Research Article

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Transplantation

Pegylated interferon plus ribavirin in HIV-infected patients with recurrent hepatitis C after liver transplantation: A prospective cohort study

Lluis Castells[1,2], Antoni Rimola[2,3], Christian Manzardo[3], Andrés Valdivieso[4], José Luis Montero[5], Rafael Barcena[6], Manuel Abradelo[7], Xavier Xiol[8], Victoria Aguilera[9], Magdalena Salcedo[10], Manuel Rodriguez[11], Carmen Bernal[12], Francisco Suarez[13], Antonio Antela[14], Sergio Olivares[7], Santos del Campo[6], Montserrat Laguno[3], José R. Fernandez[4], Gloria de la Rosa[15], Fernando Agüero[3], Iñaki Perez[3,†], Juan González-García[16], Juan I. Esteban-Mur[1,2], Jose M. Miro[3,*], on behalf of the FIPSE LT-HIV investigators[‡]

[1]*Hospital Vall d'Hebrón, Universitat Autónoma de Barcelona, Barcelona, Spain;* [2]*CIBEREHD, Barcelona, Spain;* [3]*Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain;* [4]*Hospital de Cruces, University of the Basque Country, Bilbao, Spain;* [5]*Hospital Universitario Reina Sofía-IMIBIC, Córdoba, Spain;* [6]*Hospital Universitario Ramón y Cajal-IRYCIS, Madrid, Spain;* [7]*Hospital Universitario Doce de Octubre, Madrid, Spain;* [8]*Hospital de Bellvitge-IDIBELL, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain;* [9]*Hospital Universitari La Fe, Valencia, Spain;* [10]*Hospital General Universitario Gregorio Marañón, Madrid, Spain;* [11]*Hospital Universitario Central de Asturias, Oviedo, Spain;* [12]*Hospital Universitario Virgen del Rocío, Sevilla, Spain;* [13]*Complejo Hospitalario Universitario, A Coruña, Spain;* [14]*Hospital Universitario de Santiago de Compostela, La Coruña, Spain;* [15]*Organización Nacional de Trasplantes, Madrid, Spain;* [16]*Hospital Universitario La Paz-IdiPaz, Madrid, Spain*

Background & Aims: The aim of this study was to evaluate the results of treatment with pegylated interferon and ribavirin for the recurrence of hepatitis C after liver transplantation in HCV/HIV-coinfected patients.

Methods: This was a prospective, multicentre cohort study, including 78 HCV/HIV-coinfected liver transplant patients who received treatment for recurrent hepatitis C. For comparison, we included 176 matched HCV-monoinfected patients who underwent liver transplantation during the same period of time at the same centres and were treated for recurrent hepatitis C.

Results: Antiviral therapy was discontinued prematurely in 56% and 39% ($p = 0.016$), mainly because of toxicity (22% and 11%, respectively; $p = 0.034$). Sustained virological response (SVR) was achieved in 21% of the coinfected patients and in 36% of monoinfected patients ($p = 0.013$). For genotype 1, SVR rates were 10% and 33% ($p = 0.002$), respectively; no significant differences were observed for the other genotypes. A multivariate analysis based on the whole series identified HIV-coinfection as an independent predictor of lack of SVR (OR, 0.17; 95% CI, 0.06–0.42). Other predictors of SVR were donor age, pretreatment HCV viral load, HCV genotype, and early virological response. SVR was associated with a significant improvement in survival: 5-year survival after antiviral treatment was 79% for HCV/HIV-coinfected patients with SVR *vs.* 43% for those without ($p = 0.02$) and 92% *vs.* 60% in HCV-monoinfected patients ($p < 0.001$), respectively.

Conclusions: The response to pegylated interferon and ribavirin was poorer in HCV/HIV-coinfected liver recipients, particularly those with genotype 1. However, when SVR was achieved, survival of coinfected patients increased significantly.

Keywords: Liver transplantation; HIV infection; HCV infection; Recurrence of hepatitis C; Pegylated-interferon; Ribavirin; Antiviral treatment; Survival.

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* Corresponding author. Address: Infectious Diseases Service, Hospital Clínic, Helios Building, Villarroel 170, 08036 Barcelona, Spain. Tel.: +34 93 2275586/+34 619185402; fax: +34 93 4514438.

E-mail address: jmmiro@ub.edu (J.M. Miro).

† Deceased.

‡ Spanish LT in HIV-Infected Patients Working Group investigators (see Appendix).

Abbreviations: AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy; CI, confidence interval; FIPSE, Spanish Foundation for the Investigation and Prevention of AIDS; GESIDA, Spanish Group for the Study of AIDS; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio; IQR, interquartile range; MELD, model for end-stage liver disease; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; LT, liver transplantation; SVR, sustained virological response; PI, protease inhibitor; PegIFN, pegylated interferon; RBV, ribavirin.

Introduction

Since the introduction of highly active anti-retroviral therapy (HAART) in the mid-1990s and the subsequent drastic reduction in mortality of HIV infection [1], HCV-related liver disease has become a leading cause of death in HCV/HIV-coinfected individuals [2]. Consequently, in recent years, liver transplantation (LT) has been increasingly performed in selected HIV-infected patients [3,4]. However, post-LT survival in HCV/HIV-coinfected patients has been poorer than that reported in HCV-monoinfected patients,

particularly due to higher rates of graft loss and death caused by HCV recurrence in the former [5–8]. In this regard, experience with antiviral treatment against recurrence in HCV/HIV-coinfected LT recipients with pegylated-interferon (PegIFN) and ribavirin (RBV) remains scarce, consisting of reports from small series of patients, mostly without a comparative group of HCV-monoinfected patients. In these reports, the rate of sustained virological response (SVR) was relatively low, ranging from 10% to 35% [5–7,9–12], with the exception of the study by Wojcik *et al.* [13], who reported an SVR rate of 100% in a series of 4 patients. The most detailed report, a post-LT multicentre study from the United States, included 39 HCV/HIV-coinfected patients with hepatitis C recurrence, treated with pegylated-interferon (PegIFN) and ribavirin (RBV) with an SVR of only 14% [14]. Unfortunately, this study did not include a control group of HCV-monoinfected patients and survival was analysed according to whether the end-of-therapy response was achieved or not, instead of SVR, which would have been a more logical event for this purpose.

Since 2002 [15], most Spanish LT units have performed transplants in HIV-infected patients, following the same HIV-inclusion criteria for LT [16], with the result that a sizeable cohort of HCV/HIV-coinfected patients has been prospectively followed since surgery. Based on data from this cohort, we evaluated the results of treatment with PegIFN and RBV for recurrent hepatitis C in HCV/HIV-coinfected patients. For comparison, we included a control group comprising HCV-monoinfected patients, treated for post-LT recurrence of hepatitis C.

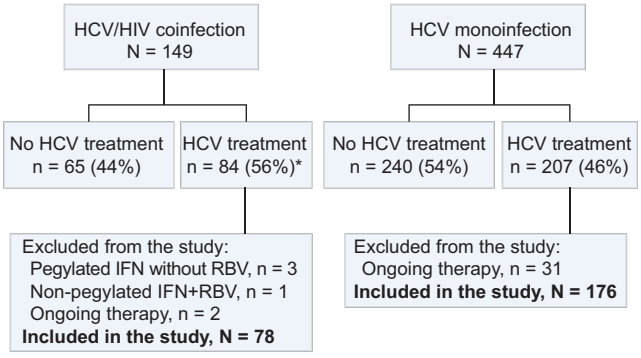

Fig. 1. Flow-chart of HCV/HIV-coinfected and HCV-monoinfected liver transplant patients according to whether they received or did not receive treatment with pegylated-interferon plus ribavirin for recurrence of hepatitis C. *p <0.05 *vs.* HCV-monoinfected patients. IFN, interferon; RBV, ribavirin.

Patients and methods

Study design

We performed a multicentre, cohort study based on 149 consecutive HCV/HIV-coinfected patients who underwent LT between 2002 and 2009 in Spain and who were prospectively followed until July 2012. These patients were matched with 447 HCV-monoinfected patients (1:3) who underwent LT during the same period at the same sites. Other matched criteria were calendar year (±1 year), age (±12 years), gender, presence of HBV coinfection, and presence of hepatocellular carcinoma (HCC). Only coinfected patients who had received post-transplant anti-HCV therapy with pegINF and RBV and who had matched monoinfected controls, treated against HCV in the same centre, were included (Fig. 1). The Institutional Review Boards of all participating sites approved the study. All patients signed the informed consent form.

As shown in Fig. 1 84 (56%) out of 149 HCV/HIV-coinfected patients and 207 (46%) out of 447 HCV-monoinfected patients ($p = 0.042$) received antiviral therapy for recurrence of hepatitis C after LT in 13 centres. After excluding 6

Table 1. Characteristics and accomplishment of anti-HCV treatment of HCV/HIV-coinfected and HCV-monoinfected liver transplant recipients.

	HCV/HIV-coinfected	HCV-monoinfected	*p* value
No. of cases	78	176	
Age (yr)*	43 (39-46)	47 (43-53)	<0.001
Male recipients, n (%)	59 (76%)	135 (77%)	0.873
Data related to HIV infection			
HIV-1 risk factors, n (%)			
Drug use	59 (76%)		
MSM	2 (3%)		
Heterosexual relations	9 (12%)		
Hemophilia	5 (6%)		
Other	3 (3%)	n.a.	
Duration of HIV-1 infection (mo)	191 (134-225)	n.a.	
AIDS-defining events, n (%)	6 (8%)	n.a.	
Data at the time of LT			
Pre-LT anti-HCV treatment, n (%)	30 (38%)	48 (27%)	0.140
Hepatocellular carcinoma, n (%)	15 (19%)	39 (22%)	0.740
MELD score at listing	15 (12-18)	15 (12-19)	0.699
Donor characteristics			
Age (yr)	53 (43-66)	50 (36-64)	0.148
Cause of donor brain death, n (%)			
Vascular	45 (58%)	112 (64%)	0.066
Cranial trauma	19 (24%)	53 (30%)	
Other	12 (15%)	11 (6%)	

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