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P-890. Treatment of Spanish HIV-infected patients with recurrent hepatitis C virus (HCV) after liver transplantation (OLT) with pegylated interferon (PEG-INF) plus ribavirin (RBV): Preliminary results of the FIPSE OLT-HIV-05 - GESIDA 45-05 Cohort Study (2002-06).

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Background: Recurrent HCV after OLT is a major cause of graft loss and death in HIV-HCV coinfected patients. We evaluate efficacy and safety of treatment with PEG-INF and RBV for recurrent HCV after OLT in this population.

Methods: Prospective multicenter cohort study. Ninety liver transplants in 88 HIV-infected patients have been performed in Spain since 2002. Nineteen patients died (22%). 92% were HIV-HCV co-infected. Thirty-three patients started anti-HCV therapy with PEG-INF (alfa-2a or alfa-2b) plus RBV planned for 48 weeks. We present the results of the first 16 evaluable patients. Sustained virological response (SVR) was defined as undetectable serum HCV-RNA viral load (VL) 6 months after therapy. We performed an intention-to-treat (ITT) analysis.

Results: Median (IQR) age was 39 (38;45) years, 81% of recipients were male and former drug use (81%) was the most common HIV-1 risk factor. Pre-OLT median (IQR) MELD was 17 (12;21). Efavirenz-based regimens were the most common pre-OLT (56%) and post-OLT (75%) antiretroviral treatment. Median (IQR) CD4 cell count pre-OLT was 288 (180;425) cells/mm3 and all but one patient had undetectable plasma HIV-RNA VL. Patients received cyclosporine- or tacrolimus-based regimens in 32% and 68% of cases, respectively. Genotypes 1/4 or 2/3 were diagnosed in 12 (75%) and 4 (25%) cases, respectively. Median (IQR) serum HCV-RNA VL before starting therapy was 1,434,000 (780,000;3,200,000) IU/mL. Treatment was started a median (IQR) of 7 (5;11) months after OLT. Overall, early virological response (decrease of 2 logs of HCV-RNA VL at 12 weeks), end of therapy response, and SVR were seen in 9 (56%), 5 (31%) and 4 (25%) cases, respectively. SVR rates for genotypes 1/4 or 2/3 were 17% and 50%, respectively. Six patients required erythro/darbopoietin and four G-CSF due to severe anemia and neutropenia. Anti-HCV treatment was stopped due to toxicity or non-virological response in 2 (17%) and 6 (37%) patients, respectively. Six of the 12 non-responders died (50%) because of graft loss due to recurrent HCV infection. Six non-responders had been treated before OLT without SVR.

Conclusions: The rate of SVR with PEG-INF plus RBV was low (25%). New strategies are necessary to improve the outcome of OLT in coinfected patients.

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

BACKGROUND

Recurrent HCV after OLT is a major cause of graft loss and death in HCV-HIV coinfected patients. Information regarding anti-HCV therapy in these patients is scarce.*

OBJECTIVE

To evaluate the efficacy and safety of treatment with pegylated-interferon (PEG-INF) and ribavirin (RBV) for recurrent HCV after OLT in this population.

* Miró JM et al. Journal of HIV Therapy. 2007 (in press).

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

PATIENTS & METHODS

- Prospective study of all HIV-1-infected patients who underwent OLT in Spain.
- HIV (stage, CD4 cell count, plasma HIV-1 RNA viral load, ART), liver disease (etiology, stage), OLT characteristics at baseline and after OLT, and anti-HCV treatment characteristics were collected using a standardized CRF.
- Each site used the same immunosuppressive regimens & prophylaxis protocols as for their HIV-negative patients.

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

OLT INCLUSION CRITERIA*

- **Liver criteria:** the same as for the non-HIV-1-infected population.
- **HIV criteria:** No previous C events (CDC, 1993) except tuberculosis, pre-OLT CD4 cell count greater than 100 cells/mm3 and undetectable plasma HIV-1 RNA viral load on HAART or detectable plasma viral load off HAART with post-transplant suppression predicted.
- **Drug abuse**: A) No heroin or cocaine abuse for >2 years; B) No alcohol abuse for >6 months.

* Miró JM et al. Enferm Infecc Microbiol Clin. 2005; 23:353-362.

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

ANTI-HCV TREATMENT (I)

- **Indication for anti-HCV treatment**: ALT elevation, positive serum HCV RNA viral load (VL), and histological evidence of HCV recurrence.
- **Treatment regimens**: Pegylated interferon (PEG-INF) α2a (Pegasys®; sc 180 µg wk) or PEG-INF α2b (Peg-Intron®; sc 1.5 µg/kg wk) plus Ribavirin (RBV)(Rebetol®; 400-1000 mg/day) for 48 wks.
- Doses were reduced according to tolerance and laboratory abnormalities.
- **G-CSF** or **Erythro/Darbepoetin** were given when necessary.

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

ANTI-HCV TREATMENT (II)

- **Definitions:**

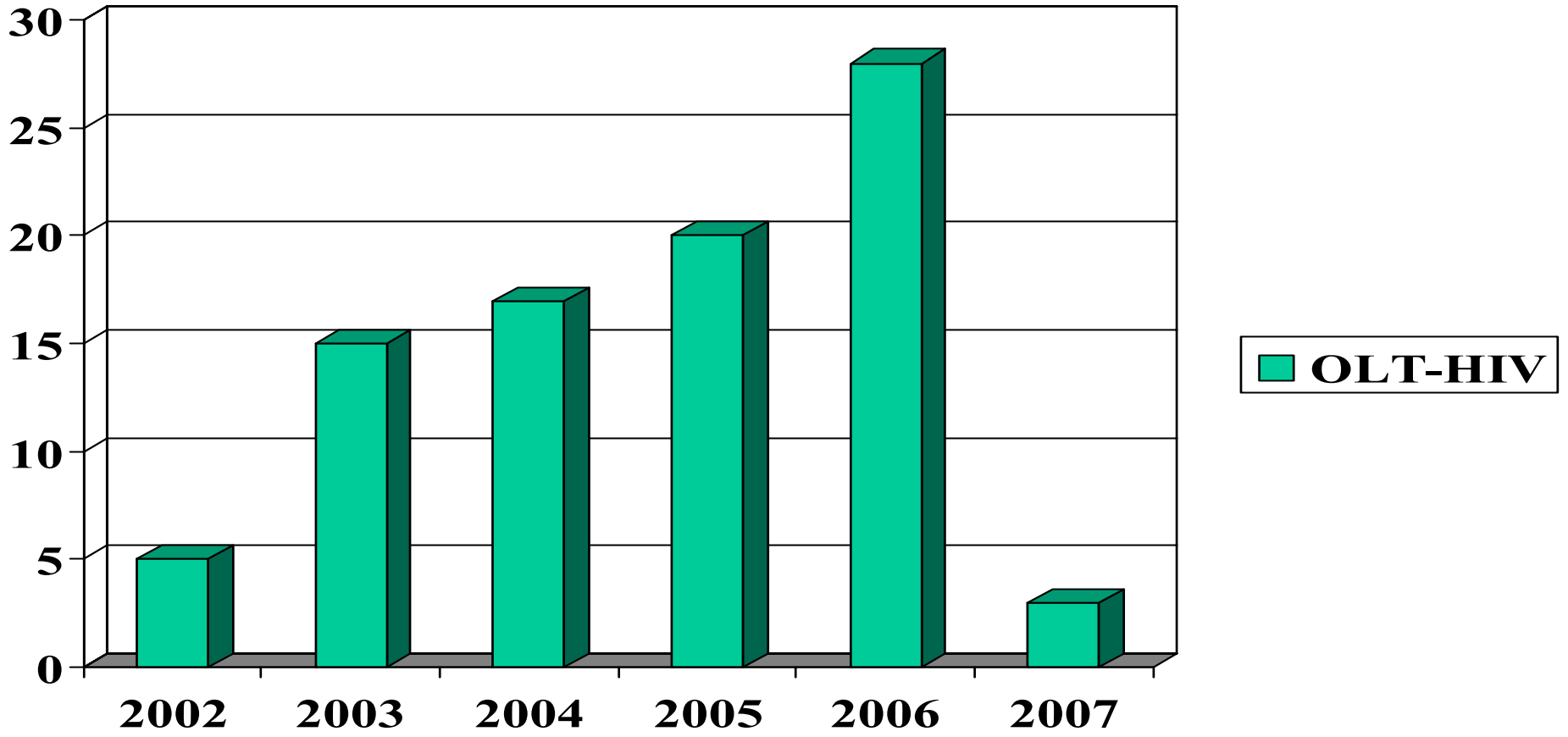
  - **Early virological response** (EVR) ↓ ≥2 log of HCV RNA viral load (VL) at 12 wks;

  - **End-of-treatment response** (ETR): negative HCV RNA VL at 48 wks; and

  - **Sustained VR** (SVR): negative HCV RNA VL 24 wks after the end of treatment.

- **Cohort study. Descriptive analysis.**
- **Responses were evaluated by ITT (NC=F) analysis.**

Spanish Cohort of OLT in HIV-infected patients (FIPSE OLT-HIV-05 / GESIDA 45-05)(N=88)



Data updated: February 20, 2007; there were 90 OLT in 88 patients.

Spanish Cohort of OLT in HIV-infected patients (FIPSE OLT-HIV-05 / GESIDA 45-05)(N=88)

	No. cases	No. deaths	No. cases anti-HCV Rx
Hosp. Cruces, Bilbao	14	3	2
Hosp. Bellvitge, Barcelona	12	2	3
Hosp. Vall d'Hebrón, Barcelona	11	1	5
Hosp. Clínic, Barcelona	8	1	2
Hosp. Ramón y Cajal, Madrid	8	1	2
Hosp. 12 de Octubre, Madrid	8	1	-
Hosp. Gregorio Marañón, Madrid	7	3	1
Hosp. La Fe, Valencia	6	2	-
Hosp. Reina Sofía, Cordoba	2	1	-
Hosp. Virgen Arrixaca, Murcia	2	1	1
Hosp. Virgen del Rocío, Sevilla	2	1	-
Hosp. Juan Canalejo, La Coruña	2	0	-
Hosp. Santiago Compostela	2	0	-
Hosp. Clinico Lozano Blesa, Zaragoza	2	0	-
Hosp. Central de Asturias	1	0	-
Hosp. Carlos Haya, Málaga	1	1	-
Hosp. Marques Valdecilla, Santander	1	1	-
Total	**88**	**19 (22%)**	**16**

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

Baseline characteristics (N=16)

Male gender	13 (81%)
Age (years)	39 (36-45)*
HIV risk factor	
- Former i.v. drug abuse	13 (81%)
- Sexual**	1 (6%)
- Hemophilia	2 (13%)
Liver cirrhosis etiology	
- Genotypes 1/4	11/1 [12, 75%]
- Genotypes 2/3	1/3 [4, 25%]

* Median (IQR) ** One homosexual man; all patients were Caucasian.

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV)

Baseline characteristics (N=16)

MELD*	17 [11;21]
Type of liver	
- Cadaveric	15 (94%)
ART Rx before anti-HCV Rx	
- Efavirenz-based ART	12 (75%)
- 3 NRTI**	4 (25%)
CD4 count (cells/mm3)*	288 (180;425)
CV < 200 copies/mL	15 (94%)

* Median (IQR) ** Abacavir-based ART

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV)

Immunosuppressive regimens (N=16)

- Cyclosporine A (CsA)	
+ Prednisone, or	2 (13%)
+ IL-2 Ra*, or	3 (19%)
- Tacrolimus	
+ Prednisone, or	6 (38%)
+ Prednisone + MMF**	2 (13%)
+ Prednisone + IL-2 Ra*	1 (6%)
+ MMF	2 (13%)
Acute Rejection	9 (56%)

*Basiliximab (Simulect®) ** MMF = Mycophenolate mophetil

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

CD4 & VL evolution

	CD4+ cells/µL*	Plasma HIV-1 RNA VL<200 copies/mL
Before OLT	288 (180;425)	94%
+ 1 mo	182 (155;266)	82%
+ 3 mo	183 (153;316)	89%
+ 6 mo	204 (155;265)	100%
+ 12 mo	231 (183;308)	92%
+ 18 mo	243 (140;310)	82%
+ 24 mo	220 (192;306)	100%

* Median (IQR).

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

Anti-HCV Rx Virological Response

- Six patients were treated before OLT without SVR. None of them had an SVR when Rx after OLT.
- Therapy with PEG-INF+RBV was started a median (IQR) of 7 (5;11) months after OLT

- EVR (N=16)	9 (56%)
- ETR (N=16)	5 (31%)
- SVR (N=16)	4 (25%)

Genotype 1/4	Genotype 2/3
N=12	N=4
2 (17%)	2 (50%)

EVR = Early virological response; ETR = End of therapy response; SVR = Sustained response.

Summary of the studies evaluating the effectiveness of the treatment of HCV re-infection in OLT with PEG-INF+RBV

Author, Year of Publication (Reference)	HIV-HCV coinfected patients	
	No. of cases	SVR[a] No (%)
Fung, 2004 (1)	12	2 (17%)
Duclos-Vallee, 2006 (2)	13	2 (15%)
de Vera, 2006 (3)	15	4 (27%)
Vennarecci, 2006 (4)	9	0 (0%)
Spanish study, 2007 (CROI-07) (5)	16	4 (25%)
Total	**65**	**12 (18.5%)**

(1) Fung, Liver Transpl 2004;10 (Suppl 2): S39-S53; (2) Duclos-Valle, Liver Transpl, 12 (Suppl 1) 2006: pp C-103; (3) de Vera, Am J Transpl. 2006; 6:2983-93; (4) Vennarcci, Liver Transpl, 12 (Suppl 1) 2006: pp C-115; and, (5) Five cases have been published: Castells, Antivir Ther. 2006; 11:1061-70.

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

Anti-HCV Rx Side Effects (N=16)

Toxicity (Grade ≥2)	11 (69%)
- Flu-like syndrome	11 (69%)
- Anemia	10 (62%)
- Neutropenia	7 (44%)
- GI intolerance	2 (12%)
- Pancytopenia	1 (6%)
- Depression	1 (6%)
Growth factors	
- Erythro/Darbepoetin-α	6 (37%)
- G-CSF (Filgastrim)	4 (25%)

Rx of HIV-infected patients with recurrent HCV after OLT with PEG-INF+RBV

Outcome (N=16)

Anti-HCV Rx D/C due to SAEs	2 (12%)
Follow-up (months)*	27 (17;35)
- New liver transplant	0 (-)
- Mortality	6 (37.5%)

Mortality**	SVR	
	No (N=12)	Yes (N=4)
- Yes	6 (50%)	0 (0%)
- No	6 (50%)	4 (100%)

* Median (IQR) ** Death was due to ESLD in 5 cases and metastasic cancer in one; p=0.23.

CONCLUSIONS

- The overall rate of SVR with PEG-INF plus RBV was low (25%): 17% for genotypes 1/4 (N=12) and 50% for genotypes 2/3 (N=4).
- None of the six patients unsuccessfully treated with INF or PEG-INF+RBV before OLT had an SVR when they were treated again after OLT.
- All patients with SVR lived, whereas 50% of patients without SVR died due to ESLD in most cases.
- New strategies are necessary to improve the outcome of HCV recurrence in OLT in co-infected patients.

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Our patients.