ELSEVIER

Journal of Hepatology 44 (2006) 717–722

Journal of Hepatology

www.elsevier.com/locate/jhep

Significant improvement in the outcome of HCV-infected transplant recipients by avoiding rapid steroid tapering and potent induction immunosuppression

Marina Berenguer[1,*], Victoria Aguilera[1], Martín Prieto[1], Fernando San Juan[2], José M. Rayón[3], Salvador Benlloch[1], Joaquín Berenguer[1]

[1]*HepatoGastroenterology Service, Servicio de HepatoGastroenterología, Hospital Universitario La Fe, Avenida Campanar 21, 46009 Valencia, Spain*
[2]*Liver Transplantation and Surgery Unit, Servicio de HepatoGastroenterología, Hospital Universitario La Fe, Avenida Campanar 21, 46009 Valencia, Spain*
[3]*Pathology Service, Servicio de HepatoGastroenterología, Hospital Universitario La Fe, Avenida Campanar 21, 46009 Valencia, Spain*

***Backgrounds/Aims*: Recurrent HCV-cirrhosis occurs in a substantial proportion of transplant recipients, with higher rates reported in patients who had recently received a transplant. Over-immunosuppression has been implicated in this more unfavorable outcome. To determine whether the implementation of specific measures aimed at reducing or avoiding negative predictive variables is associated with an improvement in the outcome of recurrent hepatitis C.**

***Methods*: Comparative study between a cohort of patients who had recently received a transplant (2001–2004) and a historical group of HCV-infected patients transplanted before the implementation of two simple measures (1999–2000): (i) use of dual initial immunosuppression (steroids + cyclosporine neoral or tacrolimus); (ii) slow steroid tapering (>6 months). Yearly biopsies were performed in these recipients, and only those with at least one protocol biopsy and those with cholestatic hepatitis (regardless of follow-up) were included in the study. End-point: rate of HCV-related severe disease (defined as bridging fibrosis, cirrhosis or fibrosing cholestatic hepatitis) within the first year post-transplantation.**

***Results*: Severe disease was significantly lower in this cohort compared to the historical group (26/90, 29% vs 25/52, 48%; $p = 0.02$). While other factors remained unchanged between the two cohorts, the proportion of patients on triple–quadruple regimes and the number of boluses of methyl-prednisolone were lower and the duration of prednisone therapy longer in more patients who had recently received a transplant.**

***Conclusions*: Improving the outcome of recurrent hepatitis C may be achieved by reducing overall immunosuppression and avoiding abrupt variations in immunosuppression.**

***Keywords*: Immunosuppression; Hepatitis C virus; Liver transplantation; Cirrhosis; Hepatocellular carcinoma; Donor age; Cyclosporine; Tacrolimus; Prednisone**

1. Introduction

Hepatitis C virus (HCV)-cirrhosis is the most frequent diagnosis in patients undergoing liver transplantation [1]. Viral recurrence occurs universally [2], with development of histologic hepatitis in the majority [3,4] and progression to cirrhosis in a substantial proportion of these [3–8]. In fact, recent data from our group [7] and from a large multicenter US study [9] show a significant negative impact of HCV infection on both graft and patient survival, an impact which appears to be more relevant in recent years [7]. Few simple variables, including the age of the donor and the immunosuppression utilized have been shown to be associated with the outcome [3–12]. In that sense, several studies have suggested that a more rapid progression to cirrhosis occurs in patients who receive organs from donors

Received 15 September 2005; received in revised form 26 December 2005; accepted 11 January 2006; available online 6 February 2006

* Corresponding author. Tel.: +34 96 386 8792; fax: +34 96 398 7333.
E-mail address: mbhaym@teleline.es (M. Berenguer).

Abbreviations: HCV, Hepatitis C virus; HCC, hepatocellular carcinoma; HAI, histologic activity index; PCR, polymerase chain reaction; F, fibrosis; ALT, alanine aminotransferase; LT, liver transplantation; IS, immunosuppression.

0168-8278/$32.00
doi:10.1016/j.jhep.2006.01.005

older than 50, those overimmunosuppressed and from those in whom steroids are withdrawn in a rapid and abrupt way [6,7,12–18]. The preferential use of organs from younger donors may hence become a strategy to improve the outcome of these patients. This strategy may, however, be unrealistic due to both ethical and 'practical' considerations. Alternatively, different schedules of immunosuppression should be performed in order to select a more rationale use of immunosuppression.

In a previous study from our group, we showed that the post-transplantation outcome of HCV-infected patients was substantially worse in patients transplanted recently compared to those transplanted years ago, with a lower survival and a higher rate of progression to cirrhosis [7]. In fact, in that study, the main cause of death was recurrent decompensated HCV-related graft cirrhosis with a probability of developing cirrhosis of 44% at 5 years. Reasons for the worse outcome were proposed and included older donor age, the use of stronger induction immunosuppression and an earlier and faster withdrawal of 'second-line immunosuppressive drugs' such as prednisone. Based on these findings, and in order to improve the outcome, we started implementing a few simple measures in 2001. These included: (i) the use of initial immunosuppression (during the first month) based on double therapy (calcineurin inhibitor + steroids) avoiding triple and quadruple regimes whenever possible; and (ii) a slow steroid tapering. We hypothesized that the implementation of these simple measures would lead to an improvement in outcome, measured as the proportion of patients developing severe recurrent disease within the first year post-transplantation. The aim of this study was therefore to determine whether the implementation of potential positive measures was associated with a reduction in the rate of severe disease. In order to test this, we compared the outcome of our study population to a historical group of patients transplanted between 1999 and 2000 just prior to the implementation of these measures. We present here the preliminary results, since this is an ongoing study that we plan to continue for two additional years.

2. Patients and methods

2.1. Patients

Study population (recent cohort): Between October 2001 and May 2004, 121 adult patients underwent primary liver transplantation at our institution for HCV-related cirrhosis ± hepatocellular carcinoma (HCC) without hepatitis B virus infection (HBV). The criteria used for selecting patients with cirrhosis and a localized HCC are those proposed previously [7]. Only HCV-RNA positive patients with at least one-year protocol biopsy performed in the absence of prior antiviral therapy and/or patients with an earlier clinical indicated biopsy showing severe recurrent disease (defined as cholestatic hepatitis and/or progression to bridging fibrosis) were included in this study. The follow-up of this preliminary analysis was terminated at the time of either the patient's death, retransplantation or at the end of the observation period (May 2005).

Control/historical group. This group consisted of patients undergoing liver transplantation for HCV-related liver disease between January 1999 and August 2000 before the implementation of simple measures to improve outcome ($n=78$) fulfilling the same criteria applied to the study cohort (i.e. patients with at least one-year protocol biopsy performed in the absence of prior antiviral therapy and/or a biopsy showing cholestatic hepatitis despite the lack of the one-year biopsy).

2.2. Histological assessment

Protocol liver biopsies were performed yearly (±4 months). Additional biopsies were performed when clinically indicated. All biopsy specimens were reviewed by a single pathologist (JMR) in a blinded fashion, and only those obtained before any antiviral therapy was instituted were evaluated in this study. Sections were stained routinely with hematoxylin-eosin, reticulin, Perls' and Orcein stains.

Liver biopsies classified as 'hepatitis' were scored evaluating both the stage of fibrosis and the degree of necroinflammatory activity, according to a slight modification of the histologic activity index (HAI) proposed by Knodell et al. [7]. The grade was determined by combining the HAI scores for periportal necrosis, lobular degeneration and necrosis and portal inflammation, and was defined as follows: 1–2, minimal; 3–6, mild; 7–10, moderate; 11–14, severe. The stage corresponded to the original HAI fibrosis score: 0, none; 1, fibrous portal expansion; 3, bridging fibrosis; and 4, cirrhosis.

Graft biopsy specimens were also examined for features of acute and chronic rejection. Cellular rejection was always based on histological findings, including mixed portal infiltrate, venous endothelitis and bile duct injury.

Cholestatic hepatitis was defined following recent recommendations[19].

2.3. Immunosuppression

During the study period, all patients undergoing liver transplantation at our institution were prospectively randomized to receive cyclosporine neoral + steroids vs tacrolimus + steroids. Additional therapies were used in cases of early calcineurin-related post-transplantation complications that required a substantial reduction in calcineurin inhibitor doses. Initial doses were as follows: methylprednisolone given intravenously with tapering of the dose from 200 to 20 mg at day 6, at which time 20 mg/day of prednisone were administered orally; cyclosporine (trough levels of 250–350 ng/ml the first month, 150–250 ng/ml the second and third months, 100–150 ng/ml until the end of the first year and around 100 ng/ml thereafter); tacrolimus (trough levels of 5–15 ng/ml the first 3 months, 5–10 ng/ml thereafter). Prednisone dose was started at 20 mg one week after transplantation and tapered down at a slow rate with final withdrawal after 9–12 months from transplantation. Only in cases where cholestatic hepatitis was diagnosed or in patients with severe side-effects related to the use of corticosteroids, prednisone was tapered down more rapidly.

Histologically confirmed episodes of moderate to severe rejection were treated with boluses of corticosteroids (1 g of methyl-prednisolone/day during three consecutive days) ± introduction of mycophenolate mofetil. Increase in baseline immunosuppression was the standard of care for mild episodes of rejection that otherwise were left untreated. Empiric treatment for suspected rejection was never done. The same criteria to treat rejection episodes was used during the two periods.

2.4. Cytomegalovirus (CMV) prophylaxis

Ganciclovir, either administered intravenously for 14-21 days or orally (1 gm/8 h for 90 days) was given under the following circumstances: (1) positive donor and negative recipient; (2) retransplantation; (3) use of monoclonal or policlonal antibodies; (4) surgery complicated with high blood-product requirements.

2.5. Outcome variables

Progression to severe disease within the first year (bridging fibrosis, cirrhosis, cholestatic hepatitis, death due to recurrent hepatitis) was used as the primary end-point. Secondary end-points included: (i) progression to fibrosis ≥ 1 in the first-year liver biopsy, (ii) percentage of patients