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EDITORIAL

Antioxidant therapy in idiopathic pulmonary fibrosis: hope is kindled

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The new American Thoracic Society/European Respiratory Society classification of the idiopathic interstitial pneumonias [1] has redefined entities previously grouped as ''idiopathic pulmonary fibrosis'' (IPF), but carrying a much better prognosis than that disorder. As a result, the core entity of IPF is now diagnosed with greater precision than ever before. The outcome has worsened correspondingly, with an average survival of ~3 yrs from the onset of dyspnoea. Until recently, therapeutic nihilism in IPF has prevailed. Treatment recommendations have come and gone, high-dose corticosteroid therapy has had its day [2], and ''standard therapy'' has essentially failed.

DEMEDTS *et al*. [3] recently reported outcome data that ought to encourage the optimists amongst us. For the first time, a widely available and inexpensive agent has effected a real difference in the rate of disease progression in a large cohort of patients. The methodology was straightforward. All patients remained on low-dose prednisolone and azathioprine throughout. The studied intervention consisted of the addition of *N*-acetylcysteine (NAC) at a dose of 600 mg *t.i.d.*, controlled against placebo. There were differences in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) at 12 months in favour of active treatment. With placebo, FVC and $D_{L,CO}$ fell 6 and 8% of predicted, respectively, but only 1.5 and 3% with active therapy. In other words, the rapidity of disease progression was curtailed by ~70% when antioxidant therapy was added to ''best current treatment''.

It appears unlikely that flaws in the study design generated a spuriously positive result. The diagnosis of IPF was more robust than in previous studies, with biopsy and high-resolution computed tomography (CT) appearances reviewed by reference panels of leading histopathologists and CT radiologists. Unfortunately, this led to the removal of a significant number of patients after randomisation but as the baseline characteristics and numbers of pre-treatment withdrawals were similar in the two arms, it seems very improbable that this somewhat unorthodox approach materially influenced the outcome. However, the study methodology does distance the population a little from patients diagnosed with IPF in routine practice, in which a review of CT and histological findings by super-specialised panels is not available. The high number of withdrawals, a further important caveat, was addressed by ''intention-to-treat'' analyses, widely viewed as the great desideratum in controlled studies and amply justifying the consideration of carried-over observations. With this approach, the statistically significant benefit was preserved in 90% of the final randomised population and, reassuringly, findings remained positive when alternative mixed-effect model analytical approaches were explored. The need to exclude 10% of subjects performing only a baseline pulmonary function test is another minor problem. Strictly speaking, intention-to-treat analyses should include all subjects. However, patients excluded from analysis were equally represented in the two arms, and it is difficult to envisage how they could have been included.

Healthy scepticism is needed even when a real therapeutic effect, amounting to a major reduction in the rate of disease progression, is reported in an inexorably progressive disease. In this instance, it is not easy to put the findings into clinical perspective. The difficulty relates in part to the nature of patients recruited into pharmaceutical studies. Given the uniformly poor survival observed in IPF, it might be imagined that 1 yr ought to suffice to show that a new treatment approach is effective. However, it should not be forgotten that IPF patients enrolled into therapeutic trials will generally contain a large subgroup of patients who have previously been followed for a lengthy period, as seen most strikingly in an early uncontrolled study of pirfenidone [4]. It is likely that a placebo-controlled approach will be more readily accepted by patients and physicians alike when disease is unusually slowly progressive. Perhaps close patient–physician relationships, fostered during prolonged follow-up, facilitate recruitment. Whatever the explanation, it is well recognised that the outcome in IPF is much better in prevalent disease than in newly diagnosed cases (''incident disease'') [5], whereas outcomes in large historical series pertain to the whole IPF population, including the significant patient subset with a rapidly fatal outcome. In the NAC study of DEMEDTS *et al.* [3], it is reassuring that the diagnosis of IPF had been made in the previous 6 months in ~50%. However, the speculation that the use of standard therapy in the inactive arm was partially efficacious, because the rate of progression was slower than expected from historical data, is difficult to sustain. In the placebo arm of the largest IPF therapeutic trial to date, disease progression was also unexpectedly indolent [6]. It is increasingly clear that the true natural history and treated course of IPF is not captured by longitudinal behaviour in pharmaceutical studies. Unless this major bias can somehow be taken into account, comparisons between the inactive arm

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of the NAC study and treatment arms in other studies must be viewed with great caution.

The problem of the selective enrolment of IPF patients with less progressive disease has major implications. It should not be argued that the relatively small average amplitude of the therapeutic benefit (~5% pred normal FVC values) is clinically insignificant. Even a ''perfect'' treatment outcome, amounting to the complete abolition of disease progression, would have equated to a treatment benefit of just 6% in predicted FVC values. This is substantially less than the 10% change regarded as clinically significant in an individual IPF patient. Given the nature of the studied population, the therapeutic effect can actually be viewed as rather striking. However, in reality, the duration of the study was too short to produce a truly definitive conclusion. As a result, the findings cannot be extrapolated with confidence to the more rapidly progressive unselected IPF population managed in routine practice. Moreover, the amplitude of the therapeutic benefit cannot yet be quantified with any real certainty. The 95% confidence intervals for the average change in $D_{L,CO}$ and FVC were wide for both placebo and active arms. Thus, the real therapeutic benefit could, in reality, amount to a much smaller effect. Plainly, a further study demonstrating a similar benefit, perhaps in a smaller cohort, would improve confidence that the degree of benefit is likely to be robust. The current results, albeit highly encouraging and indicative of a real therapeutic benefit, are tantalisingly inconclusive.

To further complicate interpretation, it has been suggested that azathioprine therapy might damage the lung and that the better outcome seen with the addition of antioxidant therapy might merely represent a ''rescue effect'', based upon the statistically significant reduction in bone-marrow toxicity in the active treatment arm [7]. This speculation could provoke considerable clinical uncertainty, as it flies in the face of a recent strong recommendation by a group of leading clinicians that azathioprine should be added routinely to low-dose corticosteroid therapy in IPF [8]. It should be acknowledged that the history of science is littered with examples of the ultimate vindication of seemingly implausible ideas. However, it is worth enumerating possible flaws in the assumptions inherent in an azathioprine toxicity hypothesis. A large number of side-effects were compared between the two treatment arms without corrections for multiple analyses. The reduction in neutropenia narrowly reached statistical significance. Drug-induced marrow and liver toxicity are not synonymous with lung toxicity. Azathioprine is widely prescribed in many other disorders, especially in connective tissue disease. As the lung disease of connective tissue disease is often stable for lengthy periods, it is difficult to imagine that lung toxicity sufficient enough to cause whole population effects would have wholly escaped notice. Perhaps it can be argued that pulmonary toxicity from azathioprine is confined to IPF, or to more progressive fibrotic lung disease in general, but where is the circumstantial support for this notion in previous IPF studies? There is no evidence that outcome in IPF is worse with azathioprine than with cyclophosphamide or high-dose corticosteroid therapy [9]. Is it likely that antioxidant treatment selectively prevents lung toxicity from azathioprine, whilst having no material effect on the damaging fibrotic consequences of pathophysiological interactions evident in IPF? It is necessary to express these doubts because clinicians must make an urgent assessment of the likelihood that ''best current treatment'' in IPF might radically increase disease progression. A genuine therapeutic effect from antioxidant treatment appears to be much more plausible, but, in the end, this question can only be settled by a placebo-controlled study. It is essential that guideline groups make recommendations on the ethical acceptability of placebo-controlled evaluations in IPF, in the light of these and other encouraging recent results [3, 10–12].

Antioxidant therapy has not been validated as a ''stand-alone'' IPF treatment because it is possible that the apparent therapeutic benefit results from synergism with azathioprine and low-dose prednisolone. The weakness of the circumstantial support for anti-inflammatory drugs in IPF [13] does not preclude important ancillary benefits when used in combination with other agents. In tuberculosis and malignancy, combination regimens are much more successful than treatments attacking single pathophysiological mechanisms and this appears intuitively likely to also be true in IPF, a highly complex disease. Is it really correct to continue to hope for a therapeutic lightning strike from a single novel treatment, or is it better to reach for an oncological approach in IPF in future trials? Exactly the same uncertainties apply to routine management. The future has never seemed more hopeful in IPF [3, 10–12], but we need an optimal therapeutic approach now. The antioxidant study of DEMEDTS *et al*. [3] is exciting because a real effect appears highly likely, whether or not this turns out to be major in isolation, and we can now hope for synergism with traditional and future treatments.

Idiopathic pulmonary fibrosis is a relentlessly progressive disease with an outcome akin to lung cancer. Therapeutic opportunities are not to be missed. The oncological principle of enrolling all patients in clinical trials is highly applicable to idiopathic pulmonary fibrosis but often impracticable. Pending further data, the routine treatment of idiopathic pulmonary fibrosis should consist of triple therapy: low-dose corticosteroid, azathioprine and antioxidant treatment.

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