Co-trimoxazole for idiopathic pulmonary fibrosis: time for TIPAC-2?

Helen Mujakperuo, Emmet E McGrath, David R Thickett

Idiopathic pulmonary fibrosis (IPF) is a devastating disease with an average life expectancy from diagnosis of 2.5 years with 5 year survival of between 20% and 40%. Currently there are no therapies proven to reduce mortality and only one drug, pirfenidone, is licensed for use in Europe that may slow the progression of the disease. Cleary developing effective therapy for IPF is a major unmet health need.

Shulgina *et al* present the results of TIPAC- a randomised placebo controlled trial of co-trimoxazole in patients with fibrotic interstitial lung disease.[1] This was a National Institute for Health Research, Research for Patient Benefit funded trial, and is to our knowledge the largest investigator led, non-commercially funded placebo controlled drug trial in IPF ever to have been undertaken in the UK.

The headline results of this paper are that co-trimoxazole treatment has no effect on pulmonary function or 6 min walk distance in patients with fibrotic idiopathic interstitial pneumonia (the vast majority of whom had IPF) but given adequate adherence to the medication may lead to a significant reduction in all-cause mortality associated with reduction in frequency of respiratory tract infections and improved overall health-related quality of life.[1]

The background to the use of co-trimoxazole in IPF started with work from Varney *et al*.[2] In 1996, Dr Varney noticed clinical improvement in a patient with oral co-trimoxazole. Subsequently, 14 patients with end stage fibrotic lung disease also responded clinically to oral co-trimoxazole. This prompted a double blind randomised placebo controlled pilot study in patients with advanced stages of idiopathic interstitial pneumonias with biopsy proven advanced fibrotic lung disease (usual interstitial pneumonia and non- specific interstitial pneumonia) to objectively measure benefit. Varney reported in this small pilot study that co-trimoxazole improved exercise capacity, breathlessness and symptom scores in the actively treated group.[2] Although the mechanism whereby co-trimoxazole achieved this was not clear from this study it may have related to altered expression of vascular endothelial growth factor which has been subsequently related to both disease severity, progression and outcome in IPF.[3 4]

In contrast to Varney's study, TIPAC saw no benefits of co-trimoxazole on the traditional markers of efficacy used in clinical trials in IPF- namely change in forced vital capacity, Medical Research Council dyspnoea score, and 6 min walk difference. Analysis of the other endpoints found significant differences in the symptom domain of the St George's respiratory questionnaire and the percentage of patients requiring an increase in oxygen therapy in favour of co-trimoxazole treatment. In the intention to treat analysis of TIPAC there was no effect of co-trimoxazole on mortality.

A problem encountered by the TIPAC investigators was that nearly one third of patients receiving co-trimoxazole withdrew due to side effects which were mostly rash and nausea. This was not a problem in the Varney study. In the per protocol analysis of patients adhering to the treatment, co-trimoxazole appeared to improve survival as there was a 5-fold reduction in mortality in those patients adhering to treatment. An astounding treatment effect if it is true.

What lessons therefore can we learn from TIPAC? First, it would appear that bacterial infection may play a greater role in IPF that previously thought. There is evidence that the innate immune response is impaired in patients with IPF with reduced functional capacity of their macrophages to kill bacteria.[5] This may explain why 36% of IPF patients grow bacteria in bronchoalveolar lavage fluid in the absence of clear signs of infection even before immunosuppression.[6] A specific role for co-trimoxazole is also suggested by a high prevalence of *Pneumocytes jirovecii* colonisation (23.3%) among patients with IPF and collagen vascular disease.[7] The importance of infection is outlined by the findings in TIPAC that 11/35 deaths were a result of pneumonia during the study. Patients receiving immunosuppressive treatment at entry into the study were more likely to die if they were in the control group (immunosuppression 12/35, no immunosuppression 2/30, p=0.015). These results confirm recent findings from the PANTHER study which demonstrated increased mortality in patients randomised to prednisolone, azathioprine and N-acetylcysteine due to infection compared with placebo.[8] It is clear therefore that further research into the role of bacterial infection in IPF, perhaps with advanced 16S sequencing to define the lung microbiota is needed for a better understanding of the pathogenesis of IPF. The potentially confounding effects of immunosuppression also need addressing although this should less important for the future as practice is changing in the light of the PANTHER study.[9]

A second lesson to be learned from TIPAC is that infections and hospital admissions may be a suitable endpoint for clinical trials of effective therapy in IPF despite an apparent consensus among commercial trialists to the contrary.[10] In our institution, admissions with IPF are both common, and associated with prolonged hospital stays (mean 12 days) and high mortality (33%) (H Mujakperuo, unpublished results). The admissions to our hospital, as with the TIPAC patients, are predominantly due to progressive effects of fibrosis and infection / pneumonia. Many patients are on oxygen therapy at home prior to admission. It is clear to us therefore, that the patients recruited to TIPAC represent a real life population of patients. This is unlike the population of patients that are currently enrolled into commercial clinical trials, the entry criteria for which have largely been shaped by the failed interferon gamma trials and currently equivocal pirfenidone trials programme in IPF.[11–13] The exclusion of patients who require oxygen or have gas transfers below 30–40% predicted means that the patient populations recruited into commercial clinical trials do not reflect real life patients. This ultimately may have an adverse effects on trial outcomes, particularly if non-progressive patients at low risk of death are recruited to placebo arms such as appears to be the case in the ongoing arms of the PANTHER study comparing placebo versus monotherapy with N-acetylcysteine in IPF.[8 9]

A third lesson for the investigators of this study is that the dosing of co-trimoxazole needs to be looked at due to the high drop out rate from side effects. In the Varney study patients received up to 3×480 mg bd of co-trimoxazole whereas in the TIPAC

Centre for Translational Inflammation and Fibrosis Research, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK

Correspondence to Dr David R Thickett, Centre for Translational Inflammation and Fibrosis Research, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; d.thickett@bham.ac.uk

study only 480 mg bd was used. These are quite high doses to the standard prophylactic doses used as anti-bacterial prophylaxis (960 mg thrice weekly) in patients taking cyclophosphamide for anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis.[14] Subsequent trials of co-trimoxazole should therefore consider lower doses and an appropriate dose reduction strategy for those with side effects.

In summary, the pilot studies and follow-up TIPAC trial of co-trimoxazole show conflicting results in the accepted trials outcomes for IPF patients. Due to significant numbers of patient drop-outs due to side effects in the treatment arm, the intention to treat analysis for mortality was negative in TIPAC. Despite this, in the per protocol analysis of patients who successfully took the drug, co-trimoxazole dramatically reduced mortality with a reduction in frequency of respiratory tract infections and improved overall health-related quality of life. In conclusion, we suggest that there is an urgent need for a large phase III trial of co-trimoxazole therapy to be conducted in IPF. It certainly seems time for TIPAC-2.

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