithromycin conferring this benefit, rather than the anti-inflammatory activity shown to be beneficial in animal models of lung fibrosis, this study does not allow us to definitively draw such conclusions.

Due to the retrospective nature of this work we could not accurately sub classify the cause of admissions (respiratory vs non respiratory) and therefore these events were left undifferentiated. The rates of all cause non-elective admissions across the CAPACITY and ASCEND trials was 18%^{10,11}. This is slightly lower than the rate observed in our cohort, which will have been enriched for those individuals prone to recurrent infections and therefore having higher numbers of admissions and antibiotic courses in the preceding year. These findings may not be generalizable to the IPF population as a whole, and could reflect regression towards the mean. However, in patients with IPF prescribed multiple courses of antibiotics in the preceding 12 months this therapy was well tolerated and had a potentially clinically significant impact. Extensive microbiological data is not available and therefore not reported, however, any prospective studies must include robust microbiological sampling and analysis. The retrospective nature also means that some antibiotic courses will not have been captured and explains the discrepancy in patient reported and objective evidence of prescribed courses of antibiotics or lower respiratory tract infections.

This study clearly demonstrates that prophylactic azithromycin is a safe and well tolerated therapy in individuals with IPF. In patients whose disease course is punctuated with multiple infective episodes prophylactic antibiotic therapy may provide a beneficial effect with a decrease in both hospital admissions and rescue antibiotic usage. Prospective randomised

placebo controlled studies are needed to support and confirm our findings, while further mechanistic work is needed to delineate the exact pathways by which macrolides confer this benefit.

1. Molyneaux, P. L. *et al.* The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **190**, 906–913 (2014).
2. Han, M. L. K. *et al.* Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. *Lancet. Respir. Med.* **2**, 548–556 (2014).
3. Molyneaux, P. L. *et al.* Changes in the respiratory microbiome during acute exacerbations of idiopathic pulmonary fibrosis. *Respir. Res.* **18**, 29 (2017).
4. Molyneaux, P. L. *et al.* Host–Microbial Interactions in Idiopathic Pulmonary Fibrosis. *Am. J. Respir. Crit. Care Med.* **195**, 1640–1650 (2017).
5. Yu, Y. F. *et al.* Patterns and Economic Burden of Hospitalizations and Exacerbations Among Patients Diagnosed with Idiopathic Pulmonary Fibrosis. *J. Manag. Care Spec. Pharm.* **22**, 414–423 (2016).
6. Raimundo, K. *et al.* Clinical and economic burden of idiopathic pulmonary fibrosis: a retrospective cohort study. *BMC Pulm. Med.* **16**, 2 (2016).
7. Ley, B. Clarity on endpoints for clinical trials in idiopathic pulmonary fibrosis. *Ann. Am. Thorac. Soc.* **14**, 1383–1384 (2017).
8. Kawamura, K., Ichikado, K., Yasuda, Y., Anan, K. & Suga, M. Azithromycin for idiopathic acute exacerbation of idiopathic pulmonary fibrosis: a retrospective single-center study. *BMC Pulm. Med.* **17**, 94 (2017).
9. Raghu, G. *et al.* An official ATS/ERS/JRS/ALAT clinical practice guideline: Treatment of idiopathic pulmonary fibrosis: An update of the 2011 clinical practice guideline. *Am. J. Respir. Crit. Care Med.* **192**, e3–e19 (2015).
10. Ley, B. *et al.* Pirfenidone reduces respiratory-related hospitalizations in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **196**, 756–761 (2017).
11. King, T. E. *et al.* All-cause mortality rate in patients with idiopathic pulmonary fibrosis: Implications for the design and execution of clinical trials. *Am. J. Respir. Crit. Care Med.* **189**, 825–831 (2014).

Table 1: Characteristics of the IPF subjects. Data are mean \pm Standard Deviation. DLCO, carbon monoxide diffusion capacity; FVC, forced vital capacity.

	IPF (N=108)
Age (yr)	68.3 (\pm 10.9)
Male Sex - number (%)	66 (61%)
FVC - %	70.0 (\pm 20)
DLCO - %	33.2 (\pm 13.8)

Figure 1: Comparison of courses of antibiotics and hospital admissions before (black) and after (grey) the use of Azithromycin per patient years

