COrrelating plasma Nintedanib COncentRations with efficacy and toxicity in patients with interstitial lung DIseAse

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To further research nintedanib PK and correlate them with clinical parameters and toxicity. Results could be used to optimize treatment of nintedanib in the future by dose individualization based on patient*s characteristics or therapeutic drug...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Observational invasive

Summary

ID

NL-OMON49088

Source
ToetsingOnline

Brief title
CONCORDIA study

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
Intestitial lung disease, lung fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Interstitial lung disease, Nintedanib, Pharmacokinetics

Outcome measures

Primary outcome

- To correlate PK parameters of nintedanib with its efficacy and toxicity in

patients with ILD.

Secondary outcome

- To correlate PK parameters of nintedanib with its toxicity.

- To determine the influence of other variables, e.g. comedication, genetics,

or food on nintedanib PK.

- To develop a population pharmacokinetic model of nintedanib

Study description

Background summary

Tyrosine kinase inhibitors (TKIs) are one of the cornerstones in the treatment of various diseases. TKIs cause cell-cycle arrest, induce apoptosis, inhibit angiogenesis, and modulate cell immunity by specifically inhibiting cellular signal transduction through blocking dysregulated protein kinases. These characteristics make them excellent candidates for treating uncontrolled cell growth or activity. The vast majority of TKIs is therefor given as targeted anti-cancer agent for multiple types of malignancies. Nintedanib however, is an oral TKI registered for both metastatic non-small cell lung cancer and as first-line treatment for idiopathic pulmonary fibrosis (IPF) and systemic sclerosis-associated interstitial lung disease (SSc-ILD), rare and fatal diffuse parenchymal lung diseases. Compared to placebo, nintedanib (Ofev ®) reduced the decline in lung function (forced vital capacity; FVC) with 100 ml (> 50%) annually, and possibly the rate of exacerbations in patients with IPF. For SSc-ILD, FVC decline was reduced with 41 ml (44%) per year. This year, the U.S. Food & Drug Administration approved nintedanib for other chronic progressive fibrotic ILD, making it the first and sole treatment of this disease class. This decision was made after the INBUILD trial showed an overall benefit of more than 100 ml (57%) reduction in FVC decline in patients with

symptoms, radiographic evidence of fibrosis and decline in lung function, as seen with progressive fibrotic ILD. The indication of nintedanib as anti-fibrotic drug has hence been enlarged significantly.
Besides beneficial effects, nintedanib causes (severe) toxicity; diarrhoea (> 60%), nausea (> 22%), vomiting (> 12%) and elevated liver enzymes. More than 30% of patients experienced serious adverse events during treatment, often leading to treatment discontinuation, thereby impacting outcomes for patients.
To further optimize this treatment, thorough research is required to establish possible plasma trough concentrations for efficacy and toxicity. Nevertheless, knowledge of the meaning of pharmacokinetic (PK) parameters in ILD patients treated with nintedanib is limited.
Additionally, the interpatient variability of nintedanib is moderate to high (coefficient of variation of 40-80%) and is influenced by multiple factors; ethnicity, body weights, smoking behaviour, and age. Nintedanib*s bioavailability is 4.7% and it is metabolized by CYP3A4 for 5%. The impact of other variables e.g. comedication, genetics, or food has yet to be established.

Study objective

To further research nintedanib PK and correlate them with clinical parameters and toxicity. Results could be used to optimize treatment of nintedanib in the future by dose individualization based on patient*s characteristics or therapeutic drug monitoring; adjusting a patients drug dose based on measurements of drug plasma concentrations.

Study design

Prospective cohort study, in which blood is withdrawn and a questionnaire has to be filled in at every scheduled hospital visit during treatment with nintedanib.

Study burden and risks

In this study,extra blood withdrawal will take place during the whole treatment with nintedanib. The first time, one extra blood sample will be taken for genetic analysis additionally to the sample taken for nintedanib plasma concentration analysis.The risk of blood withdrawal by a venous puncture for study purposes is minimal, especially when it is combined with regular diagnostic blood withdrawal (which we expect to achieve in the majority of cases). Moreover, patients are asked to fill in a questionnaire every visit.
There are no risks herewith.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

dr. Molewaterplein 40
Rotterdam 3015 GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

dr. Molewaterplein 40
Rotterdam 3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age >=18 years;
• Able to understand the written information and able to give informed consent;
• Planned treatment with nintedanib for any fibrotic interstitial lung disease according to standard of care.

Exclusion criteria

• Unable to draw blood for study purposes

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-08-2020
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO

Date:	27-07-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL73833.078.20