



## Safety and tolerability of nintedanib for the treatment of idiopathic pulmonary fibrosis in routine UK clinical practice

To the Editor:

Nintedanib, a tyrosine kinase inhibitor approved for the treatment of idiopathic pulmonary fibrosis (IPF), reduces annual forced vital capacity (FVC) decline in these patients by ~50% with combined analysis of data from clinical trials showing a trend towards reduction in mortality [1–3]. Nintedanib prescription criteria for the treatment of IPF vary between countries and in 2016, the National Institute for Health and Care Excellence approved nintedanib in England and Wales for patients with an FVC between 50% and 80% predicted [4]. Prior to this approval, nintedanib was available through a manufacturer-funded programme with varying prescribing criteria. We investigated the safety and tolerability of nintedanib in UK clinical practice during this period in which FVC prescription criteria differed from those now available in routine practice.

This was a multicentre cohort review across six National Health Service (NHS) hospital trusts. Data were collected from the clinical records of individuals eligible to commence nintedanib for the treatment of IPF between October 2014 and July 2015. During this period, nintedanib was provided through manufacturer-funded compassionate-use programmes, initially for those with an FVC >50% predicted, then for all patients with a diagnosis of IPF regardless of FVC, and finally for patients with an FVC >50% predicted who were intolerant of or could not be prescribed pirfenidone (*e.g.* FVC >80% predicted). All patients with an MDT diagnosis of IPF and a minimum of 12 months follow up (or who had discontinued nintedanib or died prior to this) were included. The most recent pulmonary function tests performed prior to starting nintedanib were used as baseline values. Nintedanib was prescribed according to the manufacturer's instructions. Patients were reviewed 3-monthly and data on adverse events, dose interruptions and/or dose changes collected.

Group comparisons were performed using t-tests, Mann–Whitney rank sum tests or Chi-squared tests as appropriate and logistic regression analysis evaluated clinical characteristics associated with nintedanib discontinuation. Statistical significance was defined as  $p < 0.05$ . Analyses were conducted using SPSS (version 22) for Mac (SPSS, Chicago, IL, USA). Results are reported as mean  $\pm$  SD or as n (%) as appropriate.

154 patients commenced nintedanib between October 2014 and July 2015; of these, 17 (11%) had a baseline FVC <50% predicted, 81 (52.6%) an FVC between  $\geq 50\%$  and <80% predicted, and 56 (36.4%) an FVC >80% predicted. The average age was  $71 \pm 7.9$  years and 124 (80.5%) were male. The pre-treatment average FVC was 72.6% predicted (range 35–137%,  $n=154$ ) and diffusing capacity of the lung for carbon monoxide was 43.3% predicted (range 19–95%,  $n=139$ ). 44 (28.6%) patients had domiciliary oxygen. The average time since IPF diagnosis was  $13.8 \pm 16.4$  months and 50 (32.5%) patients had received previous pirfenidone treatment.

At least one adverse event was reported by 77% of patients. The most common adverse events were gastrointestinal, including diarrhoea (67.5% of patients), nausea (52.6%) and reduced appetite (16.9%). Weight loss was reported by 14.3% of patients and elevations in liver function tests (alanine transaminase) greater than three times the upper limit of normal were identified in six (3.9%) patients.



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**In IPF, commencement of antifibrotic therapy in patients with preserved lung volume may increase the duration of therapy** <http://ow.ly/4HeM30IFS67>

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TABLE 1 Characteristics of patients continuing and discontinuing nintedanib in the year following commencement

Characteristic	Continued nintedanib	Discontinued nintedanib	p-value
<b>Patients n</b>	85	69	
<b>Age at treatment commencement years</b>	69.6±8.2	73.0±7.0	0.007
<b>Male</b>	69 (81.2)	55 (79.7)	0.819
<b>FVC % predicted</b>	77.1±17.2	67.0±18.8	0.001
<b>D<sub>lco</sub> % predicted</b>	45.2±14.6	40.6±14.8	0.07
<b>Domiciliary oxygen</b>	18 (21.2)	26 (37.7)	0.024
<b>Time since diagnosis months</b>	11.7±15.1	16.4±17.5	0.08
<b>Prior pirfenidone treatment</b>	23 (27.1)	27 (39.1)	0.112

Data are presented as mean±SD or n (%), unless otherwise stated. FVC: forced vital capacity; D<sub>LCO</sub>: diffusing capacity of the lung for carbon monoxide.

69 (44.8%) patients discontinued treatment over 12 months. 32 (46.8%) patients discontinued within the first 3 months of treatment, 12 (17.4%) following 3–6 months of treatment and 25 (36.2%) following 6–12 months of treatment. 34 (49.3%) out of 69 patients underwent a dose reduction before discontinuing nintedanib. 18 (11.8%) died, 12 (7.8%) patients discontinued as a consequence of non-diarrhoeal gastrointestinal side-effects and 11 (7.2%) discontinued as a result of diarrhoea. Two patients suffered an ischaemic stroke and one a myocardial infarction during the study period.

Comparison of characteristics of patients continuing and discontinuing nintedanib (table 1) identified lower pre-treatment FVC, older age and domiciliary oxygen to be associated with discontinuation. Multivariate regression analysis identified increasing age (regression coefficient 0.063,  $p < 0.001$ ) and decreasing FVC (regression coefficient  $-0.032$ ,  $p < 0.001$ ) at treatment commencement to be independently associated with nintedanib discontinuation. After 12 months, 23.5% (four out of 17) of patients with a baseline FVC  $< 50\%$  predicted, 51.8% (42 out of 81) with an FVC between  $\geq 50\%$  and  $< 80\%$  predicted, and 69.6% (39 out of 56) of patients with a baseline FVC  $> 80\%$  predicted continued nintedanib (figure 1). There was a nonsignificant trend toward discontinuation of nintedanib in those previously intolerant of pirfenidone ( $p = 0.112$ ).

Nintedanib was safe and generally well tolerated when used in routine practice, in keeping with other recent real-world experiences [5–7]. Discontinuation rates were higher than reported in clinical trials (44.8% at 12 months *c.f.* ~25% in INPULSIS) [3]. This could be related partly to the current cohort, which included 50 patients not tolerating pirfenidone and may therefore be enriched for patients with a propensity towards drug induced side-effects. The majority of adverse events were gastrointestinal with a low reported frequency of cardiovascular related events and deranged liver function. Discontinuation due to diarrhoea, at 7.2% (11 out of 154), was comparable to the INPULSIS trials where discontinuation due to diarrhoea was ~5%.

Recently, in a cohort of 57 patients followed for an average of 42 weeks, GALLI *et al.* [7] identified no association between nintedanib discontinuation and FVC when stratifying patients with an FVC  $> 50\%$  or

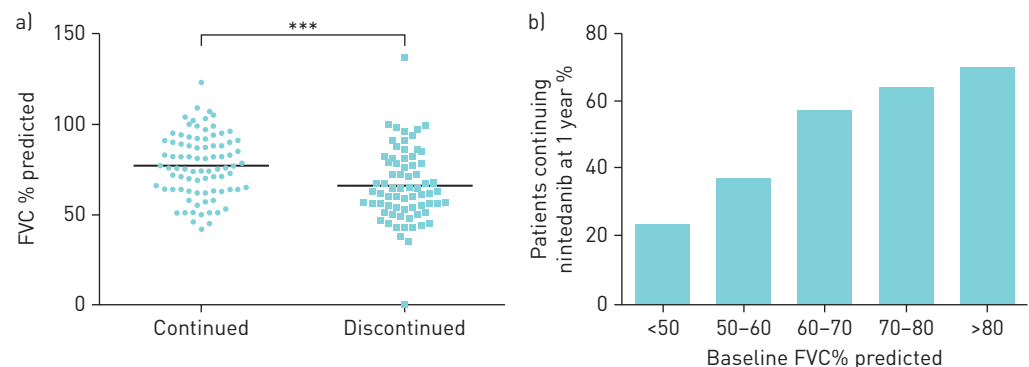


FIGURE 1 Baseline forced vital capacity (FVC) % predicted of patients continuing and discontinuing nintedanib during the year following commencement. a) Individual patient data. b) Stratified by FVC. \*\*\*:  $p < 0.001$ .

<50% predicted. Within our larger cohort, after 52 weeks of follow-up, however, increasing age and decreasing pre-treatment FVC were independently associated with discontinuation of nintedanib. The high drug discontinuation rate of 76.5% identified in the subgroup with FVC <50% predicted suggests that careful informed patient discussion is required prior to treatment commencement in this patient group. No predominant reason for discontinuation was identified in this group with no clear increase in mortality as a reason for discontinuation. It is possible in this group, the preceding longer duration of disease burden limits tolerance to any side-effects and so increases the likelihood of discontinuation.

This study has a number of limitations. It has not considered comorbid medical conditions and FVC eligibility criteria differed during the period studied. However, this has enabled the study of a real-world patient population with FVC values now excluded from routine clinical practice within England. The drug was tolerated best in the “high” FVC subgroup (>80% predicted), a significant group currently excluded from NHS-funded treatment in England and Wales. This is despite evidence demonstrating effectiveness of nintedanib in a *post hoc* subgroup analysis of those with FVC >80% predicted from the INPULSIS study [8].

Increasing age and decreasing pre-treatment FVC are associated with increased probability of discontinuation during 52 weeks of treatment. A prospective study is required to further investigate these real-world findings that suggest that commencement of antifibrotic therapy in patients with preserved lung volume (FVC >80% predicted) may increase the duration of therapy for an individual patient. This would be anticipated to lengthen the period with preserved functional capacity and quality of life, and improve mortality in this chronic invariably progressive disease.

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