the role of aberrant wound healing in the evolution of fibrosis.[2] The pathogenetic importance of inflammation has been downgraded. Furthermore, greater diagnostic accuracy has led to a better understanding of IPF disease behaviour. It is now appreciated that patients with IPF may have periods of remarkable disease stability interspersed by acute exacerbations, during which time fibrosis progresses rapidly, often with fatal consequences.[3] Better understanding of the pathogenesis of IPF has led to the development of treatments directed at various elements of the wound healing cascade.[2] Additionally, treatment strategies that aim to modify IPF disease behaviour and prevent acute exacerbations have been investigated. Consequently, there has been a recent striking increase in clinical trials in IPF. Among these trials, a number of key results not covered by the review of Williams and Wilson stand out.

In a 9-month study of 107 patients, Azuma and colleagues found that the pluripotent antifibrotic agent pirfenidone improved vital capacity and reduced the incidence of acute exacerbations compared with placebo.[4] Kubo *et al* in a relatively small group of patients, all of whom were initially hospitalised with acute exacerbations of IPF, found that treatment with warfarin and prednisolone improved survival and reduced subsequent exacerbations compared with prednisolone alone.[5] In the recently reported placebo controlled BUILD-1 study, no treatment effect was demonstrated for bosentan in the whole cohort, although a statistically significant effect was evident in the subgroup of biopsied patients.[6]

In the most important recent trial, the IFIGENIA study, Demedts *et al* demonstrated that the addition of N-acetylcysteine (NAC) 600 mg three times daily to standard therapy of prednisolone and azathioprine significantly slowed disease progression in IPF compared with prednisolone and azathioprine alone.[7] While questions have been raised concerning both the clinical significance of this finding and the mechanism by which NAC exerts a beneficial effect, this paper represents a landmark in the treatment of IPF. For the first time, primary end points have been clearly met in this relentless disease in a well-performed placebo controlled study.

In contrast to these trials, a large phase III study of interferon-γ1b, a compound that had previously shown promise as a treatment for IPF, was definitively negative with mortality (the primary end point) minimally higher in the treatment arm.[8]

The ongoing expansion in the number of new drugs being trialled in IPF offers the realistic hope that effective disease-modifying therapy may become available in the foreseeable future. Given the rapid development of novel therapies, we would urge that patients with IPF should be enrolled in clinical trials whenever possible. When this is not possible, we believe that the results of the IFIGENIA study provide a rationale for treatment in IPF.[7] NAC is non-toxic and the benefits of treatment, although uncertain in magnitude, exceed the negligible risk. In a lethal disease it does not appear logical to withhold a cheap non-toxic treatment shown to have a beneficial functional effect, even if the exact clinical significance of this effect remains uncertain.

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Authors' reply

The response to our article identifies the hazard of reviewing a topic in the middle of a paradigm shift, and was helpful in identifying pirfenidone and acetylcysteine as other potential agents for the management of idiopathic pulmonary fibrosis (IPF).[1] Our review was aimed at identifying immunological mechanisms underlying the remodelling process and did not suggest optimal management, which is at present not clear. In fact, a recent BTS study of IPF management still highlighted the importance of anti-inflammatory therapy in achieving better clinical responses.[2] Furthermore, uncertainty in the rapidly changing area of antifibrotic therapy has resulted in significant delays in producing guidelines to support clinicians.[3 4] We look forward to confirmation of promising early clinical trails of pirfenidone and acetylcysteine[5 6] and their translation into clinical practice. Our optimism is tempered by experience with ''false Messiahs'' noted by Maher and Wells in their letter.[7]

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