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REVIEW

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Nintedanib — efficacy, safety and practical aspects of treatment for patients with idiopathic pulmonary fibrosis

Abstract

Idiopathic pulmonary fibrosis (IPF) is a rare disease with progressive course and a very unfavourable prognosis. Antifibrotic drugs are a chance to reduce the rate of disease progression and extend the life of IPF patients. One of these drugs is nintedanib, an oral tyrosine kinase inhibitor. In the following article, the reader will find a summary of current knowledge on the efficacy and safety of nintedanib treatment of IPF patients. This study uses data from pivotal studies and experience from everyday clinical practice indicating a wide range of possible applications of the drug in IPF patients.

Key words: idiopathic pulmonary fibrosis; antifibrotic treatments; nintedanib; effectiveness; safety; clinical practice

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Introduction

Idiopathic pulmonary fibrosis (IPF) is one of interstitial lung diseases (ILDs), which are rare illnesses. However, in clinical practice, IPF is probably the second most common ILD and the most frequent idiopathic interstitial pneumonia (IIP) with a chronic, fibrosing course. It is estimated that the annual incidence of IPF in Poland is approximately 1600–1800 cases, and the prevalence is about 5000–6000 [1].

The disease is progressive and causes an increasing degradation of lung function and, despite varying (and unpredictable) dynamics, ultimately and inevitably leads to death [2-4]. The median survival rate, estimated at 3–5 years in the natural course of the disease, is shorter than in many malignancies [5, 6]. The progress of studies on understanding the pathogenesis of IPF and the results of numerous clinical trials, which have shown a positive effect on decelerating the progress of the disease with the use of two antifibrotic drugs, pirfenidone and nintedanib, raise hope for improvement in prognosis.

This paper will focus on the practical aspects of treatment of IPF with nintedanib.

Nintedanib has been approved and registered by the US FDA (United States Food and Drug Administration) in October 2014, and by the EMA (European Medicines Agency) in January 2015 based on the results of Phase II (TOMORROW) and Phase III (INPULSIS-1 and INPULSIS-2) clinical studies [7, 8]. Randomised clinical trials, which demonstrated both the efficacy and safety of nintedanib in the therapy of IPF patients, were essential for the approval of the drug; however, the experience gathered in the following years, observations from everyday ("real-life") practice, are no less important and valuable.

Drug availability and eligibility criteria for treatment vary from country to country. In Poland, nintedanib has been available under the National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*) reimbursement programme since March 2018.

The efficacy of IPF treatment with nintedanib

Nintedanib is an oral tyrosine kinase inhibitor with a multipoint mechanism of action, including the inhibitory effect on vascular endothelial growth factor receptors (VEGFR 1–3), plateletderived growth factor receptors (PDGFR α and β),

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and fibroblast growth factor receptors (FGFR 1–3) involved in the pathogenesis of IPF [7].

The results of clinical trials (TOMMOROW, INPULSIS-1, INPULSIS-2), conducted for the approval of the drug, confirmed that treatment with nintedanib significantly reduces the annual decrease in forced vital capacity (FVC), which was the main endpoint of these studies, indicating the efficacy in decelerating the progress of the disease.

Efficacy of nintedanib in relation to the stage of the disease

Post hoc analyses of databases collected in nintedanib registration studies have shown a beneficial effect of treatment in patients at different stages of the disease. It was demonstrated that, due to the progressive nature of the disease, in patients with IPF who do not have significant functional impairment (FVC > 90% of predicted value) and in patients without signs of honeycombing on highresolution computed tomography (HRCT) who had not undergone lung biopsy, a decline in lung function comparable to that in patients with more advanced disease may be observed [9]. This decline was significantly smaller in patients treated with nintedanib when compared to the placebo group [9, 10]. The situation is analogous for patients with more advanced disease, where the efficacy of treatment with nintedanib was comparable in patients with the baseline lung diffusion for carbon monoxide ($D_{L,co}$) ≤ 40% pred. compared to patients with $D_{L,co}$ > 40% pred. [11], as well as for patients with FVC ≤ 70% pred. *vs* those with FVC > 70% pred. [12]. Further observation in the postmarketing study INPULSIS-ON allowed to demonstrate the benefits of treatment with nintedanib also in patients with more advanced IPF at the onset of treatment, with FVC < 50% pred. [13]. More data indicating comparable efficacy of nintedanib treatment in subjects with less and more impaired lung function ($D_{L,co}$ < 35% pred.) were provided by the INSTAGE study [14]. Although this was an additional observation not included in the project objectives, it is an important finding and a reason for further targeted research to extend the indications for nintedanib regardless of the initial FVC or $D_{L,co}$ values, also in patients with more advanced lung fibrosis [15].

Reduction of acute IPF exacerbations

Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a condition defined as a rapid respiratory deterioration (occurring within one month), which cannot be explained by causative factors other than IPF (such as infection, pulmonary embolism, pneumothorax, or exacerbation of heart failure) and is accompanied by the appearance of new interstitial lesions with ground glass opacity in CT scans [16, 17]. The incidence of AE-IPF varied between the studies. Over a one-year follow-up, it ranged between 6 and 16%, but over a 3-year period, it affected from 20 to over 50% of IPF patients [18–20]. AE-IPF significantly worsens the prognosis as the mortality rate reaches 50%, regardless of the therapy applied [18].

Treatment with nintedanib seems to play a role not only in preventing the progress of lung function decline but also in risk reduction of AE-IPF. The INPULSIS-2 study found a significant extension of the time to the first acute exacerbation of the disease observed by the investigators during treatment with nintedanib [8]. The analysis of combined data from three clinical trials (TOMORROW, INPULSIS-1 and 2) showed a lower incidence of AE-IPF among patients treated with nintedanib compared to those receiving placebo (4.6 *vs* 8.7%) [21]. Further observation of patients with IPF treated with nintedanib in the INPULSIS-ON study confirmed the reduction of the risk of AE-IPF [13].

There are also reports indicating a beneficial effect of nintedanib on the natural course of AE-IPF [22]. This outcome, very attractive from the practical point of view, requires evaluation in randomised, prospective studies.

Efficacy of nintedanib in longterm treatment

The results of the already mentioned open-label study INPULSIS-ON suggest that the impact of nintedanib on slowing down the progress of IPF may last for over 5 years. This longterm continuation of nintedanib treatment was associated with a favourable safety and tolerability profile, as no new side effects that could limit the treatment were identified [13].

Effect of treatment with nintedanib on survival

Undoubtedly, the most important and anticipated therapeutic effect of any treatment is improvement in survival. In IPF, such a fully reliable assessment of this endpoint has not been possible so far and most likely, due to methodological limitations, will not be possible at all. The post hoc analysis of nintedanib registration studies showed a 30% (but without statistical significance) reduction in all cause mortality and

respiratory mortality compared to placebo [21]. Simultaneously, a significant, 43% reduction in mortality during nintedanib treatment has been demonstrated [21]. Also, the analyses of available observational studies and data from IPF patient registries show a significantly better prognosis among patients treated with antifibrotic agents compared to those who did not receive such treatment [23].

The results of an analysis of pooled data from 6 clinical trials, based on which a mathematical model was developed, are also optimistic; the average improvement in survival in patients treated with nintedanib compared to the placebo group is estimated at nearly 8 years (11.6 *vs* 3.7), and median survival is improved by 5.2 years (8.5 *vs* 3.3) [24]. No less promising are the results of a retrospective analysis of the population of 2745 patients with IPF included in the international register EMPIRE (which also includes Polish patients), presented at the congress of the European Respiratory Society (ERS) in 2019 and confirming a significant increase in overall and progression-free survival in patients treated with antifibrotic drugs as compared to untreated patients [25]. In the analysed group, the prognosis was more favourable for patients treated with nintedanib and those who changed one antifibrotic drug to the other. Nevertheless, in view of the limitations of this analysis, no definitive, generalised conclusions may be drawn [25].

Safety of IPF treatment with nintedanib

The most common side effects in pre- and post-marketing studies and recommendations for their management

Therapy with nintedanib, like any other drug, may be associated with side effects, which occurred in the majority of patients in the registration studies [7, 8]. Gastrointestinal adverse events were the most frequently reported, including diarrhoea that occurred in over 60% of patients [13]. In the registration studies, symptomatic management (medication, but also appropriate diet, hydration, probiotics, drug intake with a meal) allowed to control the symptoms in the majority (80%) of the subjects without the need to reduce the dose or discontinue treatment, which was also confirmed by later observations from everyday clinical practice [26–29]. In justified cases, there may be a need to reduce the dose or even temporarily discontinue the treatment; however, as shown by analyses from clinical studies, this does not adversely affect the effectiveness of antifibrotic treatment with nintedanib [13]. Persistent diarrhoea was the reason for discontinuation of further treatment in only less than 5% of the cases in the registration studies, and up to 11% in later observations from daily clinical practice [8, 13, 27–31]. Other, less common gastrointestinal side effects, including nausea, vomiting, loss of appetite, weight loss, hepatotoxicity, occurred much less frequently and occasionally caused clinically significant toxicity that precluded continuation of the treatment.

Due to the mechanism of action of nintedanib, the summary of product characteristics (SPC) states that the therapy may involve an increased risk of bleeding. In the INPULSIS studies, the percentage of patients with bleeding-related adverse events was slightly higher in the nintedanib arm (10.3%) than in the placebo arm (7.8%). However, these were usually minor nose bleeds or increased bruising with small injuries. The incidence of serious bleeding was very low and comparable to that observed in the group receiving placebo [26]. Post-marketing studies confirmed low bleeding rates (overall < 5%, serious < 1%) [13, 32].

Although longterm studies and real-life observations show a similar (and sometimes even better) safety profile compared to registration studies, the percentage of patients who discontinued treatment due to side effects varied from 11% to 28%, and in the nearly 5-year observation, it was as high as 40%, which could depend, among other things, on the experience of a given centre with the management of side effects [13, 27, 29, 31, 33, 34].

An important link was also demonstrated between early termination of treatment with nintedanib and low body mass index (BMI) [35]. Therefore, choosing the target well tolerated dose of nintedanib, particularly in patients with low body weight, may require the calculation of body surface area, as shown by the Japanese experience, where such management had reduced the incidence of hepatotoxicity and increased the percentage of patients who continued treatment [36].

Safety of treatment and cardiovascular diseases

Cardiovascular diseases are among the most common diseases in the general population, so it is not surprising that they are also present in patients with IPF. Subjects after recent cardiovascular incidents (such as stroke or myocardial infarction) were excluded from the registration studies, yet as many as 90%, regardless of whether

or not they received antifibrotic therapy, were at high risk of cardiovascular diseases [37]. It is noteworthy that the incidence of major adverse cardiovascular events (MACE) was comparable in patients treated with nintedanib and those receiving placebo, irrespective of the presence of elevated cardiovascular risk at baseline [37].

Although the INPULSIS studies showed a slightly higher percentage of patients with myocardial infarction in the nintedanib group than in the placebo group (2.7% *vs* 1.2%, respectively), other manifestations of ischaemic heart disease were less frequent (1.7% *vs* 3.1%, respectively) [26].

Several years of observation from the INPULSIS-ON study and from daily clinical practice have not revealed any new cardiovascular risks, and the use of nintedanib has not increased the incidence of acute coronary events in the treated population [13, 28, 29, 34]. In studies with nintedanib, both in IPF and oncological patients (who received a higher dose, 2 × 200 mg), there was no clinically significant prolongation of QT interval either [38].

The collective experience and available data allowed to formulate expert recommendations, indicating the possibility of safe use of nintedanib also in patients with cardiovascular diseases, including stable ischaemic heart disease, hypertension, or even some arrhythmias and valvular heart disease (not requiring full anticoagulation treatment with oral vitamin K antagonists), provided that the patient is carefully assessed and monitored with caution [39].

Safety of treatment in patients on anticoagulation therapy

Due to the mechanism of action of nintedanib, which includes inhibition of the VEGF receptor, nintedanib may potentially increase the risk of bleeding; therefore, patients with known increased risk of bleeding (including those receiving full anticoagulant or dual antiplatelet therapy) were *a priori* not included in the registration studies [40]. This led to the recommendation that individuals with a known risk of bleeding should only be treated with nintedanib, if the expected benefits outweigh the potential risks. Taking into account the prognosis in patients with IPF resulting from the natural course of the disease, without antifibrotic treatment, such a recommendation is very questionable and difficult to evaluate in an unequivocal and objective, standardised manner. This is especially true since in everyday practice, with passing time, the increasing experience from real-life observations in populations treated with nintedanib, more than 10% of the patients turn out to receive concomitant anticoagulation therapy, in individual cases with dual antiplatelet therapy [41–43], and bleeding events are very rare. For example, in an observational study involving 64 patients treated with nintedanib in Germany, nearly half of the subjects received concomitant anticoagulant therapy, and nearly 5% were treated with both acetylsalicylic acid (ASA) and an anticoagulant. During the observation, which lasted 11 months on average, only 1 case of bleeding was reported [34]. The choice of the anticoagulant is not without significance. Classic oral anticoagulants, i.e. vitamin K antagonists (VKA), are not the optimal choice for patients with IPF, as there are data indicating an increased risk of mortality associated with such treatment [44, 45]. This was even the reason to discontinue a clinical study on the use of warfarin in the treatment of patients with IPF [46]. Novel oral anticoagulants (NOACs), including dabigatran, which has a relatively short half-life and an antidote is available in case of side effects, seem to have the best safety profile. Moreover, additional beneficial consequences for patients with IPF cannot be excluded, which may be associated with the effects on the reduction of procollagen and collagen and the inhibition of fibroblast proliferation, as indicated by the preliminary results of *in vitro* and *in vivo* laboratory tests [47–49]. On the other hand, however, the increased risk of bleeding during NOAC treatment, including gastrointestinal bleeding, should not be underestimated; this is particularly important with simultaneous nintedanib use. Further research is needed to assess this risk.

Safety of treatment and planned surgery

Theoretically, due to its mechanism of action, nintedanib may increase the risk of bleeding and impaired healing of wounds. However, there is insufficient evidence to support such concerns. Observations from daily practice regarding patients treated with nintedanib who required urgent surgical treatment do not indicate any delay in wound healing. Retrospective experience from centres performing lung transplantation in IPF patients indicate that antifibrotic treatment (also with nintedanib), continued until the time of surgery, was not associated with an increased number of perioperative complications, bleeding, wound healing delay or vascular anastomoses [50–53]. According to the position of the international group of experts, emergency surgery or minor elective surgery does not require the

discontinuation of nintedanib treatment earlier than on the day preceding the surgery [39]. In the case of major elective surgeries (particularly abdominal surgery), the treatment should be discontinued 2–3 days prior to the procedure. The therapy should be resumed with oral feeding. In case of IPF patients waiting for lung transplantation, in addition to the potential risk of the above mentioned perioperative complications that may potentially be associated with nintedanib treatment, a higher risk of AE-IPF resulting from discontinuation of such treatment should also be considered. The authors agree with the position presented by Bendstrup *et al*. that in patients awaiting transplantation, antifibrotic treatment with nintedanib should be continued in order to maintain the best possible lung function and prevent AE-IPF [39]. There is no evidence-based data indicating the benefit of switching from nintedanib to pirfenidone prior to surgical procedures in order to reduce the risk of bleeding complications; in particular, such an approach is not recommended in patients with good tolerance and good response to treatment with nintedanib. Moreover, such a switch may result in a deterioration of antifibrotic treatment efficacy or even its intolerance.

Nintedanib in the population of IPF patients with lung cancer

In addition to age, gender and smoking, IPF itself is one of the risk factors for lung cancer, and the risk increases with the duration of the disease [54]. For this reason, the management of patients with IPF should include the, so called, oncological vigilance which means monitoring of the dynamics of focal lesions in the lungs. The incidence of lung cancer in IPF patients is significantly higher than in the general population, it is estimated at 2.7 to 48%, 13.5% on average with a nine-fold higher incidence in men than in women [54, 55]. Cancer is more often located in areas with fibrosis, i.e. it occupies the peripheral fields, especially in the inferior lobes. Unlike in the general population, squamous cell carcinoma is more common than adenocarcinoma [56, 57]. Lung cancer significantly worsens the prognosis of patients with IPF, with a 7-fold increased risk of death [58]. Nevertheless, the main, dominating cause of death of patients with IPF is the progression of lung fibrosis itself [58]. In addition to its antifibrotic activity, nintedanib has been used as a tyrosine kinase inhibitor in the treatment of lung adenocarcinoma, improving the time to progression as well as the survival of patients [59, 60]. There have been reports suggesting that treatment with nintedanib may be beneficial not only in slowing down fibrosis in patients with IPF, but also in inhibiting the development of cancer in these patients, although these findings need to be confirmed [61, 62] . There are still no standardised recommendations for diagnostic and therapeutic management in patients with concomitant IPF and lung cancer. This group of patients has been excluded from clinical trials, and many drugs currently used in chemo- and immuno-therapy are contraindicated in interstitial lung diseases, including IPF. It is believed that any form of oncological treatment (both surgical and chemo- or radio-therapy) increases the risk of AE-IPF [63–66]. The possibility of using chemotherapy in patients with IPF with coexisting lung cancer is particularly limited due to the increased risk of worsening of interstitial lesions (leading to AE-IPF) as well as due to lower performance status associated with IPF or other comorbidities. The current provisions of the NFZ drug program do not limit the possibility of nintedanib treatment in IPF patients with coexisting lung cancer, or continuation of therapy in case of appearance of a focal lesion of undetermined character in the lung. There have been single reports indicating the effectiveness of monotherapy with nintedanib in inhibiting the growth of nonsmall cell lung cancer in IPF patients [61, 62]. However, further research is needed in this area. According to current knowledge, lung cancer in a patient with IPF need not be a contraindication for nintedanib treatment, and the attending pulmonologist, preferably in consultation with an oncologist and/or oncologic surgeon, should evaluate the benefits of such management after considering the prognosis.

General rules on qualification for treatment and monitoring

The choice of antifibrotic therapy should take into account the presence of contraindications, comorbidities, the drugs used, but also the patient's preferences. In case of nintedanib, allergy to peanuts and soya should be excluded in the first place. The drug should not be used in persons with moderate to severe liver impairment either (Child Pugh B and C).

For IPF treatment, the recommended therapeutic dose of nintedanib is 300 mg per day (150 mg every 12 hours). In case of undesirable effects, symptomatic treatment and, if necessary, reduction of the drug dose to 200 mg per day

(2 × 100 mg) or temporary discontinuation of therapy is recommended.

The general rules of conduct before starting treatment should include the assessment of the following:

— cardiovascular risk,
— blood pressure,
— ECG (with QT interval measurement before and during treatment).

The drug should be used in accordance with the SPC.

To receive treatment in the NFZ drug program, the patient must meet all eligibility criteria in the absence of exclusion criteria.

As mentioned earlier, clinical situations such as stable ischaemic heart disease, atrial fibrillation, or controlled hypertension are not contraindications for the treatment, but they require special attention and close monitoring [39]. In patients with cardiac arrhythmias, if possible, the treatment should be modified to avoid concomitant use of any QT-prolonging drugs. Such schedule not be possible, a control ECG is recommended within a week from the onset of nintedanib treatment. In case of gastrointestinal adverse events, dyselectrolytemia, which may further intensify cardiac and conduction disorders, should be managed with no delay.

Situations in which it is absolutely necessary to discontinue (or not to start treatment with) the drug include as follows:

— exacerbation of ischaemic heart disease,
— full anticoagulation and dual antiplatelet treatment*,
— stent implantation**,
— QT interval > 470 ms (if the patient is receiving antiarrhythmic therapy, the treatment should be verified, and possibly modified, e.g. if the antiarrhythmic drug prolongs the QT interval; followup ECG is necessary),
— major elective surgery (2–3 days in advance).

*Data on the concomitant use of nintedanib and anticoagulants and antiplatelet agents are limited. According to the current state of knowledge and based on the available data, it seems that patients receiving antifibrotic therapy with nintedanib should not be treated with VKA or dual antiplatelet therapy. Treatment with other anticoagulants, such as NOACs, low molecular weight heparin, or single antiplatelet therapy, does not exclude simultaneous therapy with nintedanib. Each case should be assessed on an individual basis, and the patient should be informed about the potential risks and the need for increased supervision during treatment.

**In case of unstable coronary artery disease or myocardial infarction requiring implantation of a vascular stent, a riskbenefit analysis taking into account the coronary event itself, the increased risk of bleeding and the risks associated with termination of antifibrotic treatment is indicated. It is advisable to apply stents which require only short term treatment with two antiplatelet agents. In practice, it is recommended to temporarily discontinue nintedanib or, if antifibrotic treatment has not yet been initiated, to start with pirfenidone as treatment of choice (provided that there are no contraindications for this drug).

Summary

IPF is a chronic, progressive disease with very unfavourable prognosis. Antifibrotic treatment is an opportunity for IPF patients to improve this situation.

Nintedanib is one of the drugs with proven therapeutic efficacy in this group of patients, which is manifested by a reduction in the lung function decline rate as well as a reduction in the risk of AE-IPF.

The experience in the treatment of IPF patients with nintedanib gained so far from postmarketing studies and real-life observations has confirmed the effectiveness and safety of the therapy also in patients with coexisting diseases, which excluded such subjects from the registration studies.

Due to the frequent co-occurrence of cardiovascular diseases and IPF, it is not uncommon in clinical practice to treat patients who require concomitant anticoagulant therapy or have an increased risk of cardiovascular adverse events. These are persons who require special attention in both qualification and monitoring the tolerability of nintedanib treatment, which does not mean that they should be disqualified *a priori* from such treatment due to their medical history. When making therapeutic decisions, it is very important to have a holistic view of the case, taking into account comorbidities as well as concomitant medications. If necessary, a specialist consultation should be held to determine the optimal management for the patient.

Longterm observations allow to confirm the persistence of the effectiveness of nintedanib treatment, as well as the safety of such treatment also in case of longterm therapy, what is a very important aspect in view of the chronic nature of the disease. Very promising are the data indicating that nintedanib improves the survival in patients with IPF.

With the precautions discussed above, nintedanib treatment appears to be safe in most patients with IPF. It cannot be excluded that there are additional benefits of treatment with this drug (e.g. in lung cancer prevention), which require further research.

The most common reason for termination of treatment in both registration and subsequent studies is the progression of IPF itself (up to 35% in a 3-year follow-up), so it is all the more important to start treatment early, what has the potential to slow down the progression of the disease and to improve prognosis [13, 29].

Conflict of interest

MMM-B and KG reports fees for lectures, consultancy and travel to medical meetings from Boehringer Ingelheim and Roche outside the submitted work.

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