Achieving appropriate exposuRe to RIBAvirin after a dose advise based on an abbreviated AUC of a first dose of ribavirin (ARRIBA)

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Primary objective: To evaluate if adequate exposure to ribavirin can be achieved after a dose adjustment based on the AUC0-4h from a first dose of ribavirin.Secondary:• To evaluate how many patients need a dose adjustment to achieve adequate...

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

Summary

ID

NL-OMON34445

Source
ToetsingOnline

Brief title
ARRIBA

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
chronic hepatitis C infection, viral infection of the liver

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: mede gefinancierd door farmaceutische industrie,Roche

Intervention

Keyword: chronic HCV infection, dose adjustment, pharmacokinetics, Ribavirin

Outcome measures

Primary outcome

The exposure (AUC) to ribavirin.

Secondary outcome

Laboratory safety and side-effects

Study description

Background summary

Currently, the standard treatment for patients with chronic hepatitis C virus (HCV) consists of peginterferon (PEG-IFN) in combination with ribavirin (RBV). Sustained viral response (SVR), defined as undetectable HCV RNA 6 months after treatment, is achieved in 50-80% of patients. Unfortunately, still 30-50% of patients relapse or remain virological non-responders.
For a number of difficult to treat diseases, such as HIV, therapeutic drug monitoring (TDM) has been introduced to optimize treatment response rates. TDM is defined as tailoring medication doses to the individual patient based on (repeated) measurements of (plasma) drug concentrations. Although some suggest to monitor clinical signs and symptoms to maintain adequate SVR rates in patients with chronic HCV, recent data have demonstrated the usefulness of TDM of RBV to improve treatment response. Due to a large interpatient variability in RBV plasma concentrations, the RBV dose is not a good predictor of a sustained viral response (SVR), even though it is based on body weight, but plasma concentrations early after start of treatment are. There is, however, no consensus on the appropriate time of monitoring of RBV plasma concentrations as it may take 4-8 weeks before RBV reaches steady-state. Furthermore, there is no consensus yet on the target level and most appropriate pharmacokinetic parameter (Cmax, Cmin, AUC) for RBV. Finally, there is no evidence based information whether interventions such as dose adjustments or counseling for

nonadherence, are effective in improving RBV plasma concentrations and, thus, SVR.
A recent study has illustrated the importance of adequate plasma RBV concentrations achieved very early after the start of treatment. The exposure to RBV after the first dose was predictive of SVR7. In this study, RBV plasma concentrations were determined during the first dose interval of 12h through intensive blood sampling. An abbreviated RBV area under the plasma concentration vs. time curve (AUC) determined over 4 hours had a positive predictive value (PPV) of 80% and a negative predictive value (NPV) of 79% for predicting SVR. Patients with an AUC0-4h >= 1.755 mg.h/L had a significantly better chance of achieving SVR than patients with an AUC0-4h under this threshold. Given the importance of early adequate exposure to RBV and the possibility to adjust this early in or even before the treatment period, makes it an attractive and potentially highly effective TDM intervention.
We want to know if sufficient exposure to RBV can be achieved after a dose adjustment which is based on an abbreviated AUC after a first dose of RBV.

Study objective

Primary objective:
To evaluate if adequate exposure to ribavirin can be achieved after a dose adjustment based on the AUC0-4h from a first dose of ribavirin.

Secondary:
• To evaluate how many patients need a dose adjustment to achieve adequate exposure to ribavirin
• To evaluate if there are subgroups of HCV infected patients who more often need a dose adjustment to achieve sufficient exposure to ribavirin
• To evaluate the safety and tolerability of a dose adjustment of ribavirin in (formerly) HCV infected patients

Study design

This is an open-label, prospective, phase-IIa trial in 40 (formerly) HCV infected patients who have previously been treated with PEG-IFN and RBV.

After meeting the inclusion criteria and passing the exclusion criteria, subjects will receive a dose of RBV based on body weight on Day 1
Blood samples will be taken to measure plasma concentrations of RBV and the area under the concentration time curve will be calculated:
• If exposure to RBV is adequate (AUC0-4h >= 1.755 mg.h/L), there will not be a dose adjustment on Day 29
• If exposure to RBV is not adequate (AUC0-4h < 1.755 mg.h/L), the RBV dose will be adjusted on Day 29

On Day 29 subjects will receive another dose of RBV, adjusted or not. Again

blood samples will be taken to measure plasma concentrations of RBV and the AUC0-4h will be calculated.
The total duration of the study will be 4 weeks.

Intervention

Two times a single dose of ribavirin will be given and blood will taken to determine the ribavirin concentration and other biochemical parameters

Study burden and risks

Subjects will come to the hospital for screening and will be admitted for half a day twice.
Subject will receive a single dose of ribavirin twice. Side effects of ribavirin might occur, but the chance is small since it is a single dose. In addition the subjects have been treated with ribavirin for at least for weeks twice a day and they will receive two extra doses of ribavirin which is negligible when compared to the number of doses they have received before, and thus, no additional harm is expected.

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 years at screening.
2. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
3. Subject has been treated with RBV and PEG-IFN for a chronic HCV infection for at least 4 weeks
4. Female subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or female subject is of childbearing potential practicing adequate contraception, e.g. intrauterine device, hormonal contraceptives, all in combination with condom use by the sexual partner; double barrier method, vasectomized partner, or total abstinence.
They must agree to take precautions in order to prevent a pregnancy throughout the entire study and until four months after the end of this study.
5. Male subject is practicing one of the following methods of birth control during this study with RBV and for seven months after the end of the study: condoms, is vasectomized or total abstinence from sexual intercourse. Next to that, the female sexual partner should practice an adequate contraception method.

Exclusion criteria

1. Inability to understand the nature and extent of the trial and the procedures required.
2. Participation in a drug trial within 60 days prior to the first dose.
3. RBV use within 90 days prior to the first dose.
4. Pregnancy or a pregnant partner (unless subject agrees to use condoms)
5. Breastfeeding
6. Hemoglobinopathies (e.g. thalassemia, sickle-cell anaemia)
7. Serious adverse events with former treatment with RBV
8. A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months
9. A history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.
10. Hemoglobin (Hb) < 7.5 mmol/L (female) or < 8.0 mmol/L (male)
11. Creatinine clearance < 50 mL/min
12. CD4-count < 200 cells/mm3
13. Signs of progressive liver disease, such as

•Decompensated cirrhosis (Child-Pugh grade B or C), and/or
•Bilirubin > 35 µmol/L or albumin <38 g/L or PTT >4 sec or platelets < 90 x 109/L

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-10-2011
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Copegus
Generic name:	ribavirin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-10-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-05-2011

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2013
Application type:	Amendment
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	EUCTR2010-020371-22-NL
CCMO	NL33793.091.10

Study results

Date completed:	08-01-2014
Actual enrolment:	19

Summary results
Trial is onging in other countries