LETTER TO THE EDITOR

Rationale and design of the virological response and ribavirin dosage (VIRID) study in hepatitis C

The introduction of peginterferon and ribavirin (an oral nucleoside analogue) for chronic hepatitis C has led to the concept that hepatitis C virus (HCV) infection is a curable disease. Not all HCV patients respond to therapy, and especially genotype 1 and 4 patients with a high baseline viral load fare poorly. Given the low sustained virological response (SVR) rates in genotype 1 patients (currently approximately 50%), improvement of treatment efficacy is a major challenge.

The exact mechanism of ribavirin in HCV is not well understood. There appears to be no direct inhibition of HCV replication, but there is rapid and lethal mutation of virions. In addition, there is depletion of intracellular guanosine triphosphate, necessary for viral RNA synthesis.[1] Several studies indicated that optimal ribavirin dosage is essential in achieving SVR.[2] A recent trial showed significantly higher SVR in patients receiving 15.2 mg/kg/day ribavirin compared with 13.3 mg/kg/day ribavirin, both in combination with peginterferon alpha-2b.[3] A small pilot study, in which 10 genotype 1 patients were treated with ribavirin dosages up to 3600 mg/day plus peginterferon alpha-2a, led to 90% SVR.[4] These data provide the rationale of a Dutch nation-wide investigator-initiated study in HCV: the VIRID study.

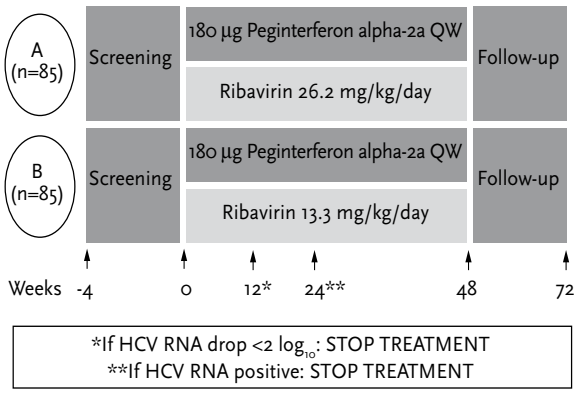
We propose a randomised controlled clinical trial that aims to compare the current standard therapy with a regimen that includes double dosage of ribavirin (*figure 1*).

Patients will be randomised 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 alpha-2a (Pegasys, Roche). Treatment duration is 48 weeks, with a follow-up of 24 weeks. Ribavirin is associated with a dose-dependent anaemia and management of this side effect is important.[5] We will treat all patients, regardless of ribavirin dosage, with epoetin beta (NeoRecormon, 30,000 IU/ml/week, Roche) once Hb drops below 6.8 mmol/l. Patients with <2 $\log_{10}$ drop of HCV RNA at week 12 or HCV RNA positivity at week 24 will discontinue treatment. We made the following assumptions: high-dose ribavirin yields 67.5% SVR, based on cautious estimation of 20-25% improvement compared to standard treatment. With a two-sided 5% significance test, a power of 80% and an estimated dropout rate of 10%, this study requires 85 patients in each arm.

We ask Dutch physicians who see and treat HCV patients to participate in this trial. Patients will be treated by their own physician in their own centre. This nation-wide HCV project will include 20-30 academic and non-academic participating centres. Recruitment will start in March 2008 and will continue until March 2009. The main inclusion criteria include: serological evidence of chronic hepatitis C genotype 1 or 4, treatment naive, high viral load (≥400,000 IU/ml) and a liver biopsy within three years of screening. The main exclusion criteria include: signs of decompensated liver disease, HBV or HIV co-infection, evidence of hepatocellular carcinoma, significant cardiovascular, pulmonary or renal dysfunction, severe psychiatric disorder, pregnancy or breastfeeding.

Since there is a clear need for optimising the current anti-HCV therapy, different strategies have been proposed: induction dosing of peginterferon, prolonging therapy duration, increased weight-based ribavirin dosing and novel antiviral agents. Induction dosing of peginterferon did not lead to a major improvement of treatment outcome and data on prolongation of treatment duration are conflicting.

Figure 1. *Study design*



The new agents (e.g.: protease inhibitors and polymerase inhibitors) seem promising but will not be available for the coming years, development of antiviral resistance may temper initial expectations, and the tandem peginterferon/ribavirin will remain the template for therapy.

These considerations have led to development of the VIRID study. This study is unique in that it is investigator-initiated, and enjoys support of the Dutch Society of Hepatology. The VIRID study will be the first large study to definitely determine the role of high-dose weight-based ribavirin for treatment naive genotype 1 and 4 patients. Additional information can be found at: www.virid.nl.

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