

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 7.4/100 000 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*-Acetylcysteine 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 medication 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 2013.⁸

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.

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.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

Published Online First 8 December 2011

Thorax 2012;67:97–98.
doi:10.1136/thoraxjnl-2011-201398

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The asbestos disease epidemic: here today, here tomorrow

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In what may be the best ever use of a Wellcome grant, Geoffrey Tweedale, in his fascinating history of the multinational asbestos company Turner & Newall,¹ reminds us that asbestos was once known as the ‘magic mineral’. Indeed, in many ways, it is the ideal construction material: tough, durable, light in weight, fire-resistant and very cheap. Unfortunately, asbestos is also, as every respiratory physician knows, highly toxic when inhaled. Total bans on its use are in place in 52 countries including those of the European Union, Australia, Japan and South Africa²; and its use is tightly restricted in the USA, New Zealand and Canada—the last, ironically, among the world’s largest exporters of the material.

Readers from these countries may be surprised to learn that elsewhere the production, sale and use of asbestos continue to flourish and even increase. In 1994, one of us (NP) edited a book³ on occupational cancer in developing countries for the International Agency for Research on Cancer and reported that global asbestos production and use had not declined; rather, the problem was simply being moved from Western countries to emergent economies. Unhappily, the situation has not improved in the intervening 17 years. In India, for example, the use of asbestos has doubled in the last decade to about 300 000 tonnes a year by an industry that now employs

an estimated 100 000 workers.⁴ Other major users include China, Brazil, Russia, Ukraine, Kazakhstan and Indonesia. In these parts of the world, where occupational exposures may be difficult to control and enforce, the great majority of asbestos is mixed with cement in the manufacture of sheets for roofing or pipes for sanitation and irrigation in contrast to the uses once common in Europe and North America.

There is a further contrast in the nature of the asbestos used in contemporary manufacturing. Almost all of the estimated 2 million tonnes mined each year is now chrysotile (‘white’ asbestos) with very little extraction of crocidolite (‘blue’), amosite (‘brown’) or other amphibole (straight-fibre) types. In part, this is a result of the disputed belief that different types of asbestos have different toxicities. Certainly, all are both fibrogenic and carcinogenic but it is often argued that chrysotile is less so than the amphiboles—at least with regard to mesothelioma—and that the exposures required to induce asbestosis and malignancies are considerably higher when chrysotile alone is being handled. It is on this basis, with the message that ‘chrysotile is safe if it is used safely’, that the powerful mining, industrial and governmental interests (particularly in Canada and Russia) justify and fight for the continuing sale and use of the mineral across the developing world. On the other hand, there are a number of studies^{5–8} which indicate that chrysotile exposure does increase the rate of lung cancer, with risks comparable to those shown with amphiboles, although the risks of mesothelioma remain uncertain and are likely to be lower than those from amphiboles.⁹ A corollary of this is that the ratio of lung cancer cases to mesothelioma

cases is likely to be higher for chrysotile than for amphiboles; thus, estimates of asbestos-related lung cancer, which are based on reported mesothelioma cases, require a larger ‘multiplying factor’ for chrysotile than for amphiboles.

The Chongqing asbestos plant in China opened in 1939 and expanded rapidly between 1958 and 1996 using up to 6000 tonnes of raw asbestos annually to manufacture textiles, asbestos cement products, rubber products and friction and heat-resistant materials. Only chrysotile asbestos extracted from mines in Sichuan has been used in the plant; a limited analysis of ore samples from these mines in 2000 was unable to detect any contamination by amphibole (tremolite) asbestos.¹⁰ Thus a study of the employees in the plant should provide important insights into the toxicology of essentially pure chrysotile.

In this issue of *Thorax*, researchers from Hong Kong and Sichuan report the results of their 37-year retrospective cohort study of employees from the Chongqing asbestos plant.¹¹ A reference group of workers in an electronics factory in the same city was established and followed for the same period. The findings are striking: a more than threefold increase in the risk of death from lung cancer (and also non-malignant respiratory disease) was observed among the asbestos workers after statistical control for smoking, in the asbestos cohort, with clear evidence of an exposure-response relationship in both non-smokers and smokers. There were two deaths from mesothelioma in the asbestos cohort—presumably the same two reported in an earlier 25-year follow-up study of the same cohort.¹⁰

The study has some significant limitations. The authors have been unable to verify the claim that the factory has only ever used tremolite-free chrysotile; and it is possible that the employees in the asbestos factory had had previous asbestos exposure elsewhere or that there were alternative, unidentified carcinogens in the study workplace, although these would have had to have been highly potent.

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