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

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**Take home message:** In IPFcommencement of anti-fibrotic therapy in patients with preserved lung volume may increase the duration of therapy

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**Competing interest statement:**

SVF reports funding to attend conferences, speaker fees and fees for advisory boards from Roche and Boehringer Ingelheim outside of the submitted work. EAR reports personal fees from Boehringer Ingelheim, Roche and Takeda outside of the submitted work. HP reports personal fees for consultancy work from Boehringer Ingelheim and Roche outside of the submitted work and and non-financial support for conference attendance from Boehringer Ingelheim and Roche. RKH reports support for an ILD specialist nurse (part time) outside of the submitted work. KS reports personal fees from Boehringer ingelheim and Roche outside of the submitted work. MT has received travel scholarships and consultancy fees from Boehringer Ingelheim and Roche outside of the submitted work. VT reports personal fees from Roche Nurse Advisory Board outside of the submitted work. TMM has, via his institution, received industry-academic funding from GlaxoSmithKline R&D and UCB and has received consultancy or speakers fees from Apellis, Astra Zeneca, Bayer, Biogen Idec, Boehringer Ingelheim, Cipla, GlaxoSmithKline R&D, InterMune, ProMetic, Roche, Sanofi-Aventis, Sanumed and UCB outside of the submitted work. CJB reports non-financial support for conference attendance from Boehringer Ingelheim. AUW reports personal fees from Intermune/Roche, Boehringer Ingelheim, Bayer, and Gilead outside of the submitted work. LR reports grants and personal fees from InterMune, and personal fees from Medimmune, Biogen, Sanofi-Aventis, Roche, ImmuneWorks, Shionogi, Boehringer Ingelheim, Celgene, Nitto, and FibroGen outside of the submitted work. LGS reports personal fees outside of the submitted work and non-financial support to attend conferences from Boehringer Ingelheim and Roche. All other authors have no competing interests to disclose.

**Funding:** None

**MAIN TEXT WORD COUNT:** 978

**NUMBER OF FIGURES:** 1

**NUMBER OF TABLES:** 1

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 approximately 50%, with combined analysis of data from clinical trials showing a trend towards reduction in mortality.1,2,3 Nintedanib prescription criteria for the treatment of IPF vary between countries, and in 2016 the National Institute for Health and Care Excellence (NICE) 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 safety and tolerability of nintedanib in UK clinical practice during this period where FVC prescription criteria differed from those now available in routine practice.

This was a multi-centre cohort review across 6 National Health Service (NHS) hospital trusts. Data were collected from 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% who were intolerant of, or could not be prescribed, pirfenidone (e.g. FVC>80%). 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 for baseline values. Nintedanib was prescribed according to manufacturer’s instructions. Patients were reviewed three monthly and data on adverse events, dose interruptions and/or dose changes collected.

Group comparisons were performed using t test, or Mann-Whitney rank sum test, or chi-square test 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 (V.22) for Mac (SPSS, Chicago, Illinois, USA). Results are reported as mean +/- SD or as a number with %, as appropriate.

154 patients commenced nintedanib between October 2014 and July 2015; of these 17 (11%) had a baseline FVC<50%, 81 (52.6%) an FVC between ≥50% and <80%, and 56 (36.4%) an FVC>80%. Average age was 71 ± 7.9 years, and 124 (80.5%) were male. Pre-treatment average FVC was 72.6% (range 35 - 137, n =154) and DLCO was 43.3% (range 19 - 95, n=139). 44 (28.6%) patients had domiciliary oxygen. Average time since IPF diagnosis was 13.8 ±16.4 months, and 50 (32.5%) of patients had received previous pirfenidone treatment.

At least one adverse event (AE) 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 (ALT) greater than 3 times the upper limit of normal identified in 6 patients (3.9%).

69 patients (44.8%) discontinued treatment over 12 months. 32 (46.8%) patients discontinued within the first 3 months of treatment, 12 (17.4%) following 3 to 6 months of treatment, and 25 (36.2%) following 6 to 12 months of treatment. 34/69 (49.3%) 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% (4/17) of patients with a baseline FVC<50%, 51.8% (42/81) with an FVC between ≥50% and <80%, and 69.6% (39/56) of patients with a baseline FVC>80%, continued nintedanib (Figure 1). There was a non-significant trend to 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 experiences5-7. Discontinuation rates were higher than reported in clinical trials (44.8% at 12 months c.f. to ~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 GI related, with a low reported frequency of cardiovascular related events and deranged liver function. Discontinuation due to diarrhoea at 7.2% (11/154) was comparable to the INPULSIS trials where discontinuation due to diarrhoea was approximately 5%.

Recently, in a cohort of 57 patients followed for an average of 42 weeks Galli *et al* identified no association between nintedanib discontinuation and FVC when stratifying patients with an FVC greater than or less than 50% predicted.7 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 sub group with FVC <50% 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 for any side effects and so increases likelihood of discontinuation.

This study has a number of limitations. It has not considered co-morbid 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 sub group (>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% 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 which suggest that commencement of anti-fibrotic therapy in patients with preserved lung volume (FVC>80%) 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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**Table 1. Characteristics of patients continuing and discontinuing nintedanib in the year following commencement.**

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| --- | --- | --- | --- |
| **Characteristic** | **Continued nintedanib**  **(n=85)** | **Discontinued nintedanib**  **(n=69)** | **p-value** |
| Age at treatment commencement - Yr  (Mean ± S.D.) | 69.6 ± 8.2 | 73.0 ± 7.0 | 0.007 |
| Male sex – no. (%) | 69 (81.2) | 55 (79.7) | 0.819 |
| FVC % of predicted value  (Mean ± S.D.) | 77.1 ± 17.2 | 67.0 ± 18.8 | 0.001 |
| DLCO % of predicted value  (Mean ± S.D.) | 45.2 ± 14.6 | 40.6 ± 14.8 | 0.07 |
| Domiciliary Oxygen – no. (%) | 18 (21.2%) | 26 (37.7) | 0.024 |
| Time since diagnosis - months  (Mean ± S.D.)  Prior Pirfenidone treatment – no. (%) | 11.7 ± 15.1  23 (27.1%) | 16.4 ± 17.5  27 (39.1%) | 0.08  0.112 |

**Abbreviations: Yr, years; Mth, months; S.D., standard deviation**

**Figure 1. Baseline forced vital capacity (% predicted) of patients continuing and discontinuing nintedanib during the year following commencement.**

