Hot off the breath: triple therapy for idiopathic pulmonary fibrosis—hear the PANTHER roar

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Idiopathic pulmonary fibrosis (IPF) is a disease characterised by alveolar epithelial damage followed by an aberrant repair mechanism characterised by fibroblast foci and activated myofibroblasts.1 Despite an incidence of 7.4–100000 person years which is increasing year on year and a median survival of only 2–3 years, there is paucity of evidence for effective therapy.2 The current British Thoracic Society guidelines weakly recommend N-acetylcysteine (NAC), prednisolone and azathioprine (based on the IFIGENIA—Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcyistine I Annual—trial) whereas the more recent guidelines of the American Thoracic Society/European Respiratory Society recommend lung transplantation or participation in a clinical trial as treatment options.3–5

Increasing recognition of the clinical need for effective IPF therapy has finally led to a number of clinical trials evaluating potential anti-inflammatory and anti-fibrotic agents. IFIGENIA demonstrated that triple therapy with NAC, azathioprine and prednisolone was better than azathioprine and prednisolone in combination in preserving lung function in IPF patients, suggesting that NAC inclusion was strongly contributing to the benefits observed.4 However, a placebo arm was not included in the study which led many to question whether triple therapy offers genuine benefit to patients compared with no treatment.

The PANTHER-IPF trial (prednisolone, azathioprine and NAC: a study that evaluates response in IPF) funded by the National Heart, Lung and Blood Institute was designed in part to answer some of the questions that arose from IFIGENIA. This phase III multicentre, randomised double blind placebo controlled trial aims to evaluate the effectiveness of NAC, an anti-oxidant, alone (at doses comparable with the IFIGENIA study) and in combination with other established IPF mediation in the prevention of lung function decline over 60 weeks. The primary outcome measure is the change in serial forced vital capacity between the study arms. Secondary outcome measures include time to disease progression, acute exacerbations, respiratory infections and maintained forced vital capacity response.6 As of last month, 238 patients (age range 48–85 years; mean 68 years) of the 390 expected recruits with newly diagnosed mild to moderate IPF were enrolled.7

On 12 October 2011, the data and safety monitoring board (DSMB) for the study met to review and analyse the interim data. They found that participants treated with triple therapy had increased mortality, serious adverse events and drug discontinuation without any evidence of therapeutic benefit.8 Eight (11%) and one (1%) patient died in the triple therapy and placebo arms respectively with approximately 50% of these resulting from respiratory disease.8 Twenty-nine per cent of the triple therapy arm required hospitalisation compared with 8% of the placebo arm and 31% of the triple therapy arm experienced a serious adverse event compared with 9% in the placebo arm.7 Seventy-eight per cent of those administered triple therapy adhered to treatment compared with 98% in the placebo group.7 As a result the DSMB recommended ceasing enrolment and abandoning drug administration to the triple therapy arm. The DSMB has not found any safety issues with NAC or placebo and has recommended that these arms of the trial continue to recruit participants facilitating an analysis of the benefits and safety of NAC over placebo once the study is completed. Results of the triple therapy arm analysis are expected in 2012 with the final PANTHER-IPF study results expected to be published in 2013.9

The mortality rate in the IFIGENIA study, where the participants’ mean total lung capacity was approximately 62% at enrolment, was 9% and 11% in the triple therapy (mean age 62 years) and azathioprine+prednisolone groups (mean age 64 years), respectively.4 These data are similar to the PANTHER-IPF interim analysis leading one to speculate that if a placebo arm had been included in this study, it may have shown a similarly significant lower mortality rate in this group thus completely changing the final conclusions and recommendations of this study. This issue will become clearer once all data is finally reported.

This leaves us with more questions than answers; however, it emphasises the need for more placebo controlled clinical trials in this disease and begs the question as to why they have not been carried out previously. We are aware of at least one placebo controlled multicentre trial unsuccessfully submitted for funding within the UK in the past. The comments suggesting that it had been felt to be ‘unethical’ to deny patients standard therapy, even when that therapy is (1) unproven and (2) has recognised toxicity.9

In addition, despite some advances in phenotyping, the apparent difference in the outcomes of clinical trials of IPF confirms the heterogeneity of the condition and perhaps increased genotyping and identification of biomarkers is the way forward.9 The situation is less clear for patients who have either cellular or fibrotic non-specific interstitial pneumonia where trials are also clearly needed.

What should be done in patients currently on triple therapy? Careful discussion and consideration to stopping immunosuppression followed by a period of close observation would seem a prudent course while we wait for PANTHER to conclude.

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REFERENCES

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