High-dose versus standard-dose weight-based ribavirin in combination with peginterferon alfa-2a for patients infected with hepatitis C virus genotype 1 or 4

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To investigate if high-dose ribavirin in combination with peginterferon alfa-2a can improve outcome in treatment naïve hepatitis C patients with genotype 1 or 4 and a high viral load (>400.000 IU/ml).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON36939

Source
ToetsingOnline

Brief title
VIRID

Condition

- Viral infectious disorders

Synonym
hepatitis C, viral hepatitis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Hoffmann-La Roche,Stichting Lever Onderzoek

Intervention

Keyword: genotype 1 and 4, hepatitis C, high dose ribavirin, treatment naive

Outcome measures

Primary outcome

· To study whether 48 weeks of daily high-dose ribavirin in combination with peginterferon alfa-2a will lead to a higher SVR rate (HCV-RNA negativity 24 weeks after end of treatment response, ETR) compared with standard-dose weight-based ribavirin

Secondary outcome

· HCV-RNA negativity at week 4 (rapid virologic response, RVR)

· HCV-RNA negativity at week 12 (complete early virologic response, cEVR)

· HCV-RNA >= 2log10 drop at week 12, but HCV-RNA still detectable (partial early virologic response, pEVR)

· HCV-RNA negativity at week 48 (end of treatment response, ETR)

· Relapse rate after end of treatment response

· Safety (serious adverse events, grade 4 NCI toxicity)

· Tolerability of peginterferon alfa-2a and high-dose ribavirin (percentage of patients completing treatment on full or >80% of total intended dose and reasons for dose adjustments)

· Normalization of serum ALT at the end of therapy and and at the end of follow-up

· Health related quality of life assessment using SF-36 questionnaires

Study description

Background summary

Treatment of hepatitis C (HCV) has shown a remarkable success. There is however a genotype factor, which reduces response rates in genotype 1 and 4, especially in patients with a high baseline viral load (1). Optimal treatment of patients with genotype 1 with peginterferon and ribavirin has led to sustained virological response (SVR) rates between 41-52% (2, 3). Further improvement of these results should be considered the greatest challenge. Different strategies are proposed for optimizing treatment outcome: induction dosing of peginterferon, prolonging therapy duration, increased weight-based ribavirin dosing and/or experimenting with new antiviral agents. These new agents (e.g.: protease inhibitors and polymerase inhibitors) seem promising but will not be available for the coming years and development of antiviral resistance may temper initial expectations. Induction dosing of peginterferon has been studied, but did not lead to major improvement of treatment outcome. Data on prolongation of treatment duration are contradictive; prolongation might only be beneficial to certain subgroups of patients.
Ribavirin is an oral nucleoside analogue with antiviral activity against several viral pathogens, although the exact mechanism of action against HCV is not completely understood (4). Direct activity against HCV replication appears minimal, but rapid and lethal mutation of virions and depletion of intracellular guanosine triphosphate, necessary for viral RNA synthesis, has been shown (5-7). Optimal ribavirin dosages are essential in achieving SVR. For genotype 1 and 4 the current European guidelines recommend weight-based ribavirin dosing dependent on the type of peginterferon used. If peginterferon alfa-2b is prescribed the recommended ribavirin dosage for all genotypes is: 800 mg/day if <65 kg, 1000 mg/day if 65-85 kg or 1200 mg/day if >85 kg. If peginterferon alfa-2a is prescribed the recommended ribavirin dosage for genotype 1 and 4 is: 1000 mg/day if <75 kg or 1200 mg/day if >= 75 kg. The initial evidence supporting higher doses of ribavirin for peginterferon alfa-2b comes from a secondary analysis of the pivotal multicenter trial of peginterferon alfa-2b and ribavirin (8). Patients receiving more than 10.6 mg/kg/day ribavirin experienced significantly higher SVR rates (48% vs. 38%). A large multicenter trial designed to test standard dose ribavirin (1000-1200 mg/day) versus low-dose ribavirin (800 mg/day) in combination with peginterferon alfa-2a, showed 52% SVR in the standard dose group versus 41% in the low-dose group for genotype 1 infected patients (3). In the pooled data from two pivotal studies with peginterferon alfa-2a and ribavirin, the probability of achieving an SVR for genotype 1 patients was influenced by the ribavirin dose per kg body weight. A 40-50% increase in the probability of SVR

was found for a 12-16 mg/kg dose increase of ribavirin (9). For peginterferon alfa-2b it was also shown among genotype 1 patients, that weight-based ribavirin (800-1400 mg/day) leads to higher SVR rates compared to fixed dose ribavirin (800 mg/day) (34% vs. 29%). Moreover, ribavirin dosing up to 1400 mg/day was safe and the rate of treatment discontinuation was the same for both treatment groups (10). In a small pilot study, 10 genotype 1 patients with a high baseline load were treated with peginterferon alfa-2a and individualized high-dose ribavirin in order to achieve a ribavirin target concentration in serum of 15 µmol/l. The mean ribavirin dose of 2540 mg/day (range 1600-3600 mg/day) was high, but resulted in 90% SVR. All patients experienced severe anemia, which was treated with concomitant epoetin beta and blood transfusion (11).

As mentioned before, the main concern of high-dose ribavirin will be a dose-dependent hemolytic anemia and the addition of epoetin alfa has shown significant increase of haemoglobin during (peg)interferon/ribavirin therapy. Erythropoietin doses from 9,000 to 60,000 IU/week have been used in order keep the highest possible ribavirin doses (11, 12-15). A recent trial showed a significant higher SVR rate in genotype 1 patients treated with peginterferon alfa-2b, increased dose ribavirin (15.2 mg/kg/day) and epoetin alfa than in patients treated with peginterferon alfa-2b and standard dose ribavirin (13.3 mg/kg/day) with or without epoetin alfa. Using the standard ribavirin dose, routine use of erythropoietin significantly decreased the frequency of anemia and the mean ribavirin dose reduction. Moreover, with the addition of erythropoietin, a significant higher mean dose could be given to patients in the increased ribavirin dose arm (15).

A fair proportion of non-responders has been related to poor patient compliance, probably influenced by neuropsychiatric adverse effects, and by doctors adjusting or stopping medication on basis of cytopenia. SVR rates could have been higher if dose reductions by either adverse events or laboratory abnormalities would have been prevented. New guidelines have been developed based on recent literature, in order to minimize dropout and non-response by this route (16).

For chronic HCV patients with genotype 1 or 4 and high baseline viral load we propose a randomized controlled clinical trial that aims to compare the currently accepted daily ribavirin dosage of 12-15 mg/kg with that of 25-29 mg/kg in combination with peginterferon alfa-2a. Optimal management of side effects, which includes the use of epoetin beta, will be essential in order to maintain the highest possible dosages of both peginterferon alfa-2a and ribavirin for 48 weeks.

Study objective

To investigate if high-dose ribavirin in combination with peginterferon alfa-2a can improve outcome in treatment naïve hepatitis C patients with genotype 1 or

4 and a high viral load (>400.000 IU/ml).

Study design

Patients will be randomized to receive either 25-29 (mean 26.2) mg/kg/day ribavirin (Copegus, Roche) or 12-15 (mean 13.3) mg/kg/day. Both groups will receive once weekly 180 µg peginterferon alfa-2a (Pegasys, Roche). Ribavirin induced anemia will be treated with epoetin beta (NeoRecormon, Roche). Therapy will be given for a total treatment period of 48 weeks. Post treatment follow-up will last for 24 weeks. 170 patients will be included, with 85 patients in each treatment group

Intervention

high dose ribavirin

Study burden and risks

Higher incidence of ribavirin-induced hemolytic anemia will be treated according protocol with epoëtin beta (neorecormon) or blood transfusion when appropriate.

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

• Hepatitis C genotype 1 or 4
• High viral load (>400,000 IU/ml)
• Indication for antiviral treatment or patient*s desire for antiviral treatment
• Hepatitis C treatment naïve
• Liver biopsy within 3 years of the date of the screening visit or when liver biopsy is contraindicated e.g. in patients with clotting diseases e.g hemophilia and von Willebrand disease or when a patient refuses to undergo a new liver biopsy in case the liver biopsy is older than 3 years, substitution by fibroscan is allowed.
• Age 18-70 years

Exclusion criteria

• Signs of progressive liver disease, beyond generally accepted criteria for HCV antiviral therapy:
* serum bilirubin >35 µmol/l, or albumin <36 g/l or prothrombin time >4 sec prolonged or platelets <90x109/l (if normal values are different at the local laboratory, upper and lower limits of the local laboratory should be used)
* decompensated cirrhosis (Child-Pugh Grade B or C)
• Hepatic imaging (ultrasound, CT or MRI) with the evidence of hepatocellular carcinoma (hepatic imaging should be performed within 3 months prior to screening for cirrhotic patients and within 6 months prior to screening for non-cirrhotic patients)
• Thrombocytosis, defined as platelet count >500.000/mm³
• History or evidence of risk of thrombosis
• Poorly controlled hypertension
• Other acquired or inherited causes of liver disease that could explain liver disease activity (if an indicator is present at screening, additional examinations should be done to confirm or rule out the diagnoses)
* Alcoholic liver disease (indicator: MCV>100)
* Obesity induced liver disease (indicators: steatosis proven by biopsy or ultrasound in association with a body mass index >30)
* Drug related liver disease (indicator: positive history of hepatic toxic drug intake with a

causal relation)
* Auto-immune hepatitis (indicators: IgG >30g/l, anti smooth-muscle or antinuclear antibodies titer >/=1:40)
* Hemochromatosis (indicator: ferritin >1000 µg/l) ;* Wilson*s disease (indicator: ceruloplasmin (<0.2 g/l) ;* Alpha-1 antitrypsin deficiency (indicator alpha-1 antitrypsin <0.8 g/L);• Co-infection with hepatitis B virus or human immunodeficiency virus (HIV);• Any cardiovascular dysfunction (e.g. decompensatio cordis, myocard infarction, present or history of arrythmia);• Other significant medical illness that might interfere with this study: significant pulmonary or renal dysfunction, malignancy other than skin basocellular carcinoma in previous 5 years, immunodeficiency syndromes (e.g.: steroid therapy, organ transplants other than cornea and hair transplant);• Contra-indications for peginterferon and/or ribavirin:;* Severe psychiatric disorder, such as major psychoses, suicidal ideation, suicidal attempt and/or manifest depression. Severe depression would include the following: (a) subjects who have been hospitalized for depression, (b) subjects who have received electroconvulsive therapy for depression, or (c) subjects whose depression has resulted in a prolonged absence of work and/or significant disruption of daily functions. Subjects with a history of mild depression may be considered for entry into the protocol provided that a pretreatment assessment of the subject*s mental status supports that the subject is clinically stable and that there is ongoing evaluation of the patient*s mental status during the study;* Visual symptoms related to retinal abnormalities;* Pregnancy, breast-feeding or inadequate contraception;* Thalassemia, spherocytosis;• Females who are pregnant or intending to become pregnant or male partners of females who are pregnant or intending to become pregnant;• Absolute neutrophil count (ANC) <1.40x109/l;• Hemoglobin (Hb) <7.5 mmol/l (female) or <8.1 mmol/l (male);• Creatinine clearance below 50 ml/min (Cockroft/Gault) at screening;• Substance abuse, such as I.V. drugs or alcohol (indicator: >28 drinks/week). If the subject has a history of substance abuse, to be considered for inclusion into the protocol, the subject must have abstained from using the abused substance for at least 1 year;• Treatment with investigational antiviral drugs e.g. protease/polymerase inhibitors within 6 months before start of therapy;• Any other condition which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in and completing the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-06-2008
Enrollment:	170
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Copegus
Generic name:	Ribavirin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NeoRecormon
Generic name:	epoetin beta
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-12-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	19-03-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	21-07-2008
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-10-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-11-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-10-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	23-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-07-2011
Application type:	Amendment
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
EudraCT	EUCTR2007-005344-25-NL
CCMO	NL20457.078.07