



Home spirometry to assess efficacy of pirfenidone in progressive unclassifiable interstitial lung disease: better the devil you know than the devil you don't

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Interstitial lung diseases (ILDs) are a complex of heterogeneous disorders characterized by varying degrees of inflammation and scarring of the lung interstitium while generally sharing a poor prognosis *quoad vitam et valetudinem* (1). Since 2002, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) advocated a multidisciplinary team (MDT) approach involving clinicians, radiologists and pathologists in an active process to increase diagnostic accuracy in patients with ILD (2) and therefore guide the appropriate choice of treatment. MDT meetings are currently considered the gold standard for the diagnosis of ILD as they have been shown to improve the diagnostic confidence as compared to individual specialists (3,4), despite some limitations exist such as the lack of specific guidelines for the optimal structure or the evidence in non-specialized centers (5). In the course of the last two decades, the scientific community particularly focused on making an accurate diagnosis of idiopathic pulmonary fibrosis (IPF) (6-8), the most severe of idiopathic interstitial pneumonias. Such efforts led to the standardization of the diagnostic approach worldwide, to significant advances in the understanding of underlying disease pathogenesis and, ultimately, to outstanding therapeutic achievements represented by the approval of pirfenidone and nintedanib, the first antifibrotic

treatments proving to slow down the lung function decline in these patients (9,10). While the agreement between multidisciplinary teams has shown to be good for a diagnosis of IPF, disagreement on diagnosis of other forms such as non specific interstitial pneumonias or chronic hypersensitivity pneumonitis is more common (4), mostly due to the lack of consensus-based guidelines. Moreover, when a thorough MDT evaluation cannot assign more than 50% confidence to an ILD diagnosis, the diagnostic process fails to yield a specific classification: these patients are assigned a diagnosis of unclassifiable ILD (U-ILD) (11) and are therefore left without evidence-based therapeutic options. Yet, the conclusion that unclassifiable ILD means untreatable disease should not be endorsed (12). Indeed, IPF and other ILDs have pathobiological similarities and may share a progressive fibrosing phenotype that could be susceptible of the same anti-fibrotic treatments approved for IPF (13). The phase 3 INBUILD study already demonstrated the efficacy of nintedanib in reducing FVC decline over 52 weeks in patients with progressive fibrosing interstitial lung disease (PF-ILD), including patients with U-ILD (14). In their work, Maher and coauthors (15) answered the call for a randomized controlled trial of pirfenidone in progressive fibrosing ILDs, focusing on a population with unclassifiable forms and thus placing a first

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milestone in the challenging path of U-ILD therapy.

This multicenter, double-blind, placebo-controlled, phase II clinical trial aimed to assess the efficacy of pirfenidone for the treatment of U-ILD by using daily home spirometry via handheld device. The authors ambitiously set the mean change of forced vital capacity (FVC) at 24 weeks as the primary endpoint, building upon previous reports that IPF progression could be reliably assessed via home spirometry (16). The required single daily measurement of FVC allowed maximize the compliance of study participants, however such choice resulted in a remarkably high intraindividual variability of FVC values, impairing the application of the planned statistical model to the primary endpoint data. As such, the trial design disappointingly prevented from obtaining proof of efficacy of pirfenidone using home spirometry, raising questions as to the choice of the primary endpoint for this study. Although measurement of pulmonary function at the study site is time consuming and requires specific staff training, it provides extremely reliable assessments through bulletproof quality checks. Most importantly, two decades of randomized clinical trials in IPF confirmed by-site FVC measurement as the most robust clinical endpoint to assess functional deterioration in these patients. In the approaching era of telemedicine, handheld spirometers represent indeed an attractive tool to monitor disease behavior in patients with chronic respiratory disorders; nevertheless, home monitoring experiences in ILD populations are still limited, and these devices have not yet been implemented in daily practice. Following an earlier report of self-monitoring of pulmonary function using a home spirometer (16), a study investigated the reliability, feasibility, and impact of home-based measurement of forced vital capacity (FVC) and dyspnea in a US population of IPF patients (17). Patients performed weekly home-based assessments of FVC and dyspnea using a mobile handheld spirometer and self-administered questionnaires. Mean adherence to measurements of FVC over 24 weeks was greater than 90%, and the weekly assessment schedule resulted in increased precision and power for a hypothetical 24-week clinical trial as compared with baseline and 24-week measurements only. Another study conducted in a specialised centre in the Netherlands confirmed feasibility of a home monitoring program including real-time wireless home spirometry in IPF patients (18). In this scenario, the courageous choice made by the authors to incorporate home spirometry as the primary endpoint in a ILD pharmaceutical trial is commendable, but the study

results underline the need for a better validation of these devices before they could be strategically implemented in the design of future research.

On the other hand, the study by Maher and coworkers delivered substantial evidence on the efficacy of pirfenidone as compared to placebo with regards to several secondary endpoints. When compared to placebo, treatment with pirfenidone significantly reduced the decline in FVC at 24 weeks by a mean difference (95.3 mL, 95% CI: 35.9 to 154.6, $P=0.002$) that is in line with the results of pirfenidone phase III trials in IPF (9,19). Such benefit was also shown in terms of categorical decline of FVC: an absolute decline of more than 10% of the predicted FVC was observed in 18 ($n=127$, 14%) patients in the pirfenidone group when compared to the 34 ($n=126$, 27%) patients in the placebo group [odds ratio (OR): 0.44, 95% CI: 0.23 to 0.84, $P=0.011$]. An impact of the antifibrotic treatment on the reduction of diffusion capacity of carbon dioxide (DL_{CO}) was also shown, since only 3 (2%) patients in the pirfenidone group underwent significant ($>15\%$ of predicted DL_{CO}) decline as compared to 11 (9%) in the placebo group (OR: 0.25, 95% CI: 0.07 to 0.93, $P=0.039$). Finally, the 24-week mean change in 6-min walking distance (6MWD) also favored pirfenidone over placebo. Considering the statistical limitations due to small sample sizes, the exploratory investigations suggested that pirfenidone might be beneficial across different subgroups of unclassifiable ILD: a greater treatment effect on FVC change at 24-week was pointed out in the following subgroups: males (108.5 mL, $P=0.0167$), ≥ 65 years (122.5 mL, $P=0.0018$), predicted FVC $\geq 80\%$ (137.3 mL, $P=0.0105$), corrected $DL_{CO} \geq 35\%$ (81.6 mL, $P=0.0149$), baseline weight ≥ 60 kg (103.9 mL, $P=0.0004$), absence of interstitial pneumonia with autoimmune features (IPAF) (121.5 mL, $P=0.0024$). Importantly, no new concerns were raised with regards to the tolerability and safety profile of pirfenidone, that showed a comparable profile with previous phase III clinical trials in IPF (9).

In summary, overlooking the disappointing findings with regard to the primary endpoint, the study by Maher and coworkers convincingly supports the efficacy of pirfenidone in slowing down FVC decline in patients with progressive unclassifiable ILD, thus paving the way for a therapeutic approach even when a consensus diagnosis cannot be achieved. Although the results on secondary endpoints should be interpreted with caution, they are encouraging for ongoing investigations of antifibrotics in progressive fibrosing ILD (20), and definitely warrant further research

investigating the role of pirfenidone in treating the unclassifiable ILD population in the longer term.

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