How to Optimize Current Therapy of Genotype 2 Patients

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Disclosures

Dr. Adrián Gadano has received research support, lecture fees and took part in clinical trials for:

- Roche
- Novartis
- BMS
- Gilead
- Janssen
- MSD
- GSK
- AbbVie
HCV-2: best friend in the HCV family...

- Distribution worldwide. High prevalence in some countries (Italy, South Korea, Argentina...).
- Easiest to treat genotype.
- New highly effective and safe therapies are changing the landscape (SOF-RBV).
- Conventional therapy may be optimized according to baseline and on-treatment predictors of response (Peg-RBV).
HCV-2: Treat or Wait?
What do the Guidelines say?

(1) All patients with compensated disease should be considered for therapy (A2).

(2) Treatment should be initiated promptly in patients with advanced fibrosis (METAVIR score F3–F4), and strongly considered in patients with moderate fibrosis (METAVIR score F2) (B2).

(3) In patients with less severe disease, indication for therapy is individual (C2).

As oral regimens with improved tolerability and efficacy are released, the optimal management in patients with mild disease may be to defer treatment until they become available.

EASL Guidelines HCV. J Hepatol 2011
HCV-2: Two different scenarios at the time of deciding therapy

- Past and Current therapy: Peg/RBV
  (still most countries)

- New therapy: SOF/RBV
  (only few countries...
Why treating HCV-2 patients with Peg/RBV now?

• Many HCV-2 patients cannot wait! (F3, F4). (also extrahepatic disease).

• Access to DAAs still uncertain in most parts of the world.

• High SVR rates with Peg-RBV (possible short duration).
Treatment Guidelines for HCV-2 patients

Peg IFN plus RBV for 24 weeks

SVR (%)

PEG-IFN + RBV 24 W

80-90 %

Genotype 2

EASL Guidelines HCV. J Hepatol 2011
“Optimized” Therapy for HCV-2

• HCV-2 is different from HCV-3 in terms of response to therapy.

• Is it possible to shorten treatment without loosing efficacy? In which patients?

• Do we need to extend therapy in “difficult to treat” patients? Which are these patients?
Genotype 2 = Genotype 3
Telaprevir in patients with HCV genotypes 2 and 3

HCV 2 – Monotherapy with TPV

HCV 3 – Monotherapy with TPV

Foster et al. Gastroenterol 2011
“Optimized” Therapy for HCV-2

• HCV-2 is different from HCV-3 in terms of response to therapy.

• Is it possible to shorten treatment without loosing efficacy? In which patients?

• Do we need to extend therapy in “difficult to treat” patients? Which are these patients?
Shorten therapy? → YES, in patients with predictors of good response...

Which are the predictors of response?

- Baseline:
  - Cirrhosis
  - BMI/IR
  - Viral load
  - IL28B (in non RVR)

- On treatment:
  - RVR

EASL Guidelines HCV. J Hepatol 2011
ACCELERATE: Treatment duration in HCV-2 and 3

PEG IFN alfa-2a 180 µg/S + RBV 800 mg/d (n= 732)

PEG IFN alfa-2a 180 µg/S + RBV 800 mg/d (n= 733)

24 W of Follow-up

W 16

W 24

20-25% → Bridging fibrosis or cirrhosis

ACCELERATE: Treatment duration in HCV-2 and 3

P< 0.001

- 16 weeks: 62% (n=455)
- 24 weeks: 70% (n=515)

RVR is the strongest predictor of treatment outcome in HCV-2 patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>RVR</th>
<th>Non-RVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangia</td>
<td>213</td>
<td>76% (40/53)</td>
<td>78% (45/58)</td>
</tr>
<tr>
<td>Schiffman</td>
<td>347</td>
<td>85% (210/247)</td>
<td>53% (53/100)</td>
</tr>
<tr>
<td>Rumi</td>
<td>230</td>
<td>83% (151/182)</td>
<td>52% (25/48)</td>
</tr>
<tr>
<td>Yu</td>
<td>150</td>
<td>95% (95/100)</td>
<td>77% (10/13)</td>
</tr>
<tr>
<td>Marcellin</td>
<td>1025</td>
<td>76% (662/858)</td>
<td>45% (70/157)</td>
</tr>
</tbody>
</table>
SVR in patients with HCV-2 that experienced RVR

RVR + / Weight-Based Dose of RBV (1000-1200 mg)

However, short therapy is not recommended in patients with baseline predictors of treatment failure such as bridging fibrosis/cirrhosis, high baseline viraemia, high BMI and insulin resistance

(RR 1.02, 95%, CI: 0.97–1.06, NS)

Di Martino et al. Hepatology 2011
“Optimized” Therapy for HCV-2

• HCV-2 is different from HCV-3 in terms of response to therapy.

• Is it possible to shorten treatment without loosing efficacy? In which patients?

• Do we need to extend therapy in “difficult to treat” patients? Which are these patients?
48 weeks therapy in HCV 2/3 patients without RVR but with EVR: N-CORE

Poor evidence to recommend extended treatment in patients with negative predictors of response

Cheinquer et al, AASLD 2012
HCV-2 Treatment with PEG-INF Plus RBV (WBD)

- HCV RNA Undetectable
  - W4
  - High Basal Viral Load
  - Bridging fibrosis/cirrhosis
  - High BMI
  - Insulin resistance
    - YES: 24 week treatment
    - NO: 16 week treatment

- HCV RNA Detectable
  - W4
  - W12 assessment:
    - HCV RNA undetectable or > 2 log drop from baseline
      - NO: Stop Treatment
      - YES: 24 week treatment

Marciano & Gadano, Liver Int 2014
Options for HCV G2 patients that did not respond to previous therapy

Patients may be re-treated with Peg-IFN + RBV (WBD) if they need immediate therapy and if measures to improve response can be introduced:

- Improve Adherence
- Correction of cofactors
  - Body weight, IR...
- Growth factors, Antidepressants

48 weeks recommended

Or → Wait for new drugs...
HCV-2: Two different scenarios at the time of deciding therapy

- Past and current therapy: Peg/RBV
  (still most countries)

- New therapy: SOF/RBV
  (only in few countries...
Approval of Sovaldi (sofosbuvir) tablets for the treatment of chronic hepatitis C.

On December 6, 2013, FDA approved SOVALDI (sofosbuvir) tablets for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. Sovaldi is the first drug that has demonstrated safety and efficacy to treat certain types of HCV infection without the need of IFN.

Recommended Regimens and Treatment Duration for SOVALDI Combination Therapy in HCV Mono-infected and HCV/HIV-1 Co-infected Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with genotype 1 or 4 CHC</td>
<td>SOVALDI + peginterferon alfa + ribavirine</td>
</tr>
<tr>
<td>Patients with genotype 2 CHC</td>
<td>SOVALDI + ribavirine</td>
</tr>
<tr>
<td>Patients with genotype 3 CHC</td>
<td>SOVALDI + ribavirine</td>
</tr>
</tbody>
</table>
The pangenotypic nucleotide polymerase inhibitor Sofosbuvir has been evaluated for the treatment of HCV G2 infection in 4 phase III studies: FISSION, POSITRON, FUSION and VALENCE
FISSION: Sofosbuvir/RBV vs PegIFN/RBV in HCV-Naive GT 2/3

- Randomized, controlled, open-label phase III noninferiority trial
  - 20% had cirrhosis; 72% had GT 3 HCV

Stratified by HCV GT (2 vs 3), HCV RNA (< vs ≥ 10^6 IU/mL), cirrhosis (yes vs no)

Treatment-naive patients with GT 2/3 HCV (N = 499)

Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day (n = 256)

PegIFN alfa-2a 180 µg/wk + RBV 800 mg/day (n = 243)

Lawitz E, et al. NEJM 2013
FISSION: SVR12 in HCV-Naive G2 and in Patients With and Without Cirrhosis

Treatment failure in SOF + RBV → Relapse.

No resistance to sofosbuvir (DS).

Lawitz E, et al. NEJM 2013
FISSION: Better tolerance with Sofosbuvir/RBV vs PegIFN/RBV

- Grade ≥ 3 AEs: 7% with SOF/RBV vs 19% for pegIFN/RBV
- Discontinuations due to AEs: 1% for SOF/RBV vs 11% for pegIFN/RBV

<table>
<thead>
<tr>
<th>AEs Occurring in ≥ 15% in Either Arm, %</th>
<th>SOF/RBV (n = 256)</th>
<th>PegIFN/RBV (n = 243)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>55</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>44</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>29</td>
<td>.0057</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>29</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>17</td>
<td>.0052</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>17</td>
<td>.0075</td>
</tr>
<tr>
<td>Irritability</td>
<td>10</td>
<td>17</td>
<td>.0328</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7</td>
<td>18</td>
<td>.0001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8</td>
<td>17</td>
<td>.0060</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>17</td>
<td>.0009</td>
</tr>
<tr>
<td>Influenzalike symptoms</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Chills</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Lawitz E, et al. NEJM 2013
POSITRON: Sofosbuvir + RBV, in HCV G2/3, IFN-Intolerant/Ineligible/Unwilling

- Randomized, double-blind, placebo-controlled phase III trial

**Stratified by cirrhosis (yes vs no)**

IFN unwilling, intolerant, or ineligible pts with GT 2/3 HCV (N = 278)

<table>
<thead>
<tr>
<th>Baseline Factor, n (%)</th>
<th>Sofosbuvir + RBV (n = 207)</th>
<th>Placebo (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 2</td>
<td>109 (53)</td>
<td>34 (48)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>31 (15)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Interferon unwilling</td>
<td>102 (49)</td>
<td>30 (42)</td>
</tr>
<tr>
<td>Interferon ineligible</td>
<td>88 (43)</td>
<td>33 (47)</td>
</tr>
<tr>
<td>Interferon intolerant</td>
<td>17 (8)</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

*Jacobson I, et al. NEJM 2013*
POSITRON: Sofosbuvir + RBV, in HCV G2/3, IFN-Intolerant/Ineligible/Unwilling

- SVR12 0% for placebo

Overall Outcomes

<table>
<thead>
<tr>
<th>HCV RNA &lt; LLOQ (%)</th>
<th>Wk 4</th>
<th>EOT</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>202/204</td>
<td>202/202</td>
<td>161/207</td>
</tr>
<tr>
<td>Overall Outcomes</td>
<td>99</td>
<td>100</td>
<td>78</td>
</tr>
</tbody>
</table>

GT 2

- No cirrhosis: 85/92
- Cirrhosis: 16/17

GT 3

- No cirrhosis: 57/84
- Cirrhosis: 3/14

Jacobson I, et al. NEJM 2013
**FUSION: Sofosbuvir + RBV, 12 or 16 weeks in treatment-experienced with HCV G2/3**

- Randomized, double-blind, placebo-controlled phase III trial
  - 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers

**Stratified by**
- HCV GT (2 vs 3), cirrhosis (yes vs no)

**Treatment-experienced pts with**
- GT 2/3 HCV (N = 201)

- **Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day** (n = 103)
- **Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day** (n = 98)
- **Placebo**

_Wk 12_  _Wk 16_

*Jacobson I, et al. NEJM 2013*
FUSION: SVR12 in G2 patients with and without cirrhosis

Jacobson I, et al. NEJM 2013
VALENCE: SVR12 With 12 Wks of SOF + RBV in Naive and Exp’d G2 Pts

- No increase in AEs seen with longer duration treatment
  - AEs seen consistent with RBV

Zeuzem S, et al. AASLD 2013
“Today’s approval represents a significant shift in the treatment paradigm for some patients with chronic hepatitis C,” said Dr. Edward Cox, director of the office of antimicrobial products at the F.D.A. But the greater convenience and effectiveness comes at a price. Gilead said the wholesale cost of Sovaldi, which is known generically as sofosbuvir, would be $28,000 for four weeks — or $1,000 per daily pill. That translates to $84,000 for the 12 weeks of treatment recommended for most patients, and $168,000 for the 24 weeks needed for a hard-to-treat strain of the virus. Sovaldi, from Gilead Sciences...
Conclusions

- The combination of Sofosbuvir and Ribavirin for 12 weeks is highly effective and safe and is currently the treatment of choice for patients with HCV G2.

- In countries where Sofosbuvir is not available, PEG IFN + RBV for 24 weeks is the recommended therapy.

- In patients without baseline predictors of treatment failure that experience RVR and receive WBD-RBV, treatment may be shortened to 16 weeks.
Unresolved issues...for HCV G2

• Facilitate access to the new therapies ?

• Is there room for other players ?

• How to treat non responders to SOF-RBV ?
  → retreat for longer period of time ?
  → back to IFN (+ SOF/RBV) ?
  → wait for other IFN-free combination ?
Sección Hepatología

- Sebastián Marciano
- Omar Galdame
- Juan Carlos Bandi
- Alejandra Villamil
- Paola Casciato
- Joaquín Solari
- Leila Haddad

Thank you !!!!