Leveraging ageing models of pulmonary fibrosis: the efficacy of nintedanib in ageing

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Shareable abstract (@ERSpublications)
Although nintedanib is overwhelmingly prescribed to elderly patients, this is the first study to demonstrate that ageing does not impact the efficacy of nintedanib. This study sheds light on the utility of aged animal models in pulmonary fibrosis. https://bit.ly/3zA9RC5

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To the Editor:

Nintedanib is one of two US Food and Drug Administration (FDA)-approved treatments for idiopathic pulmonary fibrosis (IPF). The clinical efficacy of nintedanib for inhibiting the progression of lung fibrosis is well-established [1]. However, although nintedanib is overwhelmingly prescribed to elderly patients, the impact of ageing on its efficacy is difficult to discern from clinical data due to the magnitude of confounding variables that exist among human subjects (genetics, gender, comorbidities, disease stage at the onset of treatment, *etc*.). A recent *post hoc* meta-analysis of five IPF clinical trials suggested that the effect of nintedanib in reducing the rate of forced vital capacity decline is consistent across patients with age (patients >75 *versus* patients <75 years of age) [2]. However, it is important to note that the average age of IPF diagnosis is 66 years and the average patient ages in these cohorts were 78 (>75) *versus* 64 (<75) years. Further, one could argue that patients in both cohorts represent the elderly population. This study highlights the complexity of evaluating the impact of ageing on efficacy in a clinical setting. To date, all pre-clinical efficacy studies with nintedanib have been performed in young animals. We therefore sought to determine whether ageing impacts the efficacy of nintedanib for inhibiting the development of lung fibrosis. Bleomycin-induced lung injury in young (2 month) and aged (18 month) mice was followed by treatment with nintedanib or vehicle from day 10–21 (figure 1a), using a previously described protocol [3]. We previously demonstrated in this injury model that the severity of lung fibrosis is identical in young and aged mice, in terms of the net increase in total lung collagen following injury [4]. Although some prior studies have reported seemingly contradictory results, indicating increased severity of fibrosis in aged mice [5, 6], this discrepancy could be attributed to increased baseline levels of collagen in aged mice and the methodology/analyses used for fibrosis assessment, as the net increase in collagen appear to be similar in both young and aged mice [5, 6]. In line with our previous findings, both young and aged vehicle-treated mice demonstrated similar levels of fibrosis severity and a similar decline in lung function at 3 weeks post-injury (figure 1b–d, g–h). Also consistent with numerous prior reports [7, 8], we found that in young mice, nintedanib demonstrated efficacy for inhibiting the development of fibrosis (figure 1b–g) and led to improved lung function (figure 1h). Interestingly, nintedanib also significantly inhibited the development of lung fibrosis in aged mice, to a similar extent as young cohorts (figure 1b–g). Although

nintedanib treatment resulted in lung functional improvement to a similar extent in both young (49%) and aged (57%) mice (figure 1h), results did not reach statistical significance in aged mice. Of note, there is less than 47% power to detect mean differences between the aged-vehicle and aged-nintedanib groups given the observed effect and sample sizes of aged mice; the trending p-value of 0.06 is displayed to provide a better understanding of the results. No significant differences in survival rate were observed between nintedanib- *versus* vehicle-treated groups for both young (68% *versus* 72%, respectively) and aged mice (83% *versus* 76%, respectively) during this treatment period (day 10–21). Overall, these data indicate that ageing does not impact the efficacy of nintedanib in terms of its ability to inhibit the development of *de novo* lung fibrosis.