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LETTER

Utility of nintedanib for severe idiopathic pulmonary fibrosis: a single-center retrospective study [Letter]

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Dear editor

We read with interest the study by Abe et al on the clinical utility of nintedanib in patients with severe idiopathic pulmonary fibrosis (IPF).[1] Based on the retrospective follow-up of 51 patients, the authors concluded that the survival benefit from nintedanib is reduced among patients with severe IPF (n=17) compared with those with mild-to-moderate IPF (n=34), but that the prognosis for patients with severe IPF is significantly better in those who remain on nintedanib for more than 3 months.

In our opinion, the study design does not allow conclusions to be drawn about the treatment effect of nintedanib on survival in patients with severe versus mild-to-moderate IPF. First, the two study groups present clinically meaningful differences at baseline; for example, mean body weight was significantly lower in patients with severe IPF (and body weight loss is associated with decreased survival time).[2] Second, a higher mortality rate among patients with severe IPF was to be expected independent of any pharmacological intervention, as lower FVC and lower diffusing capacity of the lungs for carbon monoxide (DL_{CO}) at baseline have been associated with a worse prognosis.[3] In addition, the study shows that patients with severe IPF had a greater FVC decline than those with mild-to-moderate IPF in the year before nintedanib administration. A higher decline in FVC over time has also been associated with a worse prognosis.[3] In the absence of an appropriate design (ie, a prospective, randomized, and placebo-controlled study), no definite conclusions can be drawn on the survival effects of nintedanib in patients with severe IPF.

The data presented by Abe et al show that initiation of nintedanib (150 mg twice daily) resulted in slower FVC decline in both mild-to-moderate and severe IPF populations, which suggest a beneficial effect of nintedanib independent of disease severity. These findings are consistent with data from the open-label extension trial INPULSIS-ON (NCT01619085)[4] and the INSTAGE trial (NCT02802345),[5] both of which suggest that IPF patients with more advanced functional impairment may receive the same benefit from nintedanib on reduction in FVC decline as those with less severe impairment. Furthermore, recently published real-world data from Korea[6] and Greece[7] also demonstrate that nintedanib reduces the rate of FVC decline in patients with more advanced IPF (FVC $\leq$50% or DL_{CO} $\leq$35% predicted).

Abe et al showed that survival was improved in patients with severe IPF who remained on nintedanib for more than 3 months, suggesting that permanence on treatment is an important therapeutic goal. As highlighted by Abe et al, management of adverse events related to nintedanib, as recommended in the prescribing information

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(including symptomatic treatment of diarrhea and close monitoring of liver enzyme levels), has the potential to allow patients to remain on treatment and derive long-term therapeutic benefits. Indeed, the adoption of a holistic approach to patient management, including nurse support and possible dosage adjustment, is important to maintain compliance and optimize long-term outcomes.

In conclusion, findings from real-world studies, even those lacking a control group or involving relatively few patients, can provide valuable clinical insights but should be interpreted in the context of data from large, randomized controlled clinical trials. The results reported by Abe et al reinforce the need for adequate adverse event management and suggest that nintedanib slows down disease progression independent of disease severity.

Disclosure

LO, JF, and MQ are employees of Boehringer Ingelheim. The authors report no other conflicts of interest in this communication.

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