Retreatment of chronic hepatitis C patients with pegylated interferon, ribavirin and amantadine; A pilot study to establish
if initial drop in viral load is predictive for sustained virological response.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27702

Source
NTR

Brief title
VKF2

Health condition

Chronic hepatitis C infection

Sponsors and support

Primary sponsor: Schering-Plough
Source(s) of monetary or material Support: Schering-Plough

Intervention

Outcome measures

Primary outcome

To determine if initial drop in viral load is predictive for virological sustained response.

Secondary outcome

To determine if other co-factors i.e. viral load or HCV genotype are predictive for sustained virological response.

Study description

Background summary

Chronic hepatitis C virus (HCV) infection usually has a progressive course and leads to severe chronic liver disease. Cirrhosis and hepatocellular carcinoma develop in a high percentage of individuals chronically infected with HCV (1).

Chronic hepatitis C infection is responsible for roughly 30-40% of chronic liver disease world-wide and is a major health problem, both from a medical and a health economic point of view (2).

Previous studies have shown that progressive liver disease in patients with chronic hepatitis C is associated with persistence of HCV-RNA in serum and elevated serum aminotransferase (ALAT) levels (3).

Successful therapy of chronic hepatitis C is associated with a loss of HCV- RNA from serum and a sustained normalisation of serum ALAT levels.

The current treatment of choice for chronic hepatitis C patients is a two drug combination therapy of Interferon-alfa and Ribavirin for 24 or 48 weeks and is associated with a sustained virological response of 38-43%. However no established treatment strategy exists for patients with chronic hepatitis C showing no response to previous Interferon-alfa therapy or patients who relapse after previous Interferon-alfa therapy. Combination therapy with Interferon-alfa plus Ribavirin did not markedly improve response rates which were in the range of 0-30% (4;5).

Recently a pegylated formulation of Interferon-alfa was developed. This Interferon has been

modified by attachment of a branched polyethylene glycol (PEG) motility, resulting in sustained delivery but reduced clearance.

During treatment with Peg-Intron 1.5 microgram/kg/week for 48 weeks approximately 49% of patients lose serum HCV-RNA. After Peg-Intron 1.5 microgram/kg/week treatment, however, the majority of patients relapse, and only 23% of patients maintain a sustained virological response (SVR), i.e. the assay for HCV-RNA remains negative 6 months after stopping the Peg-Intron therapy (6). The results of a phase 3 study were recently presented, in which 1530 HCV patients were randomized to 3 treatment arms. 61% of the patients who received pegylated Interferon-alfa 1.5 microgram/kg/week + Ribavirin 1000-1200 mg/day achieved a sustained response versus 47% rate sustained response in patients treated with Interferon-alfa 3 MU and Ribavirin 1000-1200 mg (7).

Zeuzem at al calculated, based on the half life of HCV that sustained responders should drop at last 3 log in viral load in the first 4 weeks of treatment (8) So in order to achieve more sustained responders at the end of therapy it seems reasonable to give higher dosage of Interferon in the beginning of the therapy.

There is a growing interest in investigating the efficacy of combination antiviral therapy in patients with chronic hepatitis C.
Combining drugs with demonstrated antiviral activity has the potential advantage of additive or synergistic antiviral effects and may reduce the risk of the development of resistance to antiviral therapies.

Amantadine hydrochloride is an antiviral drug developed three decades ago which is active against influenza A infection. It has been used in the treatment of patients with Parkinson’s disease.

When used in an open label pilot study as monotherapy for 6 months in patients with chronic hepatitis C, who were virological non responders (VNR) to IFN monotherapy, 18% of the 22 enrolled patients achieved a SVR, 6 month after stopping amantadine therapy. The patients who responded to amantadine treatment had significantly lower pre-treatment HCV-RNA titers than the non responders (9).

In another pilot study double combination antiviral therapy (IFN/Ribavirin) was compared with triple combination antiviral therapy (IFN/Ribavirin/Amantadine) in patients with chronic hepatitis C who were VNR to IFN monotherapy.

At the end of 6 months of therapy, 1/10 patients of the dual therapy group was HCV-RNA negative, but in the triple therapy group 7/10 were HCV-RNA negative. Only minor side effects were observed in the patients that received this triple therapy (10).

Six months after stopping the triple therapy, 3/10 exhibited a SVR.

In this study is patients with chronic hepatitis C with a previous virological relapse or a virological non response to IFN or IFN/Ribavirin combination therapy, with a high induction dose of pegylated Interferon combined with Ribavirin and Amantadine. Subsequently a lower dose pegylated Interferon combined with Ribavirin and Amantadine is given to the patients. The aim of the study is to determine if a drop in viral load in the first 4 weeks of treatment is predictive for virological sustained response.

Study objective

In this study is patients with chronic hepatitis C with a previous virological relapse or a virological non response to IFN or IFN/Ribavirin combination therapy, with a high induction dose of pegylated Interferon combined with Ribavirin and Amantadine. Subsequently a lower dose pegylated Interferon combined with Ribavirin and Amantadine is given to the patients. The aim of the study is to determine if a drop in viral load in the first 4 weeks of treatment is predictive for virological sustained response.

Study design

N/A

Intervention

This study will be an open pilot study. Data will be analysed on an intention to treat basis.

Eighty patients will be included.(See Appendix X).

All patients
2 weeks Intron A (3X6 MU daily), Ribavirin (1000-1200 mg daily) and Amantadine (200 mg daily), 2 weeks Intron A (3x3 MU daily), Ribavirin (1000-1200 mg daily) and Amantadine (200 mg daily), 2 weeks Intron A (2x3 MU daily), Ribavirin (1000-1200 mg daily) and Amantadine (200 mg daily).

After 6 weeks of induction therapy, 3 groups of patients will be divided according to their viral load decline.

Viral load decline calculated by the equation:

Viral load decline = Viral load at day 0.

Viral load at week 4.

Viral load expressed in log.

Group 1, non responders: <= 0.5 log decline in viral load;

Group 2, slow responders: > 0.5 - < 3 log decline in viral load;

Group 3, rapid responders: >= 3 log decline in viral load;

Non-responders (group 1) and slow responders (group 2).

42 weeks: Pegylated Interferon 1.5 microgram/kg/week, Ribavirin 1000-1200 mg a day, Amantadine 200 mg a day.
Treatment will be stopped at week 28 when patients are still HCV-RNA positive at week 24 of treatment.

Rapid responders (group 3)
Patients will be randomised to receive either
Group 3A 22 weeks treatment: Pegylated Interferon 1.5 microgram/kg/week, Ribavirin 1000-1200 mg a day, Amantadine 200 mg a day.

OR Group 3B 42 weeks treatment:
Pegylated Interferon 1.5 microgram/kg/week, Ribavirin 1000-1200 mg a day, Amantadine 200 mg a day.
Treatment will be stopped at week 28 in all patients who are HCV-RNA positive at week 24 of treatment.

Contacts

Public
DDMRI, Level II, room 212
719 Umbilo Road
Durban 4001
Huub C. Gelderblom
[default]
Zuid-Afrika
+27-31-2604072
Scientific
DDMRI, Level II, room 212
719 Umbilo Road

Durban 4001
Huub C. Gelderblom
[default]
Zuid-Afrika
+27-31-2604072

Eligibility criteria

Inclusion criteria

1. Patients with a chronic HCV infection, with virological relapse, or with virological non response to previous antiviral therapy diagnosed by:

a. anti-HCV positive;

b. serum HCV-RNA positive by PCR;

2. Patients who have not used antiviral or immune modulating therapy, including interferon, in the previous 6 months;

3. Male and female patients > 18 and < 65 years of age;

4. Patients who have given written informed consent after a detailed explanation of the study by the investigator.

Exclusion criteria

1. Patients who are pregnant and patients (male or female) who are not willing to practise adequate contraception during the treatment period and up to 6 months after ending the treatment period;

2. Patients who are HBsAg or HIV antibody positive or are unwilling to have these tests done;

3. Patients with decompensated cirrhosis (e.g. albumin < 32g/l, PTT prolonged > 4 s, bilirubin > upper limit of normal, AT III < 60%, ascites, GI bleeding, encephalopathy);

4. Patients with a history of i.v. drug use within 6 months prior to entry;

5. Patients with any clinically significant systemic disease other than liver disease (e.g. malignant disease, congestive heart failure, uncontrolled diabetes mellitus, renal failure (serum creatinine > 181 micromol/ml), or autoimmmune disease);

6. Patients with a history of auto-immune hepatitis;

7. Patients using immune modulating treatment during the 6 months prior to study entry;

8. Patients with a history of hypersensitivity to any component of the study drugs;

9. Patients with pre-existing bone marrow depression such as hematocrit < 32%, white blood cell count < 3.0x10E9/l, granulocytes < 10%, platelets < 100x10E9/l Neutrophil count < 1.5x10E9 or Hemoglobin < 8.1 mmol/l for males and < 7.5 mmol/l for females;

10. Patients with severe depression or other psychiatric illness;

11. Patients with a history of epilepsy, or other clinically significant CNS dysfunction;

12. Patients with any condition, that in the opinion of the investigator, might interfere with the outcome of the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2002
Enrollment:	61
Type:	Actual

Ethics review

Positive opinion

Date:	04-01-2006

Application type: First submission

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
NTR-new	NL516
NTR-old	NTR559
Other	: N/A
ISRCTN	ISRCTN81536220

Study results

Summary results
N/A