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Nintedanib

Updated: November 25, 2017.

OVERVIEW

Introduction

Nintedanib is an orally available tyrosine kinase receptor antagonist that inhibits collagen formation and is used to treat idiopathic pulmonary fibrosis. Elevations in serum enzyme levels during nintedanib therapy are not uncommon, but it has yet to be implicated in cases of clinically apparent liver injury with jaundice.

Background

Nintedanib (nin ted' a nib) is a small molecular weight tyrosine kinase receptor inhibitor that has potent activity against several growth factor receptors, including vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet derived growth factor receptor (PDGFR). The inhibition of these receptors causes modulation of many intracellular pathways including inhibition of activities of pro-fibrotic mediators such as transforming growth factor-beta (TGF-β), and decrease in synthesis of extracellular matrix proteins including collagen and fibronectin. Nintedanib has been evaluated as therapy of malignant conditions such as non-small cell lung cancer and for benign fibrotic conditions such as idiopathic pulmonary fibrosis. In several large clinical trials, therapy with nintedanib was associated with a decrease in the progressive decline in lung function in patients with idiopathic pulmonary fibrosis and well as with a decrease in symptomatic, acute pulmonary exacerbations. On the bases of these studies, nintedanib was approved for use in idiopathic pulmonary fibrosis in the United States in 2014. It has not been approved for use in cancer. Nintedanib is available as capsules of 100 and 150 mg under the brand name OFEV. The typical initial dose in adults is 150 mg orally twice daily. Temporary dose reduction is advised for management of adverse reactions or poor tolerability. Side effects are not uncommon and include diarrhea, nausea, dyspepsia, abdominal pain, decreased appetite, headache and fatigue. Rare, but potentially severe adverse events include excessive bleeding, poor wound healing, gastrointestinal perforation, embryo-fetal toxicity and arterial thrombotic events.

Hepatotoxicity

In large randomized controlled trials, serum enzyme elevations occurred in up to 14% of patients receiving nintedanib compared to 3% of controls. Aminotransferase values above 3 times the upper limit of normal (ULN) occurred in only 3% to 5% of patients (compared to <1% of controls), and discontinuation of therapy because ALT elevations was required in less than 1% of nintedanib treated subjects. The enzyme elevations during nintedanib therapy were generally not accompanied by symptoms of liver injury or jaundice and resolved even without dose modification in many subjects. Despite the frequency of ALT elevations during nintedanib therapy, clinically apparent liver injury with jaundice was not recorded in preregistration studies and has yet to be reported in the published literature since its general availability. Nevertheless, monitoring of liver tests is

recommended for patients receiving nintedanib at least monthly for the first 3 months and every 3 months thereafter. Thus, nintedanib is likely to cause clinically apparent liver injury, but careful monitoring and early discontinuation may prevent its occurrence.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which nintedanib might cause liver injury is not known. It is metabolized in the liver largely via the cytochrome P450 system and is susceptible to drug-drug interactions with strong inducers or inhibitors of CYP 3A4.

Outcome and Management

While chronic therapy with nintedanib can be associated with mild-to-moderate serum aminotransferase elevations, it has not been convincingly linked to cases of clinically apparent liver injury. Nevertheless, monitoring of serum aminotransferase levels monthly during the first 3 months and every 3 months thereafter is recommended. Patients who develop aminotransferase elevations on therapy should be monitored more carefully, and nintedanib therapy should be discontinued if jaundice or symptoms of liver injury arise or if serum ALT or AST levels rise above 5 times the ULN.

Drug Class: Pulmonary Fibrosis Agents

Other Drugs in the Class: Pirfenidone

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Nintedanib – OFEV®

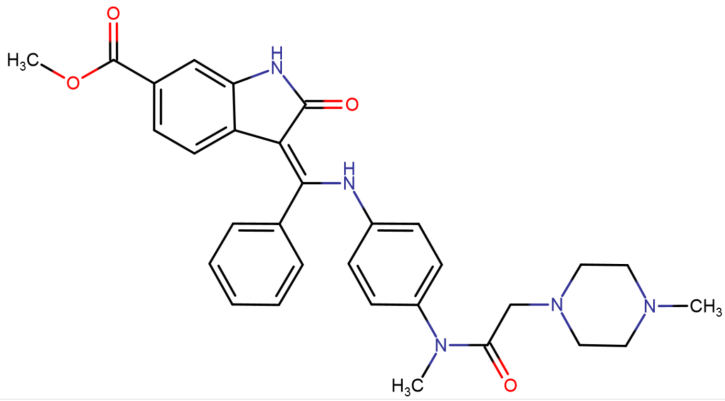
DRUG CLASS

Pulmonary Fibrosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Nintedanib	656247-17-5	C31-H33-N5-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 25 November 2017

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Multi-authored textbook of hepatotoxicity published in 2013; does not discuss nintedanib).

Rockey DC. Current and future anti-fibrotic therapies for chronic liver disease. Clin Liver Dis 2008; 12: 939-62. PubMed PMID: 18984475.

(Review of the pathogenesis and cellular pathways of fibrosis in patients with chronic liver disease and status of antifibrotic agents, none of which have been shown to be effective in treating or preventing hepatic fibrosis).

Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011; 365: 1079-87. PubMed PMID: 21992121.

(Among 1066 patients with idiopathic pulmonary fibrosis enrolled in two studies of nintedanib [150 mg twice daily] versus placebo, the decline in forced vital capacity was less with nintedanib, but adverse events were more frequent and ALT or AST elevations above 3 times ULN occurred in 4.9-5.2% vs <1% on placebo, although no patient developed clinically apparent liver injury with jaundice).

Two new drugs for idiopathic pulmonary fibrosis. Med Lett Drugs Ther 2014; 56 (1457): 123-4. PubMed PMID: 25461229.

(Concise review of the mechanism of action, efficacy and safety of pirfenidone and nintedanib for idiopathic pulmonary fibrosis mentions that both agents can increase hepatic enzyme levels and dose adjustment may be required).

Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, et al.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2071-82. PubMed PMID: 24836310.

(Among 432 patients with idiopathic pulmonary fibrosis treated with 1 of 4 doses of nintedanib or placebo for 1 year, decline in vital capacity and number of pulmonary exacerbations were less in the 86 patients who received the highest dose [150 mg twice daily], but dermatologic and gastrointestinal side effects were more frequent, as

were ALT or AST elevations above 3 times ULN [6 patients, 7.1%, vs none with placebo], but no clinically apparent liver injury was reported).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-1352. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to agents for pulmonary fibrosis).

Keating GM. Nintedanib: a review of its use in patients with idiopathic pulmonary fibrosis. Drugs 2015; 75: 1131-40. PubMed PMID: 26063212.

(Review of the mechanism of action, pharmacology, efficacy and safety of nintedanib as therapy of idiopathic pulmonary fibrosis states that serum enzyme elevations during therapy "were reversible and were not associated with clinical manifestations of liver injury").

Abdel-Rahman O, Bahie Eldin N, ElHalawani H. Risk of selected gastrointestinal and hepatic toxicities in cancer patients treated with nintedanib: a meta-analysis. Future Oncol 2016; 12: 2163-72. PubMed PMID: 27301454.

(Meta-analysis of nine controlled trials of nintedanib in various forms of cancer found, rates of ALT elevations above 5 times ULN in 9.2% of 2029 nintedanib treated vs 2.7% of 1543 controls).

Kim Y, Lee SJ, Lee JY, Lee SH, Sun JM, Park K, An HJ, et al. Clinical trial of nintedanib in patients with recurrent or metastatic salivary gland cancer of the head and neck: A multicenter phase 2 study (Korean Cancer Study Group HN14-01). Cancer 2017; 123: 1958-64. PubMed PMID: 28102887.

(Among 20 subjects with metastatic salivary gland cancer treated with nintedanib [200 mg twice daily], there were no objective responses, and adverse events including ALT elevations in 30% which were above 5 times ULN in 10%; no mention of clinically apparent liver injury).

Olin JL, Woods JA, Garner SJ. Delayed presentation of hepatocellular liver injury after nintedanib administration. Am J Ther 2017; 24: e107-e108. PubMed PMID: 27574930.

(86 year old man developed fatigue 8 months after starting nintedanib [bilirubin normal, ALT ~410 U/L, Alk P normal], ALT levels having been normal before and for the first 7 months of treatment and returning to near normal rapidly after stopping).

Ikeda S, Sekine A, Baba T, Yamakawa H, Morita M, Kitamura H, Ogura T. Hepatotoxicity of nintedanib in patients with idiopathic pulmonary fibrosis: A single-center experience. Respir Investig 2017; 55: 51-4. PubMed PMID: 28012494.

(Among 32 patients with idiopathic pulmonary fibrosis treated with nintedanib at a single Japanese referral center, 59% developed ALT elevations which were above 5 times ULN in 6%, arising usually during the first week and resolving with dose interruption or reduction; no patient developed clinically apparent liver injury or jaundice).

Marzin K, Kretschmar G, Luedtke D, Kraemer S, Kuelzer R, Schlenker-Herceg R, Schmid U, et al. Pharmacokinetics of nintedanib in subjects with hepatic impairment. J Clin Pharmacol 2017 Nov 6. [Epub ahead of print] PubMed PMID: 29106740.

(Single dose pharmacokinetic studies of nintedanib [100 mg] demonstrated an increase in exposure in patients with Child's A [2-fold] and B [8-fold] cirrhosis compared to healthy controls).