Tratamiento de la Hepatitis C
Rafael Esteban
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Barcelona
Current HCV Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>6%</th>
<th>16%</th>
<th>25%</th>
<th>34%</th>
<th>41%</th>
<th>54-61%</th>
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<tbody>
<tr>
<td>IFN 24w</td>
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<tr>
<td>IFN 48w</td>
<td>6%</td>
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<tr>
<td>Peg</td>
<td>16%</td>
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<tr>
<td>IFN-R 24w</td>
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<tr>
<td>IFN-R 48w</td>
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<td>34%</td>
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<tr>
<td>Peg-R</td>
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<td></td>
<td>41%</td>
<td>54-61%</td>
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</tbody>
</table>
Standard de Tratamiento: Peginterferon α + ribavirina

**HCV Genotype**

- **Genotype 1 (4, 5, 6)**
  - HCV-RNA quantitative at week 12
  - ≥2 log drop
  - Peginterferon-α plus 1000-1200 mg ribavirin for 48 weeks

- **Genotype 2/3**
  - Peginterferon-α plus 800 mg ribavirin for 24 weeks
## Factors Related to Therapy Response

### Virus
- Genotype
- Viral load

### Treatment
- Adherence
- Early Virologic Response
- Ribavirin Dosage
- Interfering agents (e.g., alcohol)

### Patient
- Age
- Race
- Weight
- Cirrhosis
- Hepatic steatosis
- HIV co-infection
- Pre-treatment expression of IFN-response genes
- IL28b
Impact of Genotype on SVR Rates

- PegIFN alfa-2b 1.5 µg/kg/wk + RBV 800 mg/day for 48 wks
- PegIFN alfa-2a 180 µg/wk + weight-based RBV (1000 or 1200 mg/d) for 48 wks

Patterns of Virologic Response

*Subset of Nonresponse

HCV RNA (log_{10} IU/mL)

Wks After Start of Therapy

- Undetectable
- RVR
- EVR
- ETR
- SVR

Null Response*
Partial Response*
Relapse

*Subset of Nonresponse
Viral Kinetics and Outcome Importance of Rapid Virologic Response

Virologic Response (%)

- Wk 4: 91
- Wk 12: 94
- Wk 24: 90

ETR: ETR
SVR: SVR

HCV RNA Status

- Wk 4: 91
- Wk 12: 94
- Wk 24: 90


http://www.sciencedirect.com/science/journal/01688278
What are Genome wide association scans (GWAS)?

Responders
Non-responders

Pharmacogenetic Analysis of the rs12979860 C allele
SVR by genotypes of rs12979860

Thompson et al, AASLD 2009, oral (LB5); Nature Sept. 2009; 461: 399-401
Multivariate Analysis of Baseline Predictors of SVR (Genotype 1 HCV)

- ITT analysis of patients from IDEAL study who consented to genetic testing, regardless of adherence level

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12979860 CC</td>
<td>5.2 (4.1-6.7)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>HCV RNA level ≤ 600,000 IU/mL</td>
<td>3.1 (2.3-4.1)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>White vs black</td>
<td>2.8 (2.0-4.0)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Hispanic vs black</td>
<td>2.1 (1.3-3.6)</td>
<td>.0041</td>
</tr>
<tr>
<td>METAVIR F0-F2</td>
<td>2.7 (1.8-4.0)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Fasting blood sugar &lt; 5.6 mmol/L</td>
<td>1.7 (1.3-2.2)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

HCV RNA decline in relation to IL28b in Genotype 1 patients under treatment

Thompson A et al. Gastroenterology 2010
New Drugs for Hepatitis C

Thompson A et al. J of Hepatol 2009
## Types of drugs

<table>
<thead>
<tr>
<th>Type of drugs</th>
<th>Genetic Barrier/ AV Efficacy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitor</td>
<td>Low/ High</td>
<td>Only Gen 1</td>
</tr>
<tr>
<td>Polymerase Inhibitor Nucleoside Analog</td>
<td>High / Low</td>
<td>Few in develop All genotypes</td>
</tr>
<tr>
<td>Polymerase Inhibitor Non Nucleo</td>
<td>Low/ Medium</td>
<td>Genotype 1</td>
</tr>
<tr>
<td>Ciclofilin Inhibitor</td>
<td>No/ Low</td>
<td></td>
</tr>
</tbody>
</table>

Charlton et al  AASLD 2010.
Boceprevir (BOC) is a linear peptidomimetic ketoamide serine NS3 protease inhibitor

Effective against Genotype 1

Demonstrated activity in treatment naïve and experienced populations in phase 2 clinical trials
**SPRINT 2: Study Design**

**Control**
- **48 P/R**
- **N = 363**
  - **PR lead-in**
  - **Week 4**
  - **PR + Placebo**
  - **Week 28**
  - **Follow-up**
  - **TW 8-24 HCV-RNA Undetectable**

**BOC/PR48**
- **N = 366**
  - **PR lead-in**
  - **PR + Boceprevir**
  - **Week 4**
  - **Follow-up**
  - **TW 8-24 HCV-RNA Detectable**

**Follow-up**
- **PR + Placebo**
- **Follow-up**

Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose

Boceprevir dose of 800 mg thrice daily
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (Non-black)</th>
<th>Cohort 2 (Black)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55</td>
<td>63</td>
</tr>
<tr>
<td>Region (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>65</td>
<td>72</td>
</tr>
<tr>
<td>Europe</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>BMI – mean (SD)</td>
<td>27 (5)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>HCV subtype (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>1b</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>HCV RNA level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;400,000 IU/mL (%)</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>METAVIR F3/F4 (%)</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

* Subtyping performed by NS5B sequencing (Virco, Mechelen, Belgium)
SPRINT 2: SVR and Relapse Rates (ITT)

*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (210/311), respectively and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively.
SVR Based on Week 4 PR Lead-In in Non-Black Patients

≥1 log\textsubscript{10} HCV RNA decline from baseline

<1 log\textsubscript{10} HCV RNA decline from baseline

Boceprevir Resistance-associated Variants*:

≥1 log\textsubscript{10} decline:
- BOC RGT: 4% (9/232)
- BOC/PR48: 4% (9/231)

<1 log\textsubscript{10} decline:
- BOC RGT: 47% (45/95)
- BOC/PR48: 35% (33/94)

* Boceprevir resistance-associated variants determined with population sequencing
Rationale for Lead-in Phase
4 weeks of PegIFN alfa-2b and ribavirin

- Achievement of steady-state drug levels
- Alpha interferon-mediated immune system activation
- Lower HCV burden

- May reduce the emergence of viral resistance by decreasing the pool of pre-existing viral quasi-species
Boceprevir: Adverse Events and Discontinuations

- Anemia and dysgeusia reported more frequently in BOC arms vs control in SPRINT-2\textsuperscript{[1-2]}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>4-Wk PR + Response-Guided BOC/PR (n = 368)</th>
<th>4-Wk PR + 44-Wk BOC/PR (n = 366)</th>
<th>48-Wk PR (n = 363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Anemia\textsuperscript{[1]}</td>
<td>49</td>
<td>49</td>
<td>29</td>
</tr>
<tr>
<td>▪ EPO use</td>
<td>41</td>
<td>46</td>
<td>21</td>
</tr>
<tr>
<td>▪ Dysgeusia\textsuperscript{[2]}</td>
<td>37</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>Discontinuations due to adverse events, %\textsuperscript{[1]}</td>
<td>12</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>▪ Anemia\textsuperscript{[1]}</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Poordad F, et al. AASLD 2010.
TELAPREVir - ADVANCE

- PR48 (Control)
  - Peg-IFN + RBV

- T12/PR24 (or 48)
  - Telaprevir + Peg-IFN + RBV
  - Peg-IFN + RBV
  - eRVR
    - Yes: No further treatment
    - No: Peg-IFN/RBV 24 additional weeks

- T8/PR24 (or 48)
  - Telaprevir + Peg-IFN + RBV
  - Peg-IFN + RBV

- * Stopping rule time point for Telaprevir
- ‡ eRVR = extended RVR, undetectable at W4 and 12
Efficacy Results from ADVANCE

- SVR Results (Intent to Treat Analysis)

The SVR rates observed in the two telaprevir-based treatment arms were statistically significant when compared to the control arm (p<0.0001)

AASLD 2010
57% and 58% of patients qualified for 24 weeks of therapy (assessment at Week 4) in 8-wk and 12-wk TVR arms, respectively.
ADVANCE: Response Rates According to Race/Cirrhosis

- Blacks: 8-wk TVR/PR + 16/40-wk PR
  - 58 homeschoolers / 23 of 40 people

- Bridging fibrosis/cirrhosis: 12-wk TVR/PR + 12/36-wk PR
  - 62 homeschoolers / 16 of 26 people
  - 25 homeschoolers / 7 of 28 people

- 48-wk PR
  - 53 homeschoolers / 45 of 85 people
  - 62 homeschoolers / 45 of 73 people
  - 33 homeschoolers / 24 of 73 people
Telaprevir: Discontinuations

- Discontinuations due to adverse events in Phase III ADVANCE:

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>8-Wk TVR/PR + 16/40-Wk PR (n = 364)</th>
<th>12-Wk TVR/PR + 12/36-Wk PR (n = 363)</th>
<th>48-Wk PR (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of TVR/placebo due to rash</td>
<td>7</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Discontinuation of all drugs due to AEs</td>
<td>8</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>▪ Anemia</td>
<td>3.3</td>
<td>0.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

PegIFN alfa2 and Ribavirin in treatment of Chronic Hepatitis C

Proportion of Non Response

<table>
<thead>
<tr>
<th>Genotype</th>
<th>α2b</th>
<th>α2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58%</td>
<td>54%</td>
</tr>
<tr>
<td>2 and 3</td>
<td>18%</td>
<td>24%</td>
</tr>
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</table>

Study 107: TVR/PR Retreatment of Pts With PR Failure in PROVE 1/2/3 Trials

N = 177
n = 51
n = 29
n = 8
n = 29

HCV-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 12 were considered treatment failures.

Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose

Boceprevir dose of 800 mg thrice daily
RESPOND-2 SVR and Relapse Rates
Intention to treat population

SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.
SVR by Week 8 HCV RNA Response  Intention to Treat Population

- 46% of patients in BOC RGT arm were eligible for shorter therapy
- ~6 times as many patients on BOC regimens (46-52%) achieved undetectable HCV RNA at week 8 compared to control (9%)
SVR by Week 4 PR Lead-In Response

Poorly Responsive to IFN
<1 log$_{10}$ viral load decline at treatment week 4

Responsive to IFN
≥1 log$_{10}$ viral load decline at treatment week 4
RESPOND-2: Adverse Events Over Entire Treatment Course

- Adverse events more common in BOC arms vs control
  - Anemia and dysgeusia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>4-Wk PR + Response-Guided BOC + PR (n = 162)</th>
<th>4-Wk PR + 44-Wk BOC + PR (n = 161)</th>
<th>48-Wk PR (n = 114)</th>
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<tbody>
<tr>
<td>Adverse event, %[1]</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>43</td>
<td>46</td>
<td>20</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>43</td>
<td>45</td>
<td>11</td>
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In Vitro resistance to Protease (A) and Polymerase (B) Inhibitors

**A**

<table>
<thead>
<tr>
<th></th>
<th>V36A/M</th>
<th>T54A</th>
<th>R155K/T</th>
<th>A156S/V/T</th>
<th>D168A/V/E</th>
<th>V170A</th>
<th>S489L</th>
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<tbody>
<tr>
<td>Telaprevir</td>
<td></td>
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<td>Boceprevir</td>
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<td>ITMN-191</td>
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<tr>
<td>BILN-2061</td>
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**B**

<table>
<thead>
<tr>
<th></th>
<th>S96T</th>
<th>N142T</th>
<th>S282T</th>
<th>C316Y</th>
<th>S365T/A</th>
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<tbody>
<tr>
<td>Valopicitabine</td>
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<td>MK-0608</td>
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<tr>
<td>R1626/R1479</td>
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<td>HCV-796</td>
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</table>
Combination of two oral drugs in HCV G-1 Patients
Nucleoside Polymerase (R7128) and Protease (R7227) Inhibitor

Gane EJ et al. EASL 2009
Summary

- Combination of Protease Inhibitors with PEG-IFN and RBV will increase SVR in genotype 1 patients from 40% to 60-70%
- Relapse rate decline to 5-10%
- Treatment duration may be shorten for a proportion of patients
- Discontinuation rates may increase due to AEs
- A new era in HCV therapy starts