Effects of rosuvastatin on the pharmacokinetics of imatinib.

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A possibly competitive inhibition between imatinib and rosuvastatin as substrates for the same solute carriers (i.e. OATP 1A2 and ABCG2) may result in drug-drug interactions and altered pharmacokinetics of imatinib.

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON21949

Bron
NTR

Verkorte titel
N/A

Aandoening

malignancy
sarcoma
gastrointestinal stromal tumour

Ondersteuning

Primaire sponsor: Prof. Dr. J. Verweij
Erasmus MC - Daniel den Hoed Cancer Center
Groene Hilledijk 301
3075 EA Rotterdam
Overige ondersteuning: fund=sponsor

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

- To investigate the influence of rosuvastatin on the plasma pharmacokinetics of imatinib (and its metabolite CGP74588) in GIST cancer patients.

Toelichting onderzoek

Achtergrond van het onderzoek

Since the bioavailability of imatinib is usually almost complete, it might be possible that OATP 1A2 mediated transport of imatinib is extremely efficient, so that efflux transporters (i.e. P-glycoprotein and BCRP) cannot lower the bioavailability of this compound.

A possibly competitive inhibition between imatinib and rosuvastatin as substrates for the same solute carriers (i.e. OATP 1A2 and ABCG2) may result in drug-drug interactions and altered pharmacokinetics of imatinib.
To elucidate the clinical importance of this hypothesis we study the effects of concomitant administration of rosuvastatin and imatinib on the pharmacokinetics of imatinib. In this pharmacokinetic study, we would like to expose GIST patients at steady-state concentrations of imatinib to rosuvastatin. We will compare the (plasma) pharmacokinetics of imatinib and its metabolite CGP74588 at steady state with the pharmacokinetics after exposure to rosuvastatin.

We feel this study is clinically relevant, as rosuvastatin is a widely used HMG Co-A reductase inhibitor among cancer patients in the Netherlands. Therefore possible ‘chronic’ drug-drug interactions between imatinib and rosuvastatin may be of important abundance in daily clinical practice. As our patients are exposed only for a short period of time (16 days) and monitored closely, we expect the possible negative effects of a decreased exposure to imatinib will be negligible. This is especially true, as imatinib will have its clinical effects as a result of its usage during months or even years, in contrast to chemotherapy.

Doel van het onderzoek

A possibly competitive inhibition between imatinib and rosuvastatin as substrates for the same solute carriers (i.e. OATP 1A2 and ABCG2) may result in drug-drug interactions and altered pharmacokinetics of imatinib.

Onderzoeksopzet

Study plan:

Day -28 /Day -1:

Informed consent, check of inclusion/exclusion criteria (see section 4), and registration (see section 9: registration procedure). Daily use of imatinib

· Day 1: Hospitalization of the patient; and Start of PK sampling (see section 13: tables).

· Day 2: Use of rosuvastatin at 10 AM after the use of breakfast, 30 minutes later followed by the use of imatinib.

· Day 3-15: Extramural use of rosuvastatin, 20 mg daily, and imatinib 400 or 800 mg daily.

· Day 16: Second period of PK-sampling.

· Day 17: Stop use of rosuvastatin.

Onderzoeksproduct en/of interventie

This pharmacokinetic study, we would like to expose GIST patients at steady-state concentrations of imatinib to rosuvastatin. We will compare the (plasma) pharmacokinetics of imatinib and its metabolite CGP74588 at steady state with the pharmacokinetics after exposure to rosuvastatin.

2 blood sample collections

2 PK daycurves

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Histological or cytological confirmed diagnosis of any form of irresectable and/or metastatic GIST, which is already treated with imatinib for a consecutive period of at least 4 weeks;

2. Age ³ 18 years;

3. WHO performance £ 1 (see appendix B);

4. Adequate hematological functions (ANC > 1.5 x 109/L, platelets > 100 x 1012/L);

5. Adequate renal and hepatic functions (serum creatinin < 1.25xULN, bilirubin < 1.25xULN, ALAT and ASAT < 2.5xULN, in case of liver metastasis < 5 ULN; alkaline phosphatase < 5xULN);

6. Written informed consent;

7. Complete initial work-up within four weeks prior to therapy with the combination of imatinib and rosuvastatin.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Pregnant or lactating patients; patients with reproductive potential must use a reliable method of contraception (excluding oral contraceptives), if required;

2. Serious illness or medical unstable condition requiring treatment, symptomatic CNS-metastases or history of psychiatric disorder that would prohibit the understanding and

giving of informed consent;

3. Use of imatinib therapy less than 4 consecutive weeks;

4. Major surgery within 2 weeks before start of the protocol (to be evaluated by an MD);

5. (Chronic) use of CYP3A and/or P-glycoprotein inhibiting and inducing medication (in particular cyclosporine, which may result in a severe rise of rosuvastatin plasmaconcentration) dietary supplements, or other inhibiting compounds (see Appendix D);

6. Unwillingness to change medication, or no adequate alternatives available, when drugs are taken that are known to interact with CYP3A and/or ABCB1 and/or ABCG2;

7. Asian patients;

8. Use of statins 4 weeks prior to study entry;

9. Patients suffering from myopathy (CK > 10 x ULN associated with muscle symptoms).

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Niet-gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	10-11-2008
Aantal proefpersonen:	12
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	22-10-2008
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1443
NTR-old	NTR1504
Ander register	EudraCTnumber 2008-002659-26 : 08-256
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten
Eechoute et al. Environmental and genetic factors affecting transport of imatinib by OATP1A2. Clin Pharmacol Ther. 2011;89(6):816-20