How to optimize treatment in HCV G1 naïve patients?

Raluka Pais, Pitié Salpêtrière Hospital, Paris, France
62 years old man, BMI = 25.2 kg/m²
Diagnosed with HCV G1b, IL28B = CT; HCV RNA = 6.5 log.
Never treated
Drug user at his age of 20th; HIV negative
Type 2 diabetes on oral medication, HbA1c = 6.5%
Drinking less than 30 g/day

Blood group = B +
Hb = 13.5 g/dl; Platelet = 92 000/mm³
AST = 162 IU/l; ALT = 85 IU/l; GGT = 236 IU/l; PAL = 180 IU/l.
Total Bilirubin = 32 mmol/l
Albumin = 34 g/dl; Creatinin = 130 µmol/l
TP = 50%; FV = 55%
AFP = 89 nmol/l
No hepatic encephalopathy
FT = 0.92; FS = 28 kPa
CT scan – mild ascites; 2 nodules: 2.5 cm and 1 cm, segm. V and VII typical of HCC
Upper gastroscopy: gr. II varices

HCV Cirrhosis, Child B8, MELD = 17
HCC BCLC A, Milan in, AFP Score = 0

Decision:
- Inscription on the waiting list for OLT
- Down staging HCC therapy: TACE
Q1

Treatment of HCV prior to liver transplantation – Wise or wasteful?
HCV Recurrence post OLT

Cumulative rate of progression to HCV cirrhosis

- 90% recipients have histological features of chronic HCV
- 10 – 30% progress to cirrhosis
- Median interval OLT ➔ cirrhosis = 9.5 y Post OLT HCV cirrhosis – 40% decomp. 1 year

- Reduced patient and graft survival
- Poor outcomes of re-transplantation (50 – 80% mortality on waiting list)

Gane, Liver Int. 2014
Prevent post OLT HCV Recurrence

Phase II Study
N = 61 Patients, CP A
46 LT, 43 undetectable HCV RNA at LT

Post OLT SVR 12 = 70%

> 30 days TND

→ 30 days HCV RNA ↔ LLOQ → 96% post OLT SVR

Median days TND
- No recurrence: 90
- Recurrence: 5.5

*Wilcoxon rank sum test.

Curry, Gastroenterology 2015
Significant reduction in CHILD Score

OF/LDV + RBV for 12 weeks in patients with decompensated cirrhosis

Changes in Child-Pugh Score at post treatment W4

Amélioration (n = 33)  Stabilité (n = 10)  Aggravation (n = 4)

significant reduction in CHILD Score

Flamm SL, Etats Unis, AASLD 2014, Abs. 239 actualisé
Choice of the treatment regimen:

- IFN based 1st generation PI's
- IFN based new DAA
- IFN- free DAA
SVR with IFN based regimens in cirrhotic patients

1st generation PI’s

IFN-free new DAA

Poordad, NEJM 2011
Jacobson, NEJM 2011

Lawitz, NEJM 2014
Manns, Lancet 2014
CLINICAL CASE

Q3 IFN-free DAA:

Treatment duration in cirrhotic patients?

- **12 weeks**
- **24 weeks**

Our patient:
Child B8, MELD 17
Naive
G1b, IL28B = CT
Hb = 13.5 g/dl

RBV:
- **With RBV**
- **Without RBV**
ION – 1: SOF/LDV in G1 untreated patients with or without cirrhosis

Phase III, N = 865 patients
16% had cirrhosis (compensated)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12 wks.</th>
<th>12 wks.</th>
<th>24 wks.</th>
<th>24 wks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/LDV</td>
<td>99</td>
<td>97</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>SOF/LDV/RBV</td>
<td>94</td>
<td>100</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>SOF/LDV/24 wks</td>
<td>94</td>
<td>98</td>
<td>94</td>
<td>36</td>
</tr>
<tr>
<td>SOF/LDV/RBV 24 wks</td>
<td>179</td>
<td>178</td>
<td>181</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>184</td>
<td>184</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>33</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>33</td>
<td>33</td>
<td>36</td>
</tr>
</tbody>
</table>

- **Breakthrough**: 0 (SOF/LDV 12 wks), 0 (SOF/LDV/RBV 12 wks), 1 (SOF/LDV 24 wks), 0 (SOF/LDV/RBV 24 wks)
- **Relapse**: 1 (SOF/LDV 12 wks), 0 (SOF/LDV/RBV 12 wks), 1 (SOF/LDV 24 wks), 0 (SOF/LDV/RBV 24 wks)
- **Lost of f/u**: 2 (SOF/LDV 12 wks), 6 (SOF/LDV/RBV 12 wks), 3 (SOF/LDV 24 wks), 2 (SOF/LDV/RBV 24 wks)

*\textsuperscript{1} Afdhal, NEJM 2014*
**SOF/LDV ± RBV in G1 patients with cirrhosis**

N = 513 patients with compensated cirrhosis; 31% naïve.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Naïfs de traitement</th>
<th>En échec de traitement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RVS12 globale</strong></td>
<td>96 %</td>
<td>98 %</td>
<td>95 %</td>
</tr>
<tr>
<td><strong>Durée</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 sem.</td>
<td>95 %</td>
<td>97 %</td>
<td>94 %</td>
</tr>
<tr>
<td>24 sem.</td>
<td>98 %</td>
<td>99 %</td>
<td>98 %</td>
</tr>
<tr>
<td><strong>Régime</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>95 %</td>
<td>96 %</td>
<td>95 %</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>97 %</td>
<td>99 %</td>
<td>96 %</td>
</tr>
<tr>
<td><strong>Durée ± RBV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF 12 sem</td>
<td>92 %</td>
<td>96 %</td>
<td>90 %</td>
</tr>
<tr>
<td>LDV/SOF + RBV 12 sem</td>
<td>96 %</td>
<td>98 %</td>
<td>96 %</td>
</tr>
<tr>
<td>LDV/SOF 24 sem</td>
<td>98 %</td>
<td>97 %</td>
<td>98 %</td>
</tr>
<tr>
<td>LDV/SOF + RBV 24 sem</td>
<td>100 %</td>
<td>100 %</td>
<td>100 %</td>
</tr>
</tbody>
</table>

*Bourlière M, France, AASLD 2014, Abs. 82 actualisé*
SOLAR -1: LDV-SOF + RBV in patients with decompensated cirrhosis listed for OLT

6 subjects excluded because received transplant while on study: (2 CPT B/24 week; 1 CPT 2/12 week; 3 CPT C/24 week
3 subjects had not reached SVR12 timepoint

Flamm, Abstr 239, AASLD 2014
Impact of RBV on quality of life

On treatment and EOT quality of life: SOF/LDV± RBV

Younossi Z, Etats-Unis, EASL 2014, Abs. P1324 actualisé
Sofosbuvir + Daclatasvir in previously untreated G1 patients

Phase III ALLY 1 trial: ongoing (cirrhosis and post OLT)

Sułkowski, NEJM 2014
COSMOS (cohort 2): sofosbuvir/simeprevir + RBV in F3F4 G1 naïve and non responders

Subtype and Q80K

Fibrosis Score

F4: naive or null responders

<table>
<thead>
<tr>
<th>Subtype</th>
<th>without Q80K</th>
<th>with Q80K</th>
<th>F3</th>
<th>F4</th>
<th>Null responders</th>
<th>Naives</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1b</td>
<td>18/18</td>
<td>38/40</td>
<td>44/45</td>
<td>21/22</td>
<td>16/17</td>
<td></td>
</tr>
<tr>
<td>G1a</td>
<td>25/26</td>
<td>96/95</td>
<td>37/39</td>
<td>94/96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients sans RVS12 pour raison non virologique exclus de l'analyse

Lawitz E, Etats-Unis, EASL 2014, Abs. 0165 actualisé
SOF/SMV ± RBV – Real Life Data
HCV TARGET

- Genotype 1: SOF + SIM ± RBV 12 weeks - 378 patients

Jensen DM, Etats-Unis, AASLD 2014, Abs. 45 actualisé
Turquoise 2 : ABT-450/r/ombitasvir + dasabuvir + RBV in G1 patients with cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>SVR 12%</th>
<th>SVR 24%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naives</td>
<td>94,2</td>
<td>95,9</td>
</tr>
<tr>
<td>Relapsers</td>
<td>96,6</td>
<td>100</td>
</tr>
<tr>
<td>Partial responders</td>
<td>94,4</td>
<td>100</td>
</tr>
<tr>
<td>Null Responders</td>
<td>86,7</td>
<td>95,2</td>
</tr>
</tbody>
</table>

Fried M, Etats-Unis, AASLD 2014, Abs. 81 actualisé
Q4

Predictors of SVR/AE’s

Does Albumin level and platelets count impact outcomes of patients with cirrhosis treated with the new DAA?

☑ YES

☑ NO

Our patient:

Child B8, MELD 17
Naïve, G1b, IL28B = CT
Hb = 13.5 g/dl
Albumin = 34 g/l
Platelet = 92 000/mm3
Predictors of SVR and AE’s with 1st generation PI’s

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Platelets count ≤ 100,000/mm³</th>
<th>Platelets count &gt; 100,000/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35 g/L</td>
<td>37 19 (51.4%) 10 (27.0%)</td>
<td>31 5 (16.1%) 9 (29.0%)</td>
</tr>
<tr>
<td>35 g/L</td>
<td>74 9 (12.2%) 27 (36.5%)</td>
<td>306 19 (6.2%) 168 (54.9%)</td>
</tr>
</tbody>
</table>

## SOF/LDV ± RBV in G1 patients with cirrhosis

<table>
<thead>
<tr>
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<th>Total</th>
<th>Naïfs de traitement</th>
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</thead>
<tbody>
<tr>
<td><strong>RVS 12 globale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96 %</td>
<td>98 %</td>
<td>95 %</td>
</tr>
<tr>
<td><strong>Génotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1a</td>
<td>96 %</td>
<td>98 %</td>
<td>95 %</td>
</tr>
<tr>
<td>G1b</td>
<td>97 %</td>
<td>97 %</td>
<td>96 %</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65 ans</td>
<td>96 %</td>
<td>98 %</td>
<td>95 %</td>
</tr>
<tr>
<td>≥ 65 ans</td>
<td>97 %</td>
<td>94 %</td>
<td>98 %</td>
</tr>
<tr>
<td><strong>Albumine (g/dl)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3,5</td>
<td>97 %</td>
<td>95 %</td>
<td>98 %</td>
</tr>
<tr>
<td>≥ 3,5</td>
<td>96 %</td>
<td>98 %</td>
<td>95 %</td>
</tr>
<tr>
<td><strong>Plaquettes (x 103/µl)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 75</td>
<td>84 %</td>
<td>90 %</td>
<td>82 %</td>
</tr>
<tr>
<td>≥ 75 – ≤ 100</td>
<td>99 %</td>
<td>100 %</td>
<td>98 %</td>
</tr>
<tr>
<td>≥ 100 – ≤ 125</td>
<td>95 %</td>
<td>98 %</td>
<td>93 %</td>
</tr>
<tr>
<td>≥ 125</td>
<td>98 %</td>
<td>98 %</td>
<td>98 %</td>
</tr>
</tbody>
</table>
Negative predictors with SOF-based regimens

<table>
<thead>
<tr>
<th>Predictor</th>
<th>SVR 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous treatment Male</td>
<td>100</td>
</tr>
<tr>
<td>Weight ≥ 75 kg</td>
<td>100</td>
</tr>
<tr>
<td>IL28B non CC</td>
<td>100</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>100</td>
</tr>
<tr>
<td>HCV RNA &gt; 800 000</td>
<td>100</td>
</tr>
</tbody>
</table>

SVR 12 according to the number of negative predictors and viral genotype

![Graph showing SVR 12 rates for different numbers of negative predictors and viral genotypes](image)
Q5

DAA and renal impairment

Dose adaptation according to renal function?

Our patient:

✓ YES
Child B8, MELD 17
Naive
G1b, IL28B = CT
Hb = 13.5 g/dl

✓ NO
Creatinin = 130 µmol/l; Clearence = 53 ml/min
In November 2014...

Renal excretion

AUCO SOF = 2.7 fold higher
AUCO GS 331007 = 5.5 fold higher

Less than 1% renal excretion

In 2015, Lédipasvir

Less than 1% renal excretion
Safety, Efficacy and PK of SOF and LDV in patients with renal impairment

**SOFOSBUVIR**

- 10 patients Without cirrhosis
- CrCl ↓ 30 ml/min
- SOF/RBV 24 wks

**Efficacy**

- W4 HCV RNA under LLOQ = 9/10

**Safety**

- ✓ 1 RBV STOP at W8
- ✓ 4 RBV dose reduction
- ✓ 2/3 increased dose EPO
- ✓ 3 introductions EPO
- ✓ 1 angor instable

**LEDIPASVIR**

- Same PK as patients with normal RF
- No dose adaptation

Gane, AASLD 2014 Abstr. 966

Mogalian, AASLD 2014 Abstr. 1952
Q6 Health outcomes and benefits with DAA?

- Most benefit with IFN-based DAA
- Most benefit with IFN-free DAA
Delaying treatment initiation in HCV G1 treatment naive patients would lead to a substantially more cases of CLD complications ....

Greatest benefit of treating F2 vs. F3F4

Ahmed, Younossi, AASLD 2014, Abstr. 175
Impact of future HCV treatment on LT 2013 – 2022

Avoid LT in 4425 potential candidates

Reduction in gap between the needs of LT and graft availability:

- 88% for HCC
- 42% for decompensated cirrhosis

Deuffic-Burban, Dig. Liv. Dis. 2014
Cost effectiveness in G1 patients

<table>
<thead>
<tr>
<th></th>
<th>Triple therapy</th>
<th>Oral interferon-free therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Staging</td>
<td>Treat all</td>
</tr>
<tr>
<td>Life expectancy (yr)</td>
<td>28.324</td>
<td>28.520</td>
</tr>
<tr>
<td>Progression to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis (%)</td>
<td>29.4</td>
<td>23.6</td>
</tr>
<tr>
<td>Decompensated (%)</td>
<td>13.4</td>
<td>11.8</td>
</tr>
<tr>
<td>HCC (%)</td>
<td>12.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Decompensated or HCC (%)</td>
<td>24.2</td>
<td>21.3</td>
</tr>
<tr>
<td>Transplant (%)</td>
<td>5.2</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Unit price of molecules, €/week
- Combination of pegylated interferon and ribavirin: 312
- Telaprevir: 2210
- Boceprevir: 796
- IFN-based new DAAs*: 5062

Unit price of severe adverse events, €†
- Anemia: 2564
- Depression: 1619
- Rash: 2942

Unit price of moderate anemia, €‡: 4200

Younossi, J Hepatol. 2014; Deuffic-Burban, J Hepatol 2014
"There are decades where nothing happens; and there are weeks where decades happen."

Scott Freedman, J Hepatol. 2014
Thank you!