

### Author's response: co-trimoxazole treatment in idiopathic pulmonary fibrosis

We thank Neto *et al*<sup>1</sup> for their comments on our paper<sup>2</sup> and for reiterating the points contained within it. 'The survival benefit conferred by co-trimoxazole, if real, could be due to its antimicrobial activity as there was a significant reduction in the number of infections in the group receiving active treatment', and this is likely to occur more frequently in patients receiving immunosuppressive treatment. The proportion of deaths in the intention-to-treat group on immunosuppression was 29 of 37. As stated, 'this study was not designed to collect microbiological information' however, the results were adjusted for baseline azathioprine or mycophenylate use, and a subgroup analysis of deaths by immunosuppression treatment at baseline in the per-protocol population was undertaken which could not detect a subgroup effect. Analyses from the intention-to-treat and per-protocol (PP) populations were prespecified, and reporting was appropriate.

As discussed, the results could be 'due to increased mortality in those withdrawing from the drug because of side effects, or

the higher withdrawal rate in the active group could be a marker of the disease severity. However, the reduction in mortality was not due to a disproportionate withdrawal of patients in the treatment arm immediately prior to death, as only four patients (two from each group) withdrew from the study within 1 month of death.' It would be inappropriate to present the results of the demographic details from the PP population, given the desire not to put emphasis on this type of analysis.

Likewise, the issue regarding patients' diagnosis has been discussed. The study commenced prior to current diagnostic criteria, however, a sensitivity analysis was undertaken of patients with probable or definite usual interstitial pneumonia (UIP) defined as 'honeycombing on the high resolution CT scan, a histopathological diagnosis of UIP or predicted to have a histopathological diagnosis of UIP' according to the criteria of Fell *et al*,<sup>3</sup> the results of which were similar to the full analysis.

There is a paucity of clinical trials evaluating prophylactic antibiotics in patients with interstitial lung disease, although Enomoto *et al*<sup>4</sup> showed a benefit with co-trimoxazole prophylaxis against *Pneumocystis jiroveci* pneumonia in patients with interstitial pneumonia receiving high-dose glucocorticoid therapy. From our study, the odds ratio of having an infection, corrected for azathioprine usage, was 2.17 for patients with more than 10 mg/day prednisolone, compared with those not receiving prednisolone in the control group, and 2.14 in the intervention group. The rate ratio was similar to that found by Greenberg *et al*<sup>5</sup> (1.30) with reduced rates of infection in the intervention group (70% vs 42%). Interestingly, there were high rates of infection in the control group of patients with idiopathic interstitial pneumonia even in those not receiving prednisolone (62%).

As stated clearly in the manuscript, the study did not detect a beneficial effect in terms of the primary endpoint. However, we believe that the magnitude of effect on survival in the PP analyses means that treatment with co-trimoxazole in patients with idiopathic pulmonary fibrosis warrants further investigation.

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