



The road to hell is paved with good intentions: a look back at the PANTHER-IPF trial

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The PANTHER-IPF trial was a turning point in treatment of idiopathic pulmonary fibrosis (#IPF) highlighting the importance of randomised controlled trials in determining treatment strategies, even for rare diseases and/or potentially fatal acute events <https://bit.ly/3Oi0KwD>

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most severe and the most common idiopathic interstitial lung disease (ILD), characterised by irreversible fibrosis with progressive lung function deterioration. IPF is currently hypothesised as a disharmonious alveolar healing process after multiple micro-aggressions in genetically predisposed subjects, with impaired crosstalk between senescent epithelial alveolar cells and activated fibroblasts, leading to the accumulation of extracellular matrix components in the pulmonary interstitium [1]. This current pathophysiological conception is the result of progressive evolution over the past decades.

State of the art in IPF in the 2000s

IPF was formerly called “cryptogenic fibrosing alveolitis”, a term that also comprised nonspecific interstitial pneumonia (NSIP) before this entity was later individualised [2, 3]. IPF was initially considered to be mainly a chronic inflammatory disorder. Immune effector cells were thought to cause pulmonary damage, which was then followed up by impaired repair processes which led to end-stage, irreversible fibrosis [4]. On this basis, corticosteroids or immunosuppressant drugs (ISDs) were the conventional approach in the treatment of patients with IPF in the 2000s. Despite the absence of a prospective, double-blind, randomised, placebo-controlled clinical trial (RCT) evaluating their efficacy in the treatment of IPF, corticosteroids had been the first-line therapy since the 1950s. In case series of IPF patients treated with corticosteroids, objective improvement was uncommon (seen in ~12% of cases only). However, in trials comparing corticosteroids against no treatment, none of the untreated IPF patients improved [5]. In a RCT published in 1991, the combination of prednisone and azathioprine (AZA) seemed to be associated with modest functional improvement and better survival, when compared with a group receiving prednisone and a placebo [6]. However, data supporting the use of such treatments remained controversial [7, 8]. In 2000, the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines stated that “therapy [was] not indicated for all patients with IPF” and “the potential benefits of any treatment protocol for an individual patient with IPF may be outweighed by increased risk for treatment-related complications” [9].

As oxygen radicals were theorised to contribute to epithelial injury in IPF, it was hypothesised that antioxidant strategies might prove beneficial. N-acetylcysteine (NAC), a precursor of the antioxidant glutathione, was suggested as an adjunct to maintenance immunosuppressant therapy in IPF patients. In



2005, the IFIGENIA study focused on high-dose NAC added to “standard” therapy consisting of prednisone plus AZA. Patients in the three-drug regimen arm showed better-preserved pulmonary function at 1 year than the “standard” two-drug regimen plus placebo arm. However, no difference in mortality rate was observed, and since this study included no placebos for AZA and prednisone, the efficacy of this three-drug regimen remained controversial [10].

Concurrently, pathophysiological hypotheses were evolving. Evidence suggested that inflammation might not play a pivotal role, as it was not a prominent histopathological finding. Moreover, even in the absence of ongoing inflammation, epithelial injury was shown to be sufficient to stimulate pulmonary fibrogenesis by itself. In addition, clinical measurements of inflammation failed to correlate with disease stage or outcome [11]. Thus, a trial testing the benefit of an anti-inflammatory and antioxidant strategy *versus* placebo was deemed necessary.

Design and results of the PANTHER-IPF trial

The PANTHER-IPF trial (ClinicalTrials.gov identifier: NCT00650091) was designed by the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet) steering committee and conducted in 25 clinical centres in the USA [12, 13]. Recruitment began in December 2009. In the previous year, a practice survey showed that almost 50% of pulmonologists used either a two-drug regimen (prednisone plus AZA) or a three-drug regimen (prednisone, AZA and NAC) [14]. The design of the PANTHER-IPF trial consisted of three treatment arms with double-blinding: 1) prednisone plus AZA plus NAC (“combination-therapy” group); 2) NAC alone plus placebos for prednisone and AZA; and 3) a placebo group. The target sample size was determined as 130 patients per group, with 1:1:1 randomisation. Patients <85 years of age with “definite IPF” and mild-to-moderate lung function impairment, as defined by forced vital capacity (FVC) $\geq 50\%$ and diffusing capacity of the lung for carbon monoxide (D_{LCO}) $\geq 30\%$ of the predicted value, were eligible. The primary outcome was the change in FVC after 60 weeks, because the target recruitment number would have been too high if survival was used as the primary end-point.

A planned mid-point interim analysis took place in October 2011, leading the data and safety monitoring board to recommend discontinuation of the three-drug regimen, owing to an increase in overall serious adverse events, including death. At that time, 77 patients had been enrolled in the combination-therapy group, and 78 in the placebo group. 75% were male, was a mean age of 68 years, mean FVC 71% predicted and mean D_{LCO} 44% predicted. The two groups were similar with respect to demographics, clinical characteristics and coexisting illnesses. Mean follow-up was 32 weeks. Combination therapy seemed to show no benefit for lung function preservation compared with matched placebos. There was no significant difference in the primary outcome for the few patients who completed the 60-week follow-up, in terms of the change in FVC and D_{LCO} at previous time-points, nor in disease progression (composite outcome of death or decrease in FVC of $>10\%$). More importantly, there was a statistically significant increase in the number of deaths in the combination-therapy group which had eight deceased patients (10%) compared to one (1%) in the placebo group. Kaplan–Meier estimates of 60-week mortality for combination-therapy and placebo groups were 19.8% and 2%, respectively (hazard ratio 9.26, 95% CI 1.16–74.1; $p=0.01$). The combination-therapy group also demonstrated increased hospitalisations (23 *versus* 7; $p<0.001$), acute exacerbations (AEs; 6 *versus* 0; $p=0.03$), and serious adverse events (24 *versus* 7; $p=0.001$) compared with placebo. Although drug discontinuation was higher in the combination-therapy group, having completed the 15-week visit 73% of the patients were still taking all three study drugs, and between 60% and 66% of them were at later time-points. Mortality rates were considered to be consistent with data from previous RCTs, and the increased mortality was attributed to combination therapy, or at least one of its components. The NAC monotherapy and placebo arms were continued as previously planned, but no benefit was observed after 60 weeks for any primary or secondary outcome [15].

A paradigm shift in IPF treatment

The trial had several limitations, one of which was early termination of the combination-therapy group; hence, the effect of treatment on the primary outcome (change in FVC over the 60-week period) could not be assessed in all subjects. Nevertheless, the significance of the results prompted clinicians to stop using corticosteroids and ISDs in IPF treatment [16]. In subsequent years, RCTs assessing pirfenidone (CAPACITY, ASCEND) and nintedanib (INPULSIS) have demonstrated retardation of lung function decline with antifibrotic use [17–19]. However, further trials studying IPF treatment have been negative, and antifibrotic therapy remains the only established guideline therapy for IPF [16], and in some cases of progressive pulmonary fibroses due to other aetiologies [20].

When the PANTHER-IPF results were first published, the reason for the increased death and hospitalisation rates was unknown. One postulation was the initial high dose of corticosteroids used in the

PANTHER-IPF trial resulting in significant toxicity in an elderly population [21]. *Post hoc* analysis of PANTHER-IPF subjects showed that subjects with short leukocyte telomere lengths, that measured below the 10th percentile of normal controls, who received the three-drug regimen had a higher composite end-point (death, lung transplantation, hospitalisation or FVC decline), which remained significant after adjustment for age and baseline percentage predicted FVC [22]. In addition, it was hypothesised that earlier case series which reported therapeutic success with corticosteroids or ISDs may have involved patients who no longer fulfilled the ATS/ERS guideline criteria for the diagnosis of IPF, and rather had progressive pulmonary fibrosis from other causes, including NSIP [23].

As regrettably highlighted by the coronavirus disease 2019 pandemic, observational case series and small-sized controlled trials tend to overestimate the proposed efficacy of a treatment [24, 25]. This emphasises the importance of evaluating (and sometimes re-evaluating) standard clinical practice with well-designed and well-powered RCTs, even for rare diseases and serious events such as IPF AEs. Although they are no longer used to treat IPF, corticosteroids and sometimes ISDs are still used to treat AEs. In current IPF guidelines, there is no recommendation against their administration for the treatment of AEs [26, 27]. However, cohort studies examining AE outcomes suggested that steroid use was associated with poorer outcomes and survival [28, 29]. More recently, the phase 3 EXAFIP trial demonstrated that pulsed intravenous cyclophosphamide, in addition to methylprednisolone, in AEs of IPF increased 3-month mortality [30]. One proposed theory is the effect of immunosuppression on the lung microbiome and pulmonary epithelium, although trials studying the use of doxycycline and cotrimoxazole in IPF have been negative thus far [31, 32].

Following PANTHER-IPF, the PANORAMA trial, which studied the safety and efficacy of oral NAC added to pirfenidone, showed higher rates of photosensitivity and FVC decline over 6 months in the NAC group compared with placebo [33]. More recently, a Japanese study found that inhaled NAC combined with pirfenidone resulted in a faster rate of FVC decline over 48 weeks compared with pirfenidone monotherapy [34]. However, *post hoc* analysis of PANTHER-IPF suggests that some patients may still benefit from NAC treatment. Subjects with the rs3750920 (TOLLIP) TT genotype had a reduced risk of a composite end-point of death, lung transplantation, hospitalisation or 10% FVC decline, whilst those with a rs3750920 (TOLLIP) CC genotype had a nonsignificant increase in composite end-point risk. These findings were further replicated in an independent IPF cohort [35]. The TT genotype frequency in this study was 25%, while the CC genotype was found in over 80% of IPF subjects in Japanese population, possibly accounting for the differences in the outcomes with NAC between the cohorts.

Summary

The PANTHER-IPF trial was a turning point in IPF treatment and highlighted the importance of RCTs in determining treatment strategies for patients. The *post hoc* analysis has been significant in paving the way to further study pharmacogenomic interactions in ILD treatment and further research is needed to determine which genotypes are of clinical relevance in drug selection and disease prognostication.

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