The role of paroxetine in patients taking telaprevir-based HCV therapy: lack of a drug-drug interaction? (ROLEX)

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Primary objective:To show that concomitant use of telaprevir (1125 mg BID) does not lead to a relevant decrease (> 20%) in the paroxetine parameter AUC0-24h compared to paroxetine alone.Secondary objectives:To determine the ratio of the geometric…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON38871

Source
ToetsingOnline

Brief title
ROLEX

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders
- Mood disorders and disturbances NEC

Synonym
depression, HCV

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: farmaceutische industrie,Janssen-Cilag

Intervention

Keyword: interaction, paroxetine, pharmacokinetic, telaprevir

Outcome measures

Primary outcome

Geometric Mean Ratio (GMR) of the area under the curve (AUC) of paroxetine in combination with telaprevir versus paroxetine alone.

Secondary outcome

Geometric Mean Ratio (GMR) of paroxetine Cmax en C24h of paroxetine in combination with telaprevir versus paroxetine alone.

Adverse events of combined use of paroxetine 20mg QD with telaprevir-containing HCV treatment.

HCV RNA response at week 4 of telaprevir-containing HCV treatment with concomitant use of paroxetine.

Telaprevir pharmacokinetics (AUC0-12h, Cmax C12h) of telaprevir in combination with paroxetine.

Study description

Background summary

HCV infected patients are often in need for an antidepressant. First, depression is common in patients with HCV infection. Second, PEG-interferon

alfa causes depressive symptoms in a large proportion of patients. Inadequate treatment of depression during HCV treatment has a negative effect on adherence to HCV treatment, with suboptimal response as a potential result.

The introduction of Direct Acting Antivirals such as telaprevir has greatly improved treatment outcome of HCV infected patients. Tela-previr, however, causes some significant drug-drug interactions and hence co-administration of other medications should preferably only be done based on clinical evidence that such a combination is safe.

Telaprevir has been studied with one antidepressant, escitalopram: plasma concentrations of the antidepressant were reduced by 35% and without dose adjustment this may lead to inadequate treatment of depressive symptoms. Dose titration of escitalopram may be needed but it may take several weeks before a patient has reached a therapeutic dose.

There is a need for more data on telaprevir drug interactions with other antidepressants. First, the data above show that a negative in-teraction occurs with escitalopram and dose-titration of the antide-pressant may take too long to prevent the (re-)occurrence of depres-sive symptoms. Second, not all patients benefit from escitalopram and those with (prior) treatment failure on escitalopram may require an alternative agent. Third, although escitalopram is generally well-tolerated, side effects may occur and necessitate treatment discon-tinuation. Finally, especially in the previous intravenous drug users on methadone, escitalopram might not be the antidepressant of choice, since escitalopram as well as methadone are drugs that can lead to QTc interval prolongation and have a risk of Torsades de Pointes.

For a number of reasons, paroxetine may be a good candidate for use together with telaprevir-containing HCV treatment. First, paroxetine has been shown to prevent depressive symptoms in patients initiating HCV treatment with elevated depressive symptoms at baseline. Sec-ond, paroxetine is an inhibitor of and is metabolized by CYP2D6 while telaprevir is an inhibitor of and is metabolized by CYP3A, and therefore no drug-drug interaction is expected. Third, paroxetine is one of the most widely prescribed antidepressants with a well-established efficacy and safety profile.

Study objective

Primary objective:
To show that concomitant use of telaprevir (1125 mg BID) does not lead to a relevant decrease (> 20%) in the paroxetine parameter AUC0-24h compared to paroxetine alone.

Secondary objectives:
To determine the ratio of the geometric means (medians) of the par-oxetine PK parameters Cmax and C24h for the combination therapy of telaprevir (1125 mg

BID) and paroxetine (20 mg QD) versus paroxet-ine (20 mg QD) alone.

To determine the short-term safety of combined use of paroxetine 20mg QD with telaprevir-containing HCV treatment.

To assess the short-term HCV RNA response of telaprevir-containing HCV treatment (week 4 response) with concomitant use of paroxetine.

To assess telaprevir pharmacokinetics 1125 mg BID (AUC0-12h, Cmax, C12h) when co-administered with paroxetine 20mg QD.

Study design

An Investigator-initiated open label two-period, one-sequence, non-randomized, multi-centre, phase II study

Study burden and risks

The study will be performed in HCV infected patients who will be treated with telaprevir containing HCV treatment. Patients are already on antidepressant therapy with paroxetine or should have an indication for antidepressant therapy (with paroxetine). We chose to conduct this study in this population because these patients will be treated with telaprevir and paroxetine anyway and will be exposed to these drugs in regular care.

Since no drug-drug interaction is expected between telaprevir and paroxetine we think it is safe to perform this study in HCV infected patients on paroxetine.
No decreased concentrations of either paroxetine or telaprevir are expected and therefore an adverse effect on antiviral or antidepressant therapy is unlikely to occur.

The burden of participation in the trial is limited. We only perform a minimal change in the standard treatment regimen, since included patients are already on antidepressant therapy with paroxetine and are eligible for start of a TVR-containing regimen for treatment of their HCV infection. To further limit the burden, study visits are mostly planned in accordance with the regular visiting scheme for HCV treatment. Two visits are specifically planned for this study; two confinements for the duration of 9 hours each.

Patients may experience adverse events of paroxetine and telaprevir.
Telaprevir may cause skin reactions. Patients are being asked to contact their physician immediately if they experience any skin reaction.
The needles used for blood sampling may cause sligth discomfort at the injection site.

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

1. Subject is at least 18 and not older than 65 years of age at screening.;2. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.;3. Subject has a chronic HCV infection with genotype 1. ;4. Subject is eligible for telaprevir containing HCV treatment.;5. Subject is on a stable dose of 20 mg paroxetine QD for at least 4 weeks.

Exclusion criteria

1. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.;2. Pregnant female (as confirmed by an HCG test performed less than 6 weeks before Day -1) or breast-feeding female. Female subjects of childbearing potential without adequate contraception, e.g. hysterectomy, bilateral tubal ligation, (non-hormonal) intrauterine device, total

abstinence, double barrier methods, or two years post-menopausal. They must agree to take precautions in order to prevent a pregnancy throughout.;3. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion. ;4. Inability to understand the nature and extent of the trial and the procedures required.;5. Participation in a drug trial within 60 days prior to the first dose of telaprevir.;6. Use of relevant concomitant medication, as assessed by a hos-pital pharmacist (member of the study team). ;7. Hemoglobin < 12 g/dL (females) or < 13 g/dL (males) (7.4 respectively 8.0 mM). ;8. Poor- or ultrarapid metabolizer CYP2D6

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-09-2013
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Incivo
Generic name:	telaprevir
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Paroxetine Sandoz

Generic name:	paroxetine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-03-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-06-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2012-005372-34-NL
CCMO	NL43778.091.13