INTERFERON (IFN)-FREE ANTIVIRAL THERAPY IN CIRRHOTIC PATIENTS INFECTED WITH HEPATITIS C ON THE WAITING LIST FOR LIVER TRANSPLANTATION. EFFICACY AND IMPACT ON DELISTING AND LIVER FUNCTION

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BACKGROUND

- Hepatitis C (HCV) reinfection after liver transplantation (LT) in patients who reach LT with HCV-RNA positive is universal.
- Management of LT patients is more complex in the setting of hepatitis C recurrence.
- There is little information on the efficacy and potential benefit of IFN-free antiviral therapy in HCV-infected cirrhotics awaiting LT.

AIMS

- To analyze the efficacy of IFN-free therapy with different combinations of direct-acting antivirals (DAAs) in HCV-cirrhotic patients awaiting LT.
- To assess the impact of therapy on liver function and delisting.

PATIENTS

- Observational multicenter retrospective study with data collected from 18 Spanish hospitals with LT Units.
- Patients with HCV-related cirrosis awaiting LT (for first LT or retransplantation -re-LT) who had received antiviral treatment from January-2013 to November-2015 with the different DAAs combinations (compassionate or commercial use) were included.
- Patients who continued antiviral therapy after LT were excluded from the study.

RESULTS

BASELINE CHARACTERISTICS

Patients/Treatments	n=238/245
Age (years), mean ± SD (range)	56 ± 7,6 (28-70)
Male gender	195 (80%)
Listed for re-LT (treatments)	19 (8%)
Diabetes	58 (24%)
Genotype	
- 1b / 1a/ 1	116 (47%) / 53 (22%) / 13 (5%)
- 3/4/5	40 (16%) / 22 (9%) / 1 (<1%)
HCV-RNA (logs IU/mL)	5,7 (2,4-7)
- > 800.000 (5,9 logs) IU/mL	87/242 (36%)
Non-responders (NR) to previous treatment:	
- NR PEG-IFN+RBV	121 (49%)
- NR PIs/Simeprevir	19 (8%)
- NR SOF+RBV±PEG / 2 DAAs	8 (3%) / 6 (2%)
Decompensation	172 (70%)
- Ascites	173 (65%)
- Encefalopathy	105 (43%)
- Variceal bleeding	40 (16%)
Esophageal varices	207 (85%)
Child-Pugh	8 (5-13)
- A	75 (31%)
- B	109 (45%)
- C	58 (24%)
- Non-cirrhosis (HCC)	1 (<1%)
MELD score	13 (6-24)
- ≤ 10	77 (32%)
- 11-15	103 (43%)
- 16-20	53 (22%)
- > 20	8 (3%)
Hepatocarcinoma (HCC)	119 (49%)
INR	1,30 (0,91-2,25)
Bilirubin (mg/dL)	1,9 (0,3-21,3)
Creatinine (mg/dL)	0,79 (0,36-2,2)
Albumin (g/dL)	3,2 (1,7-5,2)
* Alb ≤ 3,5 g/dL	173 (71%)
GPT (IU/L)	64 (14-250)
GGT (IU/L)	70 (8-1808)
Hemoglobin (g/dL)	12,7 (7,3-17,1)
Neutrophils/mm³	2.500 (320-8.380)
Platelets/mm³	69.500 (12000-272000)
* Platelets ≤ 75.000	132/244 (54%)

Data are expressed as median (range) unless otherwise indicated

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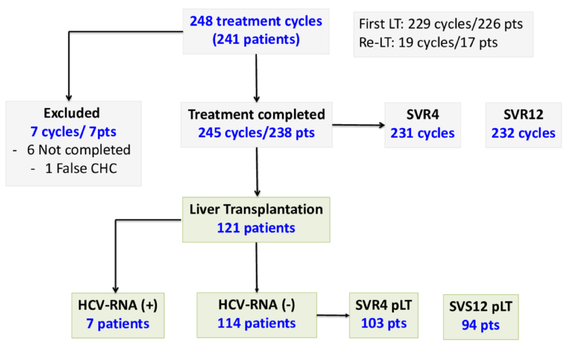
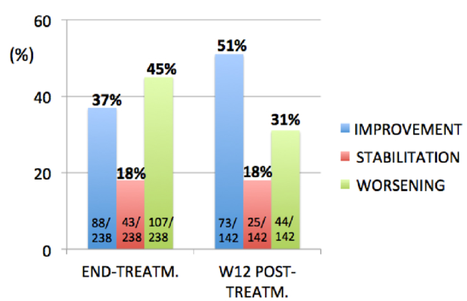
FLOWCHART OF PATIENTS



IMPACT OF TREATMENT ON LIVER FUNCTION (MELD CHANGE AFTER TREATMENT)



COMBINATIONS OF DAAs

DAAs Regimen	n	(%)	Availability of use
SOF + RBV	45	(18)	Compassionate / Commercial
SOF + DCV	60	(25)	Compassionate / Commercial
SOF + DCV + RBV	55	(22)	Compassionate / Commercial
SOF + SMV	18	(7)	Commercial
SOF + SMV + RBV	27	(11)	Commercial
SOF-LDV	7	(3)	Commercial
SOF-LDV + RBV	27	(11)	Commercial
3D	1	(<1%)	Commercial
3D + RBV	3	(1%)	Commercial
2D + RBV	1	(<1%)	Commercial

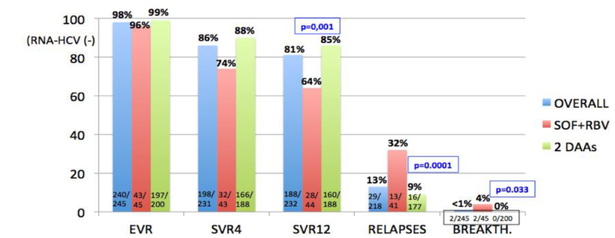
Regimens with RBV: 158 (64%)	Maximum dose RBV (median, rango):	
* 2 DAAs:	113 (57%)	1000 (200-1200)
Duration of treatment (median, range):	23 (2-50) weeks	
* 2 DAAs:	18 (2-28) weeks	

PATIENTS REMOVED FROM THE WAITING LIST

- **Disease progression** 13 (6%) → 11/13 due to HCC progression
- **Death** 9 (4%) → 6 HCC, 1 SPB, 1 diverticulitis, 1 brain tumor
- **Removed from the LT waiting list due to improvement:** 23 / 238 (10%)
  - HCC: 3 / 116 (3%)
  - Cirrhosis (for first LT)*: 20 / 110 (18%)
  - Re-LT: 0/17 (0%)
- **Delisting in patients without HCC listed for the first LT according to MELD score¥§**
  - MELD ≤ 18 20/95 (21%)
  - MELD > 18 0/15 (0%)

*Delisting due to improvement: MELD < 15 and compensated disease→10 (43%) without treatment, 11 (26%) diuretics and/or rifaximin and 2 (9%) TIPS
¥ p=0.049
§ In delisted patients, MELD score improved from 13.8± 2.4 to 11.3±2.4 (p=0.001) (follow-up, median (range): 31 weeks (10-71)

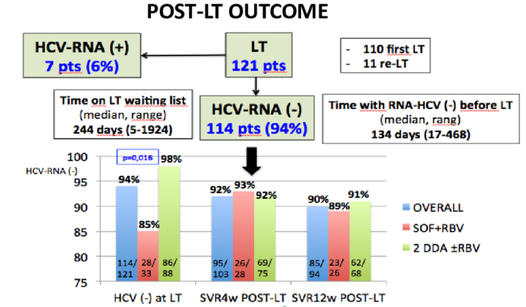
VIROLOGICAL RESPONSE



TREATMENT FAILURES (PRE AND POST-LT)

	OVERALL		SOF + RBV		2 DAAs ± RBV	
ALL	44 /232	(19%)	16/ 44	(36%)	28/ 188	(15%)
VIROLOGICAL	31	(13%)	15	(33%)	16	(9%)
- Relapses	29	(13%)	13	(29%)	16	(9%)
- Breakthrough	2	(<1%)	2	(4%)	-	
NON-VIROLOGICAL	13	(6%)	1 (Exitus)	(2%)	12 (11 Exitus)	(6%)

POST-LT OUTCOME



FAILURES (POST-LT)	OVERALL		SOF+RBV		2DAAs±RBV	
ALL	9/94	(10%)	3/26	(12%)	6/68	(9%)
VIROLOGICAL	6	(>6%)	3 Relapses	(12%)	3 Relapses	(>4%)
NON-VIROLOGICAL	3	(>3%)	-		3 Exitus	(>4%)

CONCLUSIONS

1) The combination of 2 DAAs showed high efficacy (SVR 85%) in cirrhotic patients awaiting LT. 2) The treatment with DAAs improved liver function in about 40% and led to delisting of 10 % (18% of those without HCC and listed for first LT). 3) No patient with baseline MELD >18 points coud be removed from the waiting list for clinical improvement. 4) 98% of patients treated with 2 DAAs reached LT with undetectable HCV-RNA and less than 5% had a graft reinfection. 5) These results support the use of antiviral treatment in patients awaiting LT, especially in those without HCC, listed for the first LT and MELD ≤ 18 (at least 20% of these patients could avoid a LT).