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Early View

Research letter

Safety and tolerability of nintedanib in patients with IPF in the United States

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Safety and tolerability of nintedanib in patients with IPF in the United States

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Take-home message: The safety and tolerability profile of nintedanib in the clinical setting is consistent with the product label.

Nintedanib has been approved for the treatment of IPF in more than 60 countries, including the US [1]. In the two Phase III INPULSIS® trials, nintedanib reduced disease progression by reducing decline in forced vital capacity [2]. Most patients were able to manage the side effects of nintedanib, with 19.3% of patients treated with nintedanib versus 13.0% treated with placebo permanently discontinuing study medication due to adverse events. The most frequent adverse events were gastrointestinal, particularly diarrhoea. The proportion of patients who had ≥1 serious adverse event was similar between nintedanib and placebo (30.4% vs 30.0%).

Following the launch of nintedanib as a treatment for IPF, information on its safety and tolerability in the real-world setting has been collected via post-marketing surveillance. Here we report an analysis of data collected in the US between the launch of nintedanib on 15 October 2014 and 31 October 2015. Data on adverse events in patients with IPF treated with nintedanib, irrespective of causality, were collected via proactive communications with specialty pharmacies and a spontaneous reporting system. In addition, reports of adverse events were collected via direct contact with patients and caregivers as part of a patient support programme (OPEN DOORS™). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Based on the mechanism of action of nintedanib and data from the INPULSIS® trials, adverse events of interest in the post-marketing surveillance data were defined as diarrhoea, bleeding, hepatic disorders, arterial hypertension, major adverse cardiovascular events (MACE), myocardial infarction (MI), and stroke. For the purposes of this post marketing safety analysis, the rates of these adverse events were assessed using the same definitions as used in the INPULSIS® trials. Epidemiological data on the incidence of diarrhoea (in the general population) and other adverse events of interest (in unmatched patients with IPF) were obtained from literature [3–9] and from a proprietary research database of patients representative of the commercially insured population of the US [10].

Our post-marketing surveillance data came from 6758 patients with IPF treated with nintedanib. Median duration of exposure was 113 days (range 6–390 days). Estimated cumulative exposure was 2715 patient–years. Diarrhoea (2858 events [not individuals reporting at least one event], nausea (1476 events) and vomiting (705 events) were the most frequent adverse events. Most (95.0%) adverse events were non-serious. A total of 4062 adverse events defined as of interest in the post-marketing surveillance data were reported. Of these, 322 had a fatal outcome, including 27 cases of MACE, eight of MI, three of stroke, and two of bleeding. In 123 cases, the cause of death was not reported. The most frequent causes of death that were

reported were progression of IPF (81 cases), respiratory failure (27 cases) and pulmonary fibrosis (18 cases).

The incidence of diarrhoea in the post-marketing surveillance data was 1053 per 1000 patient–years. Understanding that diarrhoea is a very common side effect of nintedanib therapy, this was lower than the rate reported in INPULSIS® (1331 per 1000 patient–years) and similar to the rate in epidemiological data from the general population (980 per 1000 patient–years) [5–8] (Figure 1A).

Based on its inhibition of VEGFR, nintedanib may increase the risk of bleeding. Patients at known risk for bleeding, including those treated with full-dose anticoagulants or high-dose antiplatelet therapy, were excluded from clinical trials, and the US product label specifies that patients at known risk for bleeding should receive nintedanib only if the anticipated benefit outweighs the potential risk [1]. The incidence of bleeding events in the post-marketing surveillance data was similar to that in INPULSIS® (119 vs 118 per 1000 patient–years). Most bleeding events were non-serious; the most frequent were epistaxis, contusion and rectal haemorrhage. The rate of bleeding events in patients with IPF based on healthcare claims data was lower than in the post-marketing surveillance data (Figure 1B). This was not unexpected, as bleeding events that are not severe enough for a patient to seek medical attention (e.g. epistaxis) are generally not captured in claims-based data. Not surprisingly, known use of anticoagulants was higher in patients with bleeding than non-bleeding adverse events. Of 324 cases of bleeding in the post-marketing surveillance data, concomitant use of anticoagulants was reported in 37.7% and was unknown in 34.3% of cases. Of 4739 adverse events that were not bleeding, concomitant use of anticoagulants was reported in 25.4% and was unknown in 46.3% of cases.

In the INPULSIS® trials, cardiac disorder adverse events were reported in 10.0% and 10.6% of patients treated with nintedanib and placebo, respectively, but there was a numerical imbalance in the proportion of patients with MI based on the standardised MedDRA query “myocardial infarction” (2.7% versus 1.2%, respectively) [11]. The US product label for nintedanib states that caution should be exercised in patients at higher cardiovascular risk [1]. The incidence of MI in the post-marketing surveillance data (10 per 1000 patient–years) was lower than in INPULSIS® (17 per 1000 patient–years) or in epidemiological data from unmatched patients with IPF (22 per 1000 patient–years) [4,7,10]. The incidence of MACE was lower than in INPULSIS® (29 vs 39 per 1000 patient–years) (Figure 1B). The incidence of hypertension in the post-marketing surveillance data was similar to that in INPULSIS® (74 and 57 per 1000 patient–years, respectively) and lower than in epidemiological data from

unmatched patients with IPF (229 per 1000 patient–years) [10]. The incidence of stroke reported in the post-marketing surveillance data was similar to that reported in INPULSIS® (14 and 10 per 1000 patient–years, respectively) and lower than in epidemiological data from unmatched patients with IPF (34 per 1000 patient–years) [7,9,10]. The incidence of hepatic disorders (78 per 1000 patient–years) was lower than that in INPULSIS® (162 per 1000 patient–years), perhaps reflecting less frequent measurement of liver enzymes.

Randomised controlled clinical trials provide the most robust data on the safety and tolerability of a drug in a specific patient population, but are necessarily of short duration and conducted in a population that is not fully representative of potential drug recipients. Post-marketing surveillance studies provide further data on the safety and tolerability of a drug and help quantify rare adverse event rates [12–14]. However, post-marketing surveillance studies have a number of limitations, including under-reporting of non-serious adverse events [13,15] and a lack of comprehensive documentation on adverse events, their outcomes (including dose adjustments and permanent discontinuations) and the characteristics of the patients who reported them. The relatively short median duration of exposure in this set of post-marketing data (113 days) should be noted as a limitation but data continue to be collected. Differences in methodologies mean that comparisons of data from post-marketing surveillance, clinical trials and epidemiological studies should be approached with caution. In addition, clinicians in practice may offer prescriptions with a safety bias, resulting in lower rates of certain adverse events in clinical practice than in clinical trials.

In conclusion, post-marketing surveillance data collected for approximately one year after the US launch of nintedanib as a treatment for IPF suggest that the safety and tolerability profile of nintedanib in the real-world clinical setting is consistent with the product label. As in clinical trials, the most frequent adverse events reported in clinical practice were non-serious gastrointestinal events, particularly diarrhoea.

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Figure legends

Figure 1A. Incidence rates of diarrhoea across populations

Figure 1B. Incidence rates of other adverse events of interest across populations

No data from epidemiological studies on hepatic disorders or MACE was available from the published literature. MACE, major adverse cardiovascular events. *Range 53–229 [3,6,7,10]; †[10]; ‡Range 14–22 [4,7,10]; §Range 11–34 [7,9,10].