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Long-term antiviral treatment for recurrent hepatitis C after liver transplantation

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ABSTRACT

Background and aims: The management of patients treated for hepatitis C recurrence after liver transplantation and not achieving virological response following treatment with interferon plus ribavirin is controversial.
Methods: A retrospective analysis of the outcomes of 70 patients non-responders to antiviral treatment after liver transplantation was performed. Twenty-one patients (30.0%; Group A) were treated for ≤12 months and 49 (70.0%; Group B) for more than 12 months.
Results: The 2 groups were comparable for main demographic, clinical and pathological variables. Median duration of antiviral treatment was 8.2 months in Group A and 33.4 months in Group B. No patient achieved a complete virological response. The 5-year patient hepatitis C-related survival rate was 49.2% in Group A and 88.3% in Group B ($P = 0.002$), while the 5-year graft survival rate was 49.2% in Group A and 85.9% in Group B ($P = 0.007$). The median yearly fibrosis progression rate was 1.21 per year in Group A and 0.40 per year in Group B ($P = 0.001$).
Conclusions: Prolonged antiviral treatment showed an overall beneficial effect in transplanted patients with a recurrent hepatitis C infection and not responding to conventional therapy. The treatment should be continued as long as it is permitted, in order to improve clinical and histological outcomes.

1. Introduction

Hepatitis C virus (HCV) infection is the major cause of chronic liver disease, cirrhosis and hepatocellular carcinoma in most developed countries and it is the most frequent indication for orthotopic liver transplantation (OLT) in Europe and in the United States [1,2].

Although OLT is an effective treatment to reduce morbidity and mortality in this population, almost all recipients develop recurrent infection of the graft; the principal factor related to a more severe HCV recurrence is advanced donor age [3–5]. Because of immunosuppression, histological progression of HCV infection is more rapid than in non-transplanted patients, with 5-year cirrhosis progression between 20 and 40% [6]. Subsequently, HCV patients have a poorer prognosis after OLT compared to those with other indications [7].

Treatment options for HCV recurrence after OLT include antiviral treatment (AVT), based on a combination of standard interferon (IFN) or pegylated interferon (PEG-IFN) plus ribavirin (RBV), or re-transplantation (re-OLT). re-OLT is reserved for a small percentage of patients [8–10] when virological response (VR) is not achieved and decompensated graft cirrhosis has been established; AVT is recommended worldwide when histological evidence of recurrent hepatitis C is documented [11]. Unfortunately, a sustained virological response (SVR) is achieved in only 20% to 40% of patients treated with AVT [12,13]. Factors related to a lower probability of VR include high pre-treatment viral load, genotype 1, absence of early virological response and the administration of antiviral therapy at a reduced dosage due to side effects [8,13–16].

Although it has been recognized that IFN plus RBV treatment is crucial for HCV recurrence prognosis after OLT, no standard strategy has yet been established [13–16]; in particular, patient selection, timing of initiation, dosage schedule and duration are still controversial issues.

In addition, little is known about the use of long-term maintenance therapy in transplanted patients without VR [17–22]. Walter et al. [21] reported a decreased fibrosis progression in patients

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treated for more than 6 months, even in the absence of VR. Conversely, Ikegami et al. [22] described a stabilization in fibrosis stage, regardless of AVT duration, in VR patients without SVR and in non-responders (NR) with biochemical response (BR), but a worsening in fibrosis stage in patients who showed neither BR nor VR to AVT.

The aim of our study was therefore to evaluate the effect of prolonged AVT in NR, with particular consideration on patient survival and fibrosis progression rate.

2. Materials and methods

Between January 1st, 2000 and December 31st, 2009, 126 HCV-positive transplanted patients received AVT due to post-transplant HCV recurrence at our outpatient clinic; 88 of them (69.8%) did not achieve a complete VR. Among them, we excluded 2 patients (2.3%) because we lost them to follow-up, and 16 patients (18.2%) with early cholestatic recurrence and a rapidly progressive course, in whom the AVT was performed for a very short time. All these 16 patients died due to HCV recurrence within 12 months after transplant. Hence, study population consisted of 70 patients. Three (4.3%) patients underwent re-OLT for graft cirrhosis due to HCV recurrence. For one patient receiving AVT only before re-OLT, the follow-up was censored at the date of re-OLT, while for one patient in whom AVT was administered only after re-OLT, all the data were collected starting from this point. For the patient treated after both transplantations, the starting point was considered the first OLT.

HCV infection was defined as positivity for serum anti-HCV antibodies, while hepatitis B virus (HBV) infection was defined as positivity of hepatitis B surface antigen (HBsAg) or of anti-core antibodies (HBcAb) at the time of surgery. Human immunodeficiency virus (HIV) was defined as positivity for serum anti-HIV antibodies.

Severity of liver dysfunction was graded according to the Model for End-stage Liver Disease (MELD) score currently used by UNOS (http://www.unos.org) [23].

2.1. HCV detection and genotyping

Quantitative serum HCV-RNA was routinely determined in all patients with a branched DNA assay (Quantiplex HCV 2.0, Chiron Corp). The lowest limit of detection of the quantitative assay was 0.615×10^3 IU/mL, while the highest one was 7.692×10^6 IU/mL. Viral genotype was determined by nested reverse transcription polymerase chain reaction of the core region with type-specific primers (Inno-LiPA HCV, Innogenetics, Ghent, Belgium) and classified according to Simmonds criteria [24].

2.2. Diagnosis of hepatitis C recurrence

Three criteria had to be fulfilled to diagnose recurrent hepatitis C: (1) alteration of liver function tests in the absence of vascular, biliary, drug, or infectious causes; (2) liver biopsy confirming HCV recurrence; (3) detectable quantitative HCV-RNA in the serum. Histological staging and grading of chronic HCV-related graft hepatitis were performed according to the Ishak scoring system [25].

No routine biopsies were usually performed at our Centre. Liver biopsy samples were obtained before starting AVT and when clinically indicated. Disease progression/regression was assessed by computing the yearly fibrosis progression rate (yFPR), which was obtained dividing the absolute change in the fibrosis score by the years of observation [26].

2.3. Immunosuppression

Cyclosporine A (CyA) and tacrolimus (TAC) were the main immunosuppressive drugs used in this study population, both associated with steroids. The assignment was not dictated by a specific choice but simply reflected the increasing use of TAC as the primary immunosuppressive agent by most programmes during the study period. m-TOR inhibitors (mammalian Target Of Rapamycin inhibitors; sirolimus and everolimus) were either administrated as primary immunosuppressive agents or in combination with reduced doses of calcineurin inhibitors in the event of side-effects. During AVT, serum levels of CyA were maintained between 90 and 150 ng/mL, those of TAC were maintained between 4 and 10 ng/mL, and those of sirolimus and everolimus were maintained between 3 and 8 ng/mL.

Anti-CD25 antibodies (basiliximab or daclizumab) or anti-thymocyte globulins were used at the time of transplantation as induction therapy in a minority of patients.

2.4. Antiviral therapy

No patients received pre-emptive AVT. The minimum duration of AVT was 6 months, regardless of the achievement of a complete virological and biochemical response during this period and unless adverse events contraindicating AVT occurred. After 2002, an attempt to treat patients with genotypes 1 and 4 for 12 months was routinely made.

General criteria for dose reduction/discontinuation are those reported below, and they were fulfilled in all patients. No patient voluntarily stopped AVT in the absence of clinical indications. AVT was avoided or discontinued in patients who developed severe rejection, systemic bacterial infection, symptomatic anaemia, or severe depression despite antidepressants. The response to AVT was defined based on virological and biochemical outcomes. VR was defined as negative serum HCV-RNA during AVT; BR was defined as a serum Alanine Transaminase (ALT) level that decreased to and remained in the normal range (ALT < 31 IU/L) during the treatment for at least 3 months.

AVT was started with 1.5 MU of IFN α-2b 3 times weekly plus 400–600 mg of RBV daily for 1–2 weeks, and if well tolerated, doses were increased to 3 MU of IFN α-2b 3 times weekly plus up to 1200 mg of RBV daily. In 2002, this regimen was replaced by 135–180 μg of PEG-IFN α-2a or 50–80 μg of PEG-IFN α-2b weekly plus weight-adjusted daily RBV. Some patients who initially did not respond to IFN α-2b were subsequently switched to PEG-IFN.

Granulocyte colony stimulating factor was used when the neutrophil count was lower than 800 cells/μL. IFN doses were reduced when the neutrophil count was lower than 800 cells/μL and/or the platelet count was lower than 50,000 μL^{-1}. IFN was stopped when the neutrophil count was lower than 500 cells/μL and/or the platelet count was lower than 20,000 μL^{-1}.

Erythropoietin alpha was administered when the haemoglobin level was lower than 10 g/dL. RBV dose reduction was considered when the haemoglobin level was lower than 10 g/dL despite erythropoietin therapy, and it was stopped when the haemoglobin level was lower than 8 g/dL.

2.5. Statistical analysis

Results were expressed as median and range of values. Differences between continuous and categorical variables were calculated with the Mann–Whitney *U* test and the χ^2-test or Fisher's exact test, respectively.

HCV-related survival (HCV-S) was computed from the day of surgery or of starting of AVT to the day of death due to HCV recurrence or the last follow-up visit. Patients who died due to causes other than HCV recurrence were censored at the date of death. We conducted the analysis according to the Kaplan–Meier method and compared the differences between groups by the log-rank test. Logistic regression was used for multivariate analysis of risk factors for lower survival.