Influence of Flavonoids on the Absorption of Nintedanib: a Randomized, Cross-Over Pharmacokinetic Study (the INFLATE study)

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Ethical review	Approved WMO
Status	Pending
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON49544

Source
ToetsingOnline

Brief title
INFLATE

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
Interstitial 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: Absorption, Flavonoids, Green tea, Nintedanib

Outcome measures

Primary outcome

Change in nintedanib systemic bioavailability; area under the curve (AUC).

Secondary outcome

- Change in other pharmacokinetic parameters i.e. maximal concentration (Cmax)

and time to reach Cmax (Tmax).

- Difference in occurrence of (patient reported) toxicity; safety of the

combination of nintedanib and green tea capsules.

Study description

Background summary

Nintedanib is a multi-targeted oral tyrosine kinase inhibitor, registered as first-line monotherapy (150 mg BD) in the treatment of IPF. IPF is an orphan disease, with a prevalence and incidence of 28 and 17 patients per 100.000 people, respectively. In The Netherlands, there are over 2.000 IPF patients, of which 100-150 are treated with nintedanib in the Erasmus MC. Patients with IPF have a median survival of 3 years and a 5-year survival of only 34%. Nintedanib inhibits multiple pathways which cause progression of lung fibrosis, resulting in overall survival benefit of two years.
Recent studies showed that nintedanib has activity in interstitial lung diseases (ILD), and registration for these diseases, as hypersensitivity pneumonitis (c.q. chronic extrinstic allergic alveolitis) and non-specific interstitial pneumonia, is expected. Herewith broadening its indication by becoming the sole registered treatment for this indication, 700-800 more patients are expected to be treated with nintedanib. In the Erasmus MC, patients with IPF are treated with nintedanib, both as regular care, within clinical trials and in an early access program.
The common toxicities are: diarrhoea (> 60%), nausea (> 22%), vomiting (> 12%) and elevated liver enzymes. More than 30% of patients experienced serious

adverse events during treatment, leading to death, life-threatening situations, clinically significant disability or incapacity or hospitalization. Nintedanib is advised to be administered concomitantly with food, since then its bioavailability increases with 20% and less side effects are experienced. Nintedanib*s bioavailability is 4.7% and it is metabolized by CYP3A4 for just 5%. Drug-drug interactions with CYP-enzyme inhibitors or inducers are therefore not likely. However, nintedanib is a substrate of the efflux pump P-glycoprotein (P-gP). P-gP is present in the gastro-intestinal tract and blood-brain barrier. It plays a key role in active cellular drug excretion c.q. reducing absorption, which causes lower drug exposure. Furthermore, P-gP upregulation in (cancer) cells is one of the described resistance mechanisms to for example anti-cancer treatments. P-gP can be inhibited by flavonoids, especially by epigallocatechin gallate (EGCG). ECGC is highly concentrated found in the popular beverage green tea. Based on European Food and Safety Authority scientific opinion, 300 mg of EGCG is considered the general daily intake from consumption of green tea, which increases to 866 mg EGCG/day for high-level consumers. 300 mg EGCG is comparable to 700 ml (5 to 6 cups) of green tea. In most labels of green tea extract capsules it is advised to take at least twice this dosage, up to 1,000 mg EGCG/day. In the presence of 10 µl ECGC, drug efflux (c.q. resistance) in P-gP overexpressing cell lines decreased with 7- to 8.5-fold. Hence, the flavonoid-drug interaction could potentially lead to higher nintedanib absorption by the gastro-intestinal tract. This would cause higher systemic bioavailability and lower local gastro-intestinal drug concentrations (which is thought to be causing most of nintedanib*s toxicity). Furthermore, inter-patient variability could decrease, as also seen with other SMKI*s.

Study objective

Our objective with this proposal is to study the interaction between nintedanib and green tea capsules with > 60% ECGC in fibrotic ILD patients. Depending on the presence and magnitude of the interaction, we will be able to give practical recommendations for daily practice to physicians and patients. Outcomes of this study could change current recommendations, when green tea ECGC is found to be a potent interacting compound with nintedanib.

Study design

A randomized, two-phase cross-over pharmacokinetic study in which nintedanib will be taken seven days with water and a meal respectively with or without 500 mg green tea capsules with > 60% ECGC extract.
The two phases consist of a control phase (A) and an intervention phase (B), in which nintedanib will be taken seven days with water and a standardized meal respectively with or without one capsule of 500 mg green tea extract.
- Phase A exists of 7 days in which nintedanib is taken twice daily with water and a meal.

- Phase B exists of 7 days in which nintedanib is taken twice daily with water and a meal and concomitant with 500 mg green tea extract.
The last day of each phase patients will be admitted for 12 hour pharmacokinetic sampling at t=0h, t=0.5h, t=1h, t=1.5h, t=2h, t=2.5h, t=3h, t=3.5h, t=4h, t=5h, t=6h, t=8h and t=12h. In arm 2, to prevent interference by ECGC of phase B in phase A, a wash-out period of 14 days is designed.

Intervention

Nintedanib will be used as standard care of treatment and is given in a dosage of 100-150 mg twice daily. Dose modifications are not allowed during the whole study period. Nintedanib will be administered for at least two weeks at the same dose to guarantee steady-state. Nintedanib will be administered daily around the same time, i.e. 9.00 AM and twelve hours later at 21.00 PM with water and a meal. Green tea capsules will be given in a dosage of 500 mg twice daily concomitantly with nintedanib.

Study burden and risks

The green tea capsules in this dosage are safe to use. Any interaction would be of such a short period that differences in nintedanib concentration are also significant, but not directly clinically relevant in the form of ineffectiveness or side effects. The admission with blood draws does not pose any additional risks than with a diagnostic blood draw, which gives a very small risk of e.g. thrombophlebitis and a hematoma post-point.

Contacts

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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 ILD according to standard of care.

Exclusion criteria

- unable to draw blood for study purposes
- usage of other strong P-gP or CYP3A4 interacting compounds
- Patients with known impaired drug absorption (e.g. gastrectomy and achlorhydria)

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2020
Enrollment:	26
Type:	Anticipated

Ethics review

Approved WMO

Date:	30-09-2020
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	NL74584.078.20