Treatment of severe idiopathic pulmonary fibrosis-is sildenafil the next (in)stage?

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Editorial

Treatment of severe idiopathic pulmonary fibrosis—is sildenafil the next (in)stage?

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Despite progress in the therapeutic management of idiopathic pulmonary fibrosis (IPF) in the last decade, prognosis remains poor (1). This is particularly true of patients with severe disease, with 3-year mortality predicted at 76.8% for patients with advanced disease (2). Therapeutic trials in IPF typically exclude such patients which can subsequently have a significant impact on drug availability in the clinical setting. There is a desperate unmet need for treatment options in this advanced disease cohort.

Pulmonary hypertension frequently complicates cases of severe fibrosis, exacerbating the physiological impairment and contributing to a worsening prognosis (3). Sildenafil, a phosphodiesterase-5 inhibitor, is an oral medication which is an effective and well tolerated treatment of pulmonary arterial hypertension and is recommended for use by international guidelines (4). The potential of sildenafil as a therapeutic option in patients with IPF was assessed in the STEP-IPF study, a randomised placebo-controlled trial. The study failed to meet its primary endpoint, which was a 20% increase in 6-minute walk distance (6MWD), following 12 weeks of treatment. However, it did provide encouraging results in some secondary endpoints including improving oxygenation, diffusion capacity of the lung for carbon monoxide (D_{LCO}) and quality of life (QOL) measures (5). This led to speculation that there may be a role for sildenafil in advanced IPF with further research in this field.

The recently published INSTAGE study aimed to clarify the role of sildenafil in an IPF cohort exposed to antifibrotic therapy (6). The study included IPF patients with a D_{LCO} of 35% predicted or less, and compared nintedanib and sildenafil in combination to nintedanib alone for a period of 24 weeks. Building and learning from the STEP-IPF study, the INSTAGE study took a huge leap in IPF trial design by developing a study powered to detect a change in QOL as its primary endpoint. This was measured using the St George's Respiratory Questionnaire (SGRQ) after 12 weeks of treatment. Unfortunately, the study failed to meet this endpoint, with no significant differences between the two groups at 12 weeks, and no clear indication of any benefit in pre-specified subgroups based on age, physiological parameters or features of right heart dysfunction. The authors speculated that the study may have been underpowered to detect a significant difference in QOL in an advanced IPF cohort, particularly over a short study period. Certainly, at 24 weeks the reported difference in SGRQ score between the two groups had widened from –0.52 to –2.19, although secondary outcome measures like this were exploratory and statistical analysis was not presented. Patient-reported outcomes such as QOL measures are certainly valid alternatives to traditional endpoints in IPF, particularly where survival is so poor, however, there are limitations to their use. QOL is often considered a "noisy" signal, as symptom progression in IPF often has multiple contributors, such as co-morbidity. Additionally, many of the commonly used QOL tools, such as the SGRQ, were originally developed in airways disease, and evidence for their validity in IPF is less strong (7).

Several interesting observations were made in the secondary exploratory outcome measures in the INSTAGE study (6). There was a signal that the addition of sildenafil to nintedanib may slow FVC decline, with a smaller observed

change in FVC (–20.4 *vs.* –66.7 mL at 24 weeks) and fewer patients suffering a 5% absolute decline or death (31.4% *vs.* 50.7%). D_{LCO} decline also appeared to be reduced in the sildenafil group, although interestingly 6MWD, the primary outcome measure in the STEP-IPF study and a frequently used outcome in pulmonary hypertension trials (5), was not measured. It is unclear whether these observations were more pronounced in those patients with evidence of right heart dysfunction. It is tempting to speculate about the implications of these findings, however these results are purely exploratory and therefore must be interpreted with caution.

An encouraging observation from the study was that both nintedanib monotherapy and combination therapy were well tolerated in a severe IPF cohort (6). These patients were generally excluded from the original INPULSIS trials, although they did include patients with a D_{LCO} between 30% and 35% (8). This provides further useful evidence for the safety of nintedanib in severe IPF, an observation supported by real world studies (9,10). Likewise, this study suggests that using nintedanib and sildenafil in combination could be safe option in patients with IPF and associated pulmonary hypertension.

Despite INSTAGE being a negative study (6), this is not necessarily the end for sildenafil in IPF. A phase IIb study comparing the addition of sildenafil or placebo to pirfenidone in IPF patients is ongoing (11). This study will again target patients with advanced disease (D_{LCO} ≤40% predicted), but will also specifically recruit patients who are at risk of pulmonary hypertension secondary to lung disease. Running over 52 weeks, it will evaluate a combined endpoint of 6MWD decline, respiratory-related hospitalisations and all-cause mortality. This is one of a number of new studies evaluating novel therapies in more advanced disease, including tipelukast (NCT02503657) and co-trimoxazole (ISRCTN 17464641). Research into new treatments in IPF is rapidly evolving, and it is vital that those with advanced disease are not left behind.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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