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Q-188 . Treatment with Pegylated Interferon (PEG-INF) plus Ribavirin (RBV) of 65 HIV-infected Patients with Recurrent Hepatitis C Virus (HCV) Infection after Liver Transplantation (OLT): Results of the FIPSE OLT-HIV-Cohort Study (2002-08).

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Background: Recurrent HCV infection after OLT is a major cause of graft loss and death in HIV/HCV-coinfected patients. We evaluate the efficacy and safety of treatment with PEG-INF and RBV for recurrent HCV after OLT in 65 HIV-infected recipients.

Methods: Prospective multicenter cohort study. Between 2002 and 2008, 155 liver transplants were performed in Spain. Fifty-three patients died (34%), 147 (95%) were HIV/HCV-co-infected, and 75 (51%) started anti-HCV therapy with PEG-INF (alfa-2a [N= 24] or alfa-2b [N=51]) plus RBV planned for 48 weeks. We present the results of 65 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; M=F) and per-protocol (PP) analysis.

Results: Median (IQR) age was 42 (38;46) years, 76% of recipients were males, and former drug use (73%) was the most common HIV risk factor. Median pre-OLT (IQR) MELD was 15 (12;20). Efavirenz-based regimens were the most common post-OLT (46%) antiretroviral treatment. Median (IQR) CD4 cell count pre-OLT was 297 (202;428) cells/mm3 and 61 (91%) patients had undetectable plasma HIV-RNA VL. Patients received cyclosporine- or tacrolimus-based regimens in 26% and 63% of cases, respectively. Genotypes 1, 2, 3, 4 and others/non-typable were detected in 35 (54%), 0 (-%), 15 (23%), 11 (17%), and 4 (6%) cases, respectively. Median (IQR) peak serum HCV-RNA VL rebound after OLT was 7,500,000 (1,430,000;21,450,000) IU/mL. None of the 147 patients cleared HCV infection without anti-HCV therapy. Treatment was started a median (IQR) of 10 (6;17) months after OLT. Overall, early virological response (decrease of 2 logs in HCV-RNA VL at 12 weeks), end of therapy response, and SVR were seen in 25 (38%), 19 (29%), and 13 (20%) cases, respectively. By ITT analysis (N=65), SVR rates for genotypes 1/4 or 2/3 were 9% and 60%, respectively. Anti-HCV treatment was stopped early in 38 cases (52%) due to non-virological response (15 cases, 23%), treatment toxicity (15 cases, 23%), death (4 cases, 6%), and other reasons (4 cases, 6%). By PP analysis (N=27), SVR rates for genotypes 1/4 or 2/3 were 27% and 80%, respectively.

Conclusions: The cure rate with PEG-INF plus RBV was low (20%), especially for genotypes 1/4. New anti-HCV drugs are necessary to improve the rate of SVR in HIV/HCV-coinfected liver recipients.

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 limited.

OBJECTIVE

To evaluate the efficacy and safety of treatment with pegylated-interferon (PEG-INF) and ribavirin (RBV) for recurrent HCV after OLT in 65 HIV-infected recipients.

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.

OLT INCLUSION CRITERIA*

- Liver criteria: the same as for the non-HIV-infected population.
- HIV criteria:

  1) Clinical: no previous C events (CDC, 1993) except some OIs (TB, Can, PCP); and,

  2) Immunological: pre-SOT CD4 cell count >100 cells/mm3 for OLT; and,

  3) Virological: RNA HIV-1 viral load BDL on cART or, if detectable, post-SOT 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.

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® or Copegus®; 400-1000 mg/day) for 48 wks.
- Doses were reduced according to tolerance and laboratory abnormalities (renal function).
- G-CSF or Erythro/Darbepoetin were given when necessary.

ANTI-HCV TREATMENT (II)

- Definitions:

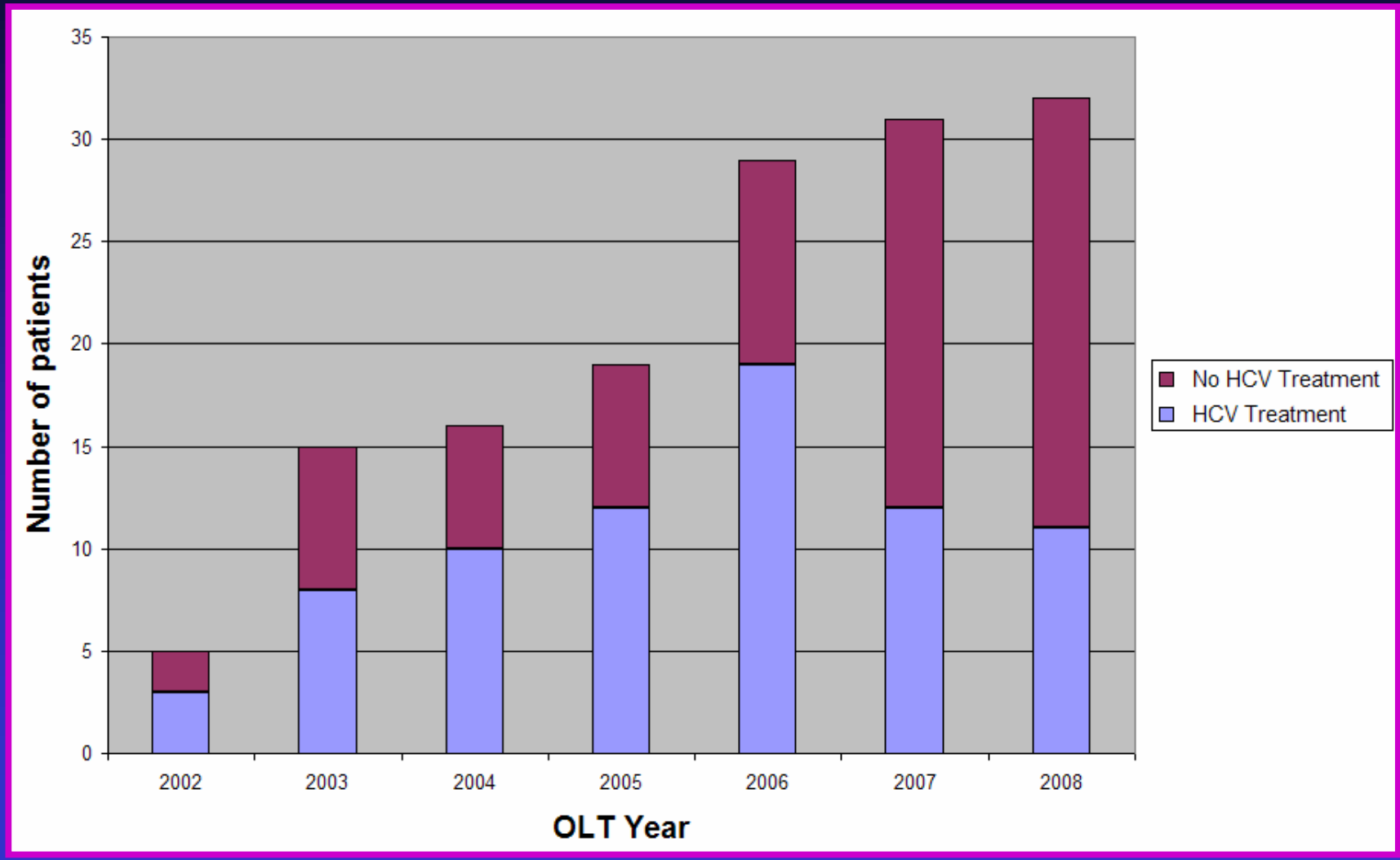
  - Early virological response (EVR) ¯ ≥2 log of HCV RNA viral load (VL) at 12 wks;

  - 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.

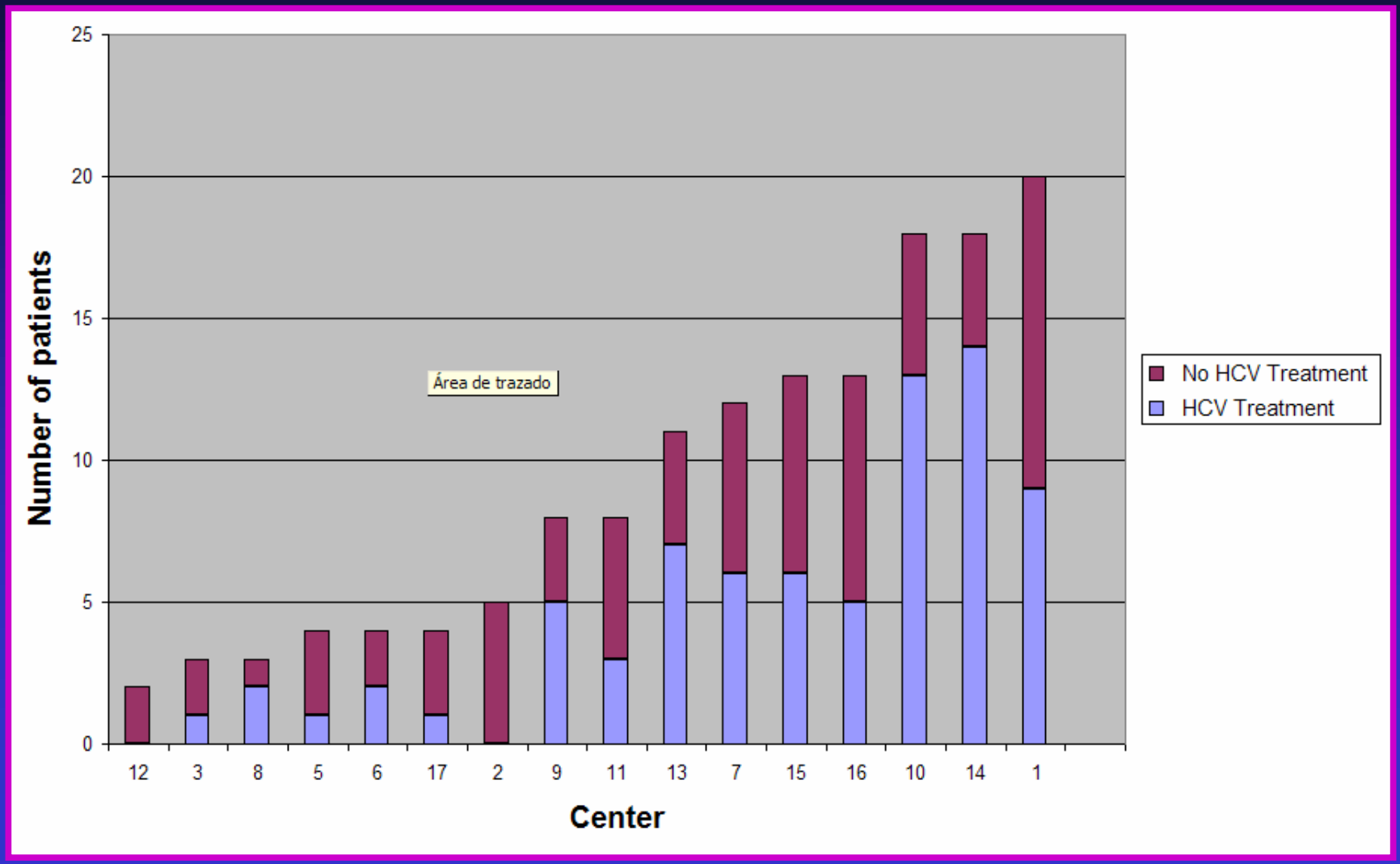
- Cohort study. Descriptive analysis.
- Responses were evaluated by ITT (NC=F) and per protocol (PP) analysis.

Annual number of HIV/HCV-coinfected OLT recipients who received anti-HCV treatment between 2002 and 2008



There were 75 patients treated (51%) among 147 HIV/HCV-coinfected OLT recipients.

Number of HIV/HCV-coinfected OLT recipients who received anti-HCV treatment per hospital between 2002 and 2008



Distribution of patients at the end of the study

Patients excluded	10*
Patients included	65

Patient distribution

- Finished anti-HCV treatment	27 (42%)
- Premature discontinuation	38 (52%)
Lack of efficacy	15 (23%)
Toxicity	15 (23%)
Death	4 (6%)
Investigator/Patient decision	4 (6%)

* Interferon monotherapy, 3 cases; classic INF+RBV, 1 case; on treatment, 6 cases.

Main characteristics before starting anti-HCV therapy with Peg-INF+RBV (N=65)

Therapy with PEG-INF+RBV was started a median (IQR) of 10 (6-17) months after OLT

- On HAART	65 (100%)
- CD4 cells before starting treatment*	292 (164-414)
- Plasma HIV viral load <50 copies/mL	55 (85%)
- Anti-HCV Rx any time before OLT	26 (40%)
- Peak RNA HCV after OLT (x10^6 IU/mL)*	7.5 (1.4-21)
- Genotypes 1 / 4	35 / 11 (46, 71%)
2 / 3	0 / 15 (15, 23%)
Other / Non-typable	2 / 2 (4, 6%)

* Median (IQR)

Anti-HCV Rx virological response (ITT)

	Overall (N=65)	G1/4 (N=46)	G3 (N=15)	Other* (N=4)
EVR	25 (38%)	11 (24%)	13 (87%)	1 (25%)
ETR	19 (29%)	7 (15%)	11 (73%)	1 (25%)
SVR	13 (20%)	4 (9%)	9 (60%)	0 (-%)

EVR = Early virological response; ETR = End of therapy response; SVR = Sustained virological response.
* Two patients had other genotypes and another two had a non-typable genotype.

Anti-HCV Rx virological response (PP)

	Overall (N=27)	G1/4 (N=15)	G3 (N=10)	Other* (N=2)
EVR	19 (70%)	8 (53%)	10 (100%)	1
ETR	17 (63%)	6 (40%)	10 (100%)	1
SVR	12 (44%)	4 (27%)	8 (80%)	0

EVR = Early virological response; ETR = End of therapy response; SVR = Sustained virological response.
* Other genotype and non-typable genotype in one case each.

Anti-HCV Rx grade 3/4 side effects (N=65)

Toxicity (Grade ≥3)*	35 (54%)
- Bone marrow toxicity	19 (29%)
- Flu-like syndrome	15 (23%)
- Gastrointestinal intolerance	6 (9%)
- Depression	6 (9%)
- Other	18 (28%)
Growth factors	
- Erythro/Darbopoetin-a	34 (52%)
- G-CSF (Filgastrim®)	15 (23%)
Rx discontinuation due to SAEs	15 (23%)

* Some patients had more than one adverse event.

Univariate analysis of predictors of SVR (I)

	No SVR N=52	SVR N=13
Male gender	39 (75%)	9 (69%)
Age (years): Recipient*	42 (38-46)	44 (41-45)
Donor*,+	55 (41-68)	48 (44-62)
HIV risk factor: - Drug abuse	37 (71%)	12 (92%)
- Other	15 (29%)	1 (8%)
Peak RNA HCV after OLT*,**	7 (1.3-19)	11 (3.8-25)
HCV Genotype: - G1/4	42 (81%)	4 (31%)
- G3++	6 (12%)	9 (69%)
- Other	4 (7%)	-

* Median (IQR); ** x10^6 IU/L; +P=0.087; ++P=0.001

Univariate analysis of predictors of SVR (II)**

	No SVR N=52	SVR N=13
MELD score	15 (12-20)	13 (12-17)
Efavirenz-based cART	22 (42%)	7 (54%)
CD4 cell count	303 (163-450)	262 (178-342)
Plasma HIV VL<50 c./mL	43 (83%)	12 (92%)
Immunosuppressive Rx		
- Ciclosporin A	14 (27%)	3 (23%)
- Tacrolimus	32 (62%)	9 (69%)
- Other regimens	6 (11%)	1 (8%)
Acute rejection	18 (35%)	7 (53%)

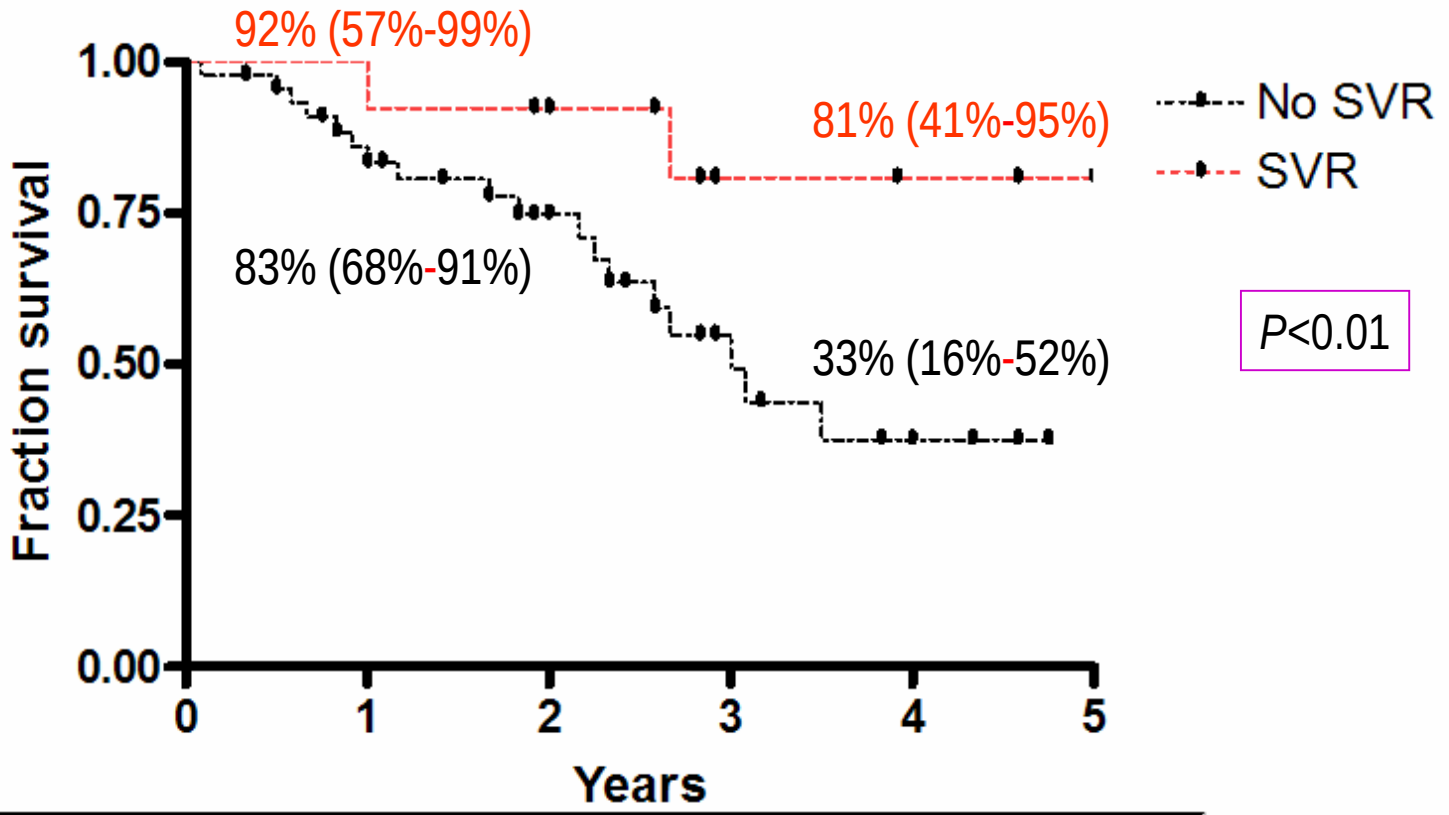
* Median (IQR); ** All *P* values were non-significant.

Univariate analysis of predictors of SVR (III)**

	No SVR N=52	SVR N=13
Type of Peg-INF		
- Peg-INF α2a	16 (31%)	5 (38%)
- Peg-INF α2b	36 (69%)	8 (62%)
Grade 3/4 adverse events	27 (52%)	3 (23%)
Erythro/Darbopoetin-α**	24 (46%)	10 (77%)
Pre-OLT anti-HCV Rx (N=26)		
- Overall	22/26 (85%)	4/26 (15%)
- Genotype 1***	15/15 (100%)	0/15 (0%)
- Other genotypes***	7/11 (64%)	4/11 (36%)

* Median (IQR); ** *P* = 0.064; *** *P*=0.099.

Survival after anti-HCV therapy according to treatment response



SVR	13	12	10	5	2	0
No SVR	49	36	21	9	3	0

CONCLUSIONS

- The overall rate of SVR with PEG-INF plus RBV was low (20%): 9% for genotypes 1/4 (N=46) and 60% for genotype 3 (N=15). Presence of genotype 3 was the only predictor of SVR.
- None of the 15 patients with genotype 1 unsuccessfully treated with PEG-INF+RBV before OLT had an SVR when they were treated again after OLT.
- Estimated 5-year survival for patients with an SVR was 81% (95%CI 41%-95%), whereas it was very poor for patients without SVR.
- Currently available anti-HCV therapy is only effective in a minority of HIV/HCV-coinfected OLT recipients with genotypes 1/4. New anti-HCV drugs are necessary to improve their outcome.

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Our patients.