Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Transplantation

Treatment of recurrent HCV infection following liver transplantation: Results of a multicenter, randomized, *versus* placebo, trial of ribavirin alone as maintenance therapy after one year of PegIFNα-2a plus ribavirin

Yvon Calmus[1,13,*], Christophe Duvoux[2], Georges Pageaux[3], Philippe Wolf[4], Lionel Rostaing[5], Claire Vanlemmens[6], Danielle Botta-Fridlund[7], Sébastien Dharancy[8], Jean Gugenheim[9], François Durand[10], Martine Néau-Cransac[11], Olivier Boillot[12], Olivier Chazouillères[13], Laurence Samelson[14], Karim Boudjema[15], Didier Samuel[16]

[1]*Hôpital Cochin, Paris, France;* [2]*Hôpital Henri Mondor, Créteil, France;* [3]*Hôpital Saint Eloi, Montpellier, France;* [4]*Hôpital Hautepierre, Strasbourg, France;* [5]*Hôpital Rangueil, Toulouse, France;* [6]*Hôpital Minjoz, Besançon, France;* [7]*Hôpital La Conception, Marseille, France;* [8]*Hôpital Huriez, Lille, France;* [9]*Hôpital L'Archet, Nice, France;* [10]*Hôpital Beaujon, Clichy, France;* [11]*Hôpital Pellegrin, Bordeaux, France;* [12]*Hôpital Edouard Herriot, Lyon, France;* [13]*Hôpital Saint-Antoine, Paris, France;* [14]*Roche Pharma, Neuilly, France;* [15]*Hôpital Pontchaillou, Rennes, France;* [16]*Hôpital Paul Brousse, Villejuif, France*

Background & Aims: We aimed at determining the effect of maintenance therapy with ribavirin alone, after a year of combined peginterferon-alfa 2a (PegIFNα-2a) and ribavirin therapy, on viral response and liver histology after liver transplantation (LT).

Methods: Hundred and one patients with recurrent HCV and a minimum of stage 1 fibrosis (METAVIR scoring), 1–5 years after LT, were enrolled. PegIFNα-2a and ribavirin were initiated at 90 μg/wk and 600 mg/d, respectively, then increased or adjusted as a function of tolerance. At 12 months, combination therapy was discontinued and patients were randomized to ribavirin or placebo for a further 12 months. Growth factor use was permitted.

Results: At 18 months, a sustained virological response (SVR) was obtained in 47.9% of patients in Per Protocol (PP) analysis, and was higher in patients with genotype 2 or 3 than in patients with genotype 1 or 4, in patients with genotypes 1 + 4 receiving ciclosporine than in those receiving tacrolimus, in patients with worse renal function, in those having received EPO, in patients with lower weight, and in those with lower viral load at 3 months. Using logistic regression, only the early viral response, recipient weight and renal function were independently associated with better SVR. SVR, viral load, activity, and fibrosis scores were similar, at M18 and M30, in patients randomized to ribavirin, or to placebo.

Conclusions: A PP SVR was achieved in 47.9% of patients with established recurrent hepatitis C after LT. Maintenance therapy with ribavirin alone does not improve the virological response or the histological parameters.

Keywords: Hepatitis C virus; Peginterferon; Ribavirin; Erythropoietin; Viral response; Fibrosis.

Received 5 October 2011; received in revised form 11 April 2012; accepted 22 April 2012; available online 18 May 2012

* Corresponding author. Address: Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, F 75012 Paris, France. Tel.: +33 1 71 97 01 58; fax: + 33 1 71 97 01 94.

E-mail address: yvon.calmus@sat.aphp.fr (Y. Calmus).

Abbreviations: EPO, erythropoietin; HCV, hepatitis C virus; ITT, intention to treat; LT, liver transplantation; PegIFN, peginterferon; PP, Per Protocol; RBV, ribavirin; SVR, sustained virological response.

Introduction

Recurrence of hepatitis C virus (HCV) infection is almost universal after liver transplantation (LT), leading to accelerated disease and impaired patient and allograft survival [1–4]. However, a substantial proportion of patients have a slow progressive disease and histological findings in the early biopsies are helpful in predicting subsequent progressive disease [5]. Moreover, therapy with interferon in the transplant population is associated with serious side-effects. Therefore, antiviral therapy should be preferentially recommended in patients whom disease progression is histologically evidenced. In the present trial, patients with established recurrent HCV infection received antiviral therapy at least an year after LT.

While substantial improvements have been made in the treatment of chronic hepatitis C in the immunocompetent host, results in the liver transplant setting have been less impressive. In patients with established recurrent HCV infection, conventional interferon associated with ribavirin or PegIFNα alone resulted in a sustained virologic response (SVR) in only 12–21% of patients [6–8]. Factors of lower response include high viral load, high prevalence of genotype 1, and low tolerability with difficulties in achieving full-dose treatment. With PegIFNα and ribavirin, reported SVR ranged from 26 to 45% [9–13]. Most data though are based on retrospective and/or small series. In a large retrospective study, an SVR was obtained in 38% of cases [14],

whereas, in a prospective randomized trial *vs.* no treatment, 13/27 (48%) patients with fibrosis stage F0–F2 achieved an SVR [15].

Finally, the beneficial effect of maintenance therapy has not been assessed. Interferon monotherapy is a possibility, mainly to improve histological lesions. However, interferon monotherapy has been associated with a poor virologic response (<10%)[6], and has been associated, in kidney or liver transplant recipients, with severe rejection [16,17]. A metanalysis based on 14 randomised trials shows that ribavirin alone had no significant effect on SVR, but significantly improved biochemical and histological response in non-immunosuppressed patients [18]. Ribavirin monotherapy has been investigated in kidney graft recipients with HCV infection, resulting, in one series, in improved histologic lesions [19]. After LT, the concept of ribavirin maintenance therapy after interferon and ribavirin has been addressed in two pilot studies [20,21], suggesting that maintenance monotherapy with ribavirin alone can maintain the biochemical and histological response.

This randomized, double-blind, multicenter study was designed to determine whether 12 months of ribavirin maintenance monotherapy following 12 months of combination therapy with PegIFNα-2a and ribavirin, might ensure maintenance of viral eradication or improve biochemical or histologic parameters. The aims of this report were: (1) to determine, in a prospective series of 100 patients, the SVR rate when combining PegIFNα and ribavirin, associated with growth factors in order to reduce the proportion of dose reductions or premature discontinuations of therapy; (2) to identify baseline and on-treatment factors associated with SVR; (3) to define the rate of severe side effects; (4) to evaluate the effects of maintenance ribavirin monotherapy on viral eradication, tolerance, and biochemical and histological findings.

Patients and methods

Patients

Adult (age 18–70 years) first-time LT recipients from 15 French centers, with recurrent HCV and fibrosis ⩾F1 (METAVIR) at liver biopsy obtained 1–5 years after LT, were included between May 2003 and January 2005. Patients were included if they had undergone transplantation for end-stage HCV-positive, hepatitis B surface antigen (HBsAg)-negative liver disease. All patients had histopathologically proven chronic hepatitis defined by METAVIR at liver biopsy performed ⩽6 months prior to study entry, with detectable serum HCV RNA by polymerase chain reaction (PCR), irrespective of liver enzyme levels. Patients must have been taking calcineurin inhibitors (cyclosporine or tacrolimus), with a stable immunosuppressive regimen for at least 6 months.

Patients were excluded if they met any of the following criteria: previous treatment with interferon alfa after transplantation, retransplantation, associated organ transplantation, recurrent hepatocellular carcinoma after LT, serum human immunodeficiency virus positivity, acute rejection episode within the past 6 months or histologic features compatible with acute or rejection at screening biopsy (i.e. acute rejection, loss of >25% of interlobular bile ducts, centrilobular ischemia), fibrosing cholestatic hepatitis, unresolved biliary complications, serum creatinine level >200 μmol/L, gamma-glutamyltransferase (GGT) level >20 × upper limit of normal (ULN), bilirubin level >100 μmol/L, neutrophil count <1500/mm^3, platelet count <50,000/mm^3, hemoglobin level <10 g/dl (women) or <11 g/dl (men).

Study design

All eligible patients received combination therapy with PegIFNα-2a plus ribavirin for 12 months. Study design is shown in Fig. 1. Accurate guidelines were given for antiviral therapy. PegIFNα-2a was initiated at 90 μg/wk and ribavirin at 600 mg/day, then increased to 180 μg/wk and 1000 mg/day, or adjusted as a function of hematologic tolerance (see below). Growth factor use (erythropoietin [EPO] and/or G-CSF), according to local practices, was encouraged to maintain adherence to antiviral therapy. Suppression of steroids was recommended, as well as a reduction of the dose of mycophenolate mofetil in case of hematologic disorder.

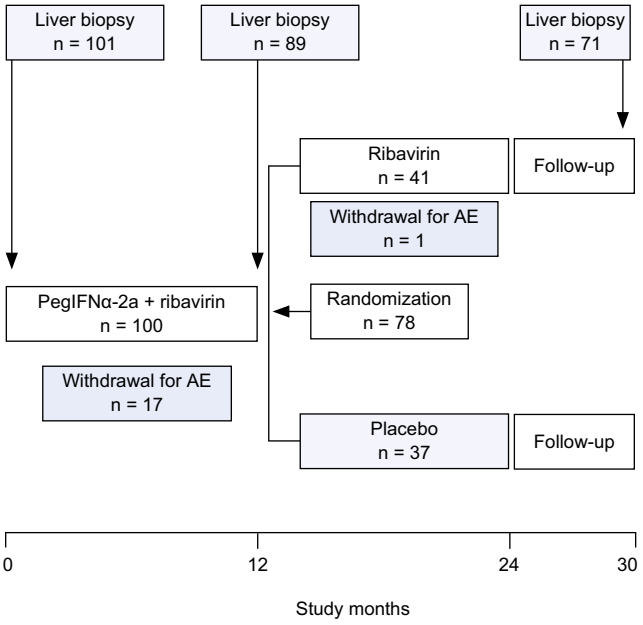

Fig. 1. Trial design. AE, adverse events.

After 12 months of combination therapy, patients were randomized in a 1:1 ratio, to receive either ribavirin at the same dosage, or a placebo, for a further 12 months (period 2). Randomization was performed on a central basis, with local balance, by questioning an internet site. All patients were followed-up for 6 months (period 3) following the end of therapy (Fig. 1).

A liver biopsy was demanded in all patients during the screening period ⩽6 months prior to study entry, at 12 months, and at 30–33 months (end of follow-up). Evaluation of the biopsy specimens was performed by a senior local pathologist blinded with respect to patient identification, treatment group allocation, and time of the biopsy relative to treatment.

Safety monitoring

Patients were assessed at months 1, 2, 3, 6, 12 (combination therapy), 18 and 24 (randomized part), then 30 (end of follow-up). Adverse events and concomitant medications were recorded at each visit. Adverse events were managed by dose reduction or discontinuation of study medication(s). For combination therapy, one-step dose reduction was allowed; PegIFNα-2a was reduced from 90 to 45 μg a week, and ribavirin from 600 to 400 mg/day for decreased neutrophil counts <750/mm^3 or decreased platelet counts <50,000/mm^3. Permanent discontinuation of PegIFNα-2a was required for neutropenia <500/mm^3 or thrombocytopenia <20,000/mm^3. For ribavirin, the dose was reduced for a decrease in hemoglobin levels <10 g/dl and the drug was discontinued for a decrease <8 g/dl. Both drugs were discontinued if serum creatinine level was >300 μmol/L. Patients who experienced moderate or severe rejection (Banff score, 4–9) according to Banff criteria [22] discontinued antiviral therapy.

End points

The main time points in the analysis were: baseline, 12 months (end of combination therapy), 18 months (6 months after the end of combination therapy), and 30 months (end of follow-up).

The primary end point was virologic response, defined as undetectable serum HCV RNA using the Roche Amplicor™ HCV test (lower limit of detection 50 IU/ml). The secondary end points were: (1) change in serum HCV RNA levels from baseline; (2) change from baseline in histology as assessed by the METAVIR activity and fibrosis scores [23]; (3) alanine aminotransferase (ALT) and GGT values over time; (4) number and severity of rejection episodes; (5) occurrence of other adverse events.