TREATMENT OF HEPATITIS C IN THE LIVER TRANSPLANT SETTING

Dra. Zoe Mariño
Liver Unit. Hospital Clinic
Barcelona
Hepatitis C after LT

Survival (%) vs. Time from LT (years)

- HCV negative
- HCV positive
HCV treatment strategies

1. Waiting List ("preventive strategy"):  
   Compensated and decompensated cirrhosis.

2. After LT:  
   - When?  
   - Why?  
   - How?
IFN-based therapies in the waiting list

**Peg-IFN+RBV**

Duration (median) 12 w

<table>
<thead>
<tr>
<th>HCV-RNA indetectable (%)</th>
<th>All (n=117)</th>
<th>G1 (n=84)</th>
<th>G2/3 (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOT (LT)</td>
<td>42</td>
<td>32</td>
<td>72</td>
</tr>
<tr>
<td>Post LT</td>
<td>23</td>
<td>15</td>
<td>48</td>
</tr>
</tbody>
</table>

**Peg-IFN+ RBV+ IPs (TLV/BOC)**

**ANECDOTAL EXPERIENCE (n=29)**

SVR12 67% (8/12)

Better SVR rates in cirrhosis (~50%) but......

...... High rate of adverse events (infections, liver decompensation... >40%).


IFN-based therapies in the waiting list

Peg-IFN+ RBV+ DAAs: SOF/ SIM/DCL
From general cirrhotic patients

Gambato et al, J Hepatol 2014

IFN-based therapies in the waiting list

IFN should NOT be used in patients with decompensated liver disease (Child B>7 y/o MELD>18) as it is related with high rate of bacterial infections and liver impairment.

Carrión et al, J Hepatol 2009
IFN-free treatments in the waiting list (DAAs)

Containment trial (phase II):
**Sofosbuvir + RBV WB** until LT (or max 48w) in 61 HCV compensated cirrhotic patients enlisted for LT (Child A/ B7)

*3 patients >LLOQ at LT
† 3 deaths, 10 recurred after LT

* Curry et al, Gastroenterol 2014
**IFN-free treatments in cirrhosis (DAAs)**

**TURQUOISE II trial:**

Paritaprevir (ABT-450)/r/Ombitasvir (ABT-267) + Dasabuvir (ABT-333) + RBV

380 compensated CH, 12-24 weeks, 70% G1a, naive/TE

* Treatment failure was associated with G1a infection and null response → 90%

Poordad et al, NEJM 2014
**IFN-free treatments in cirrhosis (DAAs)**

**Sofosbuvir/ Ledipasvir + RBV**

Pooled report: G1 compensated cirrhosis  
(n=513)

* SVR12>95% in all arms except:  
CH /TE / wo RBV/ 12 weeks: 90%  
In pats with <70 000 and TE: 82%

Bourlière et al, AASLD 2014
IFN-free treatments in cirrhosis (DAAs)

Cohort A, SOLAR-1: **Sofosbuvir/Ledipasvir + RBV** (12/ 24 weeks)
108 G1 or G4 decompensated cirrhotics: **Child B (7-9) or C (10-12)**

* No available data in MELD>20

* Flamm et al, AASLD 2014
IFN-free treatments in cirrhosis (DAAs)

Impact of treatment on liver function and clinical status

<table>
<thead>
<tr>
<th>Child B</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
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<tbody>
<tr>
<td>MELD</td>
<td>(+10)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>60%</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Child C</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>65%</td>
<td></td>
<td>79%</td>
</tr>
</tbody>
</table>

Flamm et al, AASLD 2014
IFN-free treatments in cirrhosis (DAAs)

Sofosbuvir + Simeprevir ± RBV 12 weeks (n=147)

Cirrhotic patients included (n=114), **93 were in WL**, (MELD 12), 65%
TE (~18% PI-failures); 70% G1a

No cirrhosis 100% vs **cirrhosis 81%**
Child A 83% vs Child B 79%

Similar results reported from the HCV-TARGET, SVR4 in cirrhosis was
87% *(Jenssen, AASLD 2014)*

* 14 treatment failures (relapse), all cirrhosis

Agel et al, AASLD 2014
IFN-free treatments in cirrhosis (DAAs)

SAFETY PROFILE

IFN-free treatments are generally **SAFE** when used in cirrhotic patients (no significant difference from non cirrhotic patients)

There is still **lack of data** regarding safety and efficacy of DAAs in more advanced liver disease: Child >12 and/or MELD>20.

*Afshal et al, AASLD 2014; Aqel et al, AASLD 2014; Flamm et al, AASLD 2014; Bourliere et al, AASLD 2014; Gambato et al, J Hepatol 2014*
HCV treatment strategies

1. Waiting List ("preventive strategy"): Compensated and decompensated cirrhosis.

2. After LT:
   - When?
   - Why?
   - How?
### HCV treatment after LT: WHEN?

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Pre-emptive     | 1. It may prevent the infection of the graft  
|                 | 2. It may prevent the development of liver fibrosis | 1. Difficult administration (renal function, potential for DDI, ability to take oral medications)  
|                 |                                                       | 2. No data on safety and efficacy with DAAs. |

Mariño et al, Curr Op Organ Transplant 2015 (submitted); Gambato et al, J Hepatol 2014
HCV treatment after LT: WHY?

Beneficial effects of SVR on graft and patient survival after LT

Log-rank < 0.001

HCV treatment after LT: HOW? - IFN based

**Peg IFN+RBV** and **triple Peg IFN+RBV+ IPs** (telaprevir/ boceprevir) after LT

**EFFICACY**

- **RVS12 (%)**
  - Peg IFN+ RBV: 30 (n=611, todos)
  - Peg IFN+RBV+ IP: 50-72 (n=524, G1, n>400, G1)

**SAFETY**

- Anemia (HB≤10g/L): 85-95%
- RBV DR/EPO/Transfusion: 95%/~50%
- ACR (biopsy-proven): 4-6%
- Renal failure: 13-40%
- Infections: ~20%
- Early D/C (NR/EAs): 25-56%
- SAEs: 25%
- Mortality rate: 1-5%

Berenguer M, J Hepatol 2008
Faisal, J Hepatol 2013; Coilly, Liver Int 2013; Stravitz, Hepatol 2013; Pungpapong, Hepatol 2013; Forns, J Hepatol 2014
**HCV treatment after LT: HOW?- IFN free**

**Sofosbuvir + RBV** (initial 400mg) (24 weeks) in 40 liver recipients: 63% F3-4, 83% G1, 88% previous TE after LT

**EFFICACY**

<table>
<thead>
<tr>
<th></th>
<th>Sem 4</th>
<th>EOT</th>
<th>SVR4</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-RNA indetectable (%)</td>
<td>100</td>
<td>100</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

**SAFETY**

- Anemia: 20%
- ACR: 0%
- Renal failure: 0%
- Early D/C: 5%
- SAEs: 15%
- Mortality: 0%

No on-treatment virological failures; all relapse after EOT.

*No expected DDIs with IMS*

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*Samuel D et al, J Hepatol 2014*
HCV treatment after LT: HOW? - IFN free

Paritaprevir/R/Ombitasvir + Dasabuvir + RBV in 34 HCV stable liver recipients.

F0-2, naive, 85% G1a → extension to F3-4 soon

**EFFICACY**

- W4: 100%
- EOT: 100%
- SVR4: 96*
- SVR12: 96*

**SAFETY**

- Anemia: 17%
- ACR: 0%
- Renal failure: 0%
- Early D/C: 3%
- SAEs: 6%
- Mortality: 0%

*Expected DDIs: reduce TAC 0.2-0.5/weekly and CyA to 1/5 of baseline dose.*

- 1 relapse*; the patient showed RAVs not seen at baseline.

Kwo et al, J Hepatol 2014
**Cohort B SOLAR-1 trial:** 223 G1 o G4 patients, naïve or TE after LT. F0-F3, CPT A, B C

- **LDV/SOF+RBV (N=112)**
- **LDV/SOF+RBV (N=111)**

**Treatment was SAFE**
7 reported deaths (2 CPT A, 5 CPT B), diverse causes and no related with medication

*Reddy et al, AASLD 2014*
HCV treatment after LT: HOW? - IFN free

Good SAFETY profile
Anemia was 42% in RBV vs 2% in non-RBV
1 reported death (pharmacological lung toxicity?)

Week 24
Week 12
SVR12

G1 (G1a 62%), F3-F4 29%, cholestatic recurrence 11%, TE to PR 69%/ PI-failures in12%

Pungpapong et al, AASLD 2014
HCV treatment after LT: HOW?- IFN free

G1, G2, G3 patients after Lt, DAA-based therapies, including cirrhotic and treatment experienced after LT (HCV-TARGET Consortium)

TREATMENT OPTIONS

G1
- SOF SMV
- SOF SMV RBV
- SOF PEG RBV
- SOF RBV

G2
- SOF SMV
- SOF RBV

G3
- SOF SMV
- SOF PEG RBV
- SOF RBV

Efficacy

SVR4 (%)

G1* (SOF SMV ± RBV)
- 61/68
- 90%

G2 (SOF +RBV)
- 9/10
- 90%

G3 (SOF +RBV)
- 3/5
- 60%

*SVR4 86% in cirrhosis (77% if MELD>10)

Brown et al, AASLD 2014
Antiviral therapies in HCV severe recurrences

Compassive use program: **Sofosbuvir + RBV (± PEG-IFN),**
Fibrosing cholestatic hepatitis (FCH) or graft cirrhosis after LT (n=104)

- Early Cholestatic recurrence: SVR12 73%
- Cirrhosis after LT: SVR12 43%

Patients receiving a liver graft while on treatment (n=12) were excluded from the efficacy analysis.

Forns et al, Hepatology 2015
Clinical outcomes: impact of treatment (SOF + RBV ± PEG-IFN, n=104)

79% of treated patients showed a clinical stabilization or improvement

*Significant decrease in hepatic encephalopathy, improvement or disappearance of ascites, or improvement in liver-related laboratory values.

** 8 worsened and 13 died.

Forns et al, Hepatology 2015
Antiviral therapies in HCV severe recurrences

French cohort of FCH: CUPILT (N=23)
All TE after LT, ascitis/ EH 27-50%

Clinical and analytical improvement in the majority of patients.

* Relapse, n=1, coinfected HIV-HCV, F4, G1b

Dumortier et al, AASLD 2014
Summary

- **IFN-free regimens** in cirrhotic patients before LT are generally safe, although data is lacking concerning patients with Child>12 and/or MELD>20.

- In the next few years, the **current scenario of hepatitis C in the transplant setting will radically change**, as we will be able to cure almost all patients on the waiting list, or easily after LT.

- Trials and real-clinical practice with **IFN-free regimens after LT** are encouraging. Their safety profile and virological results are very good. Efficacy is reduced in advanced cirrhosis after LT, and therefore treatment should be done before advanced disease is reached.

- Data in patients with **severe hepatitis C recurrence**, including FCH, are good and importantly, clinical outcomes improve in those achieving viral clearance.

_Mariño et al, Curr Op Organ Transplant 2015 (submitted); Gambato et al, J Hepatol 2014_