

## Idiopathic pulmonary fibrosis or not: antibiotic prophylaxis for all patients on immunosuppressants

Shulgina *et al*<sup>1</sup> reported the effects of co-trimoxazole on outcomes in fibrotic idiopathic interstitial pneumonia (IIP). We have some concerns about their conclusions and the emphasis of their findings.

With nearly half (43%) of subjects taking  $\geq 10$  mg of prednisolone daily, a dose that increases infection risk,<sup>2</sup> and over 30% taking a steroid-sparing agent, a valid alternate explanation for their results is that the beneficial effects of co-trimoxazole were due to prevention of adverse effects of immunosuppressive drugs. The occurrence of fewer pneumonias in the treated group

supports this alternate hypothesis, as does the observation that the main driver of the between-groups mortality difference in the so-called per protocol analysis was the large proportion of deaths (12 of 17) among subjects in the placebo group on immunosuppression. It would be helpful to see a similar between-groups breakdown in the intention to treat (ITT) analysis. The authors state infection was not the cause of death based on the slow rate of progression, but they fail to mention how infection was excluded as a contributing factor.

The authors do admit the more rigorous intention to treat analysis did not yield positive outcomes, but we believe they overemphasise the per protocol analyses in the abstract and discussion. Unappreciated covariates besides co-trimoxazole could explain the per protocol results. For example, it is possible that those individuals who were deteriorating most rapidly were the ones who stopped co-trimoxazole, thus eliminating them from a per protocol analysis. It would be helpful if the authors could provide information similar to table 1 for the per-protocol population.

Another issue is the facility with which the authors translate the results from a mixed population of IIP patients to idiopathic pulmonary fibrosis (IPF). With only 44% of the 'IPF' subjects having definite usual interstitial pneumonia by radiological/pathological criteria, more than half had an uncertain diagnosis based on current guidelines.<sup>3</sup> Furthermore, the time from diagnosis to randomisation was longer than most major IPF trials, suggesting we may be dealing with a population other than IPF.

In summary, we are concerned about the high likelihood of substantial bias introduced by the method of analysis and by the authors' failure to reject the alternate hypothesis that the beneficial effects of co-trimoxazole were due to prevention of acute or indolent infections. If nothing else, their data remind us that, as is standard practice for other patients taking similar medications, IIP patients on immunosuppressive drugs should be prescribed antibiotic prophylaxis.

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