Predictors of Response to Hepatitis C Therapy in the DAA Era

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Why Predicting HCV Response?

- Select candidates for therapy
  - Prioritizing expensive drugs
  - Wait for newer compounds
- Determine type of therapy
  - Dual therapy
  - Adding DAAs
- Decide duration of therapy
- Motivate patients

- In summary, tailor hepatitis C treatment
Main Predictors of Response to Hepatitis C Treatment

- Level of viremia
- Genotype / Subtype
- Drug resistant polymorphisms
- Treatment history
- Initial response (RVR)
- RBV doses / levels
- Type of ARV and DDI
- Race
- IFN cascades genotypes
- Liver fibrosis stage
- Insulin resistance
- CD4 counts
HCV Genotype and HCV-RNA Level

Rate of Sustained Virological Response

PEG-IFNα-2a + RBV

- Total
- Genotype 1
- Genotype 2 or 3

PEG-IFNα-2b + RBV

- Total
- Genotype 1 or 4
- Genotype 2 or 3

HCV-RNA at baseline

- High (>800,000 IU/ml)
- Low (<800,000 IU/ml)

Torriani et al. NEJM 2004

Crespo et al. J Viral Hep 2007
IL28B Polymorphisms & SVR in HIV/HCV Coinfected Patients

- All: 75% CC, 38% CT/TT, p<0.0001
- HCV-1: 65% CC, 30% CT/TT, p=0.001
- HCV-3: 86% CC, 81% CT/TT, p=0.684
- HCV-4: 67% CC, 25% CT/TT, p=0.087

Predictors of Response in HIV-HCV Coinfection

- HCV-RNA <600,000 IU/ml
- HCV genotype 3
- rs12979860 CC genotype
- Liver fibrosis stage F0-F2

Rallon et al. AIDS 2010

Odds ratio (95% confidence interval)

- HCV-RNA <600,000 IU/ml: OR 11.9, p<0.001
- HCV genotype 3: OR 8.0, p<0.001
- rs12979860 CC genotype: OR 3.7, p=0.002
- Liver fibrosis stage F0-F2: OR 3.5, p=0.009

Modeling the Probability of Sustained Virological Response to Therapy with Pegylated Interferon plus Ribavirin in Patients Coinfected with Hepatitis C Virus and HIV

IL28B polymorphism at rs12979860
- CC

Liver stiffness by FibroScan (in kPa)
- 13

HCV genotype
- 1 or 4

Baseline HCV-RNA level (in log IU/mL)
- 6.5

Prometheus Index

Probability of SVR: 59.04 %


http://www.fundacionies/prometheusindex.php
Viral Factors in DAAs Era
Baseline Viral Load as a Predictor of SVR
Boceprevir for naive (SPRINT-2)

SVR was defined as undetectable HCV RNA at the last available value in the period at or after follow-up Week 24. If there was no such value, the follow-up Week 12 value was carried forward.

Baseline HCV-RNA Levels as Predictor in Patients with Poor IFN Response before Boceprevir Therapy

Influence of HCV-1 Subtype
Telaprevir

Advance Study

Realize Study

% of patients with SVR

Influence of HCV-1 Subtype
Boceprevir

Lower Genetic Barrier of HCV-1a Subtype

Distribution of RAVs by genotype

Frequency and Distribution of RAVs by genotype
(Expressed as a percentage of RAVs detected for each genotype)

Total n=342*

*1 patient excluded due to indeterminate Genotype 1 subtype; Gt = Genotype
Differences in Virological Response to PegIFN plus RBV in HCV/HIV-Coinfected Patients by HCV Subtype (1a vs 1b)

Rallón, AIDS 2011;25:1025-33
PROVIDE Study Interim Results: Boceprevir + PegIFN + RBV

Pretreated patients

% of patients with SVR

- No RAVs: 79%
- RAVs: 76%
- Hot RAVs*: 78%
- Other RAVs: 80%

*V36M, R155K, T54S/A and V55A

Brass et al. EASL 2011
Host Factors in DAAs Era
SVR by Fibrosis Stage in Naïve Patients (SPRINT-2- Boceprevir)

No, minimal or portal fibrosis (F0–F2)

- PR48: 38/123 (38%)
- BOC RGT: 67/213 (67%)*
- BOC44/PR48: 67/211 (67%)*

Bridging fibrosis or cirrhosis (F3/F4)

- PR48: 38/9 (38%)
- BOC RGT: 41/14 (41%)
- BOC44/PR48: 52/22 (52%)**

*p<0.001 for both boceprevir arms vs PR48; †p=1.00 for boceprevir vs PR48
**p=0.31 for boceprevir vs PR48

SVR by Fibrosis Stage in Pretreated Patients (REALIZE- Telaprevir)

Samples were available for 454/1088 (42%) patients (Caucasian) enrolled in ADVANCE. SVR: sustained virologic response, defined as undetectable HCV RNA 24 weeks after last planned dose.

SVR rates in *IL28B* CC with RVR

Telaprevir for naive (ADVANCE)

78% of CC patients in the T12PR arm were treated with 24 weeks of treatment

RVR: rapid viral response (undetectable HCV RNA at Week 4)

SOUND-C2: Efficacy According to Study Arm, HCV Subtype, and *IL28B*

SVR According to *IL28B* and HCV Subtype (ITT)

Lower SVR in Blacks Regardless of IL28B Genotype

SPRINT-2: SVR to Boceprevir According to Race

- Phase III: genotype 1, treatment naive

ADVANCE: SVR to Telaprevir According to Race and Ethnicity

- Phase III: genotype 1, treatment naive

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>T12PR</th>
<th>T8PR</th>
<th>PR48</th>
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<tbody>
<tr>
<td>White</td>
<td>75</td>
<td>70</td>
<td>46</td>
</tr>
<tr>
<td>Black</td>
<td>62</td>
<td>58</td>
<td>25</td>
</tr>
<tr>
<td>Latino</td>
<td>74</td>
<td>66</td>
<td>39</td>
</tr>
<tr>
<td>Non-Latino</td>
<td>75</td>
<td>69</td>
<td>44</td>
</tr>
</tbody>
</table>

n = 325 315 318 26 40 28 35 44 38 328 320 323

IFN-gamma Inducible Protein 10 kDa (IP-10)

- Expressed in HCV-infected hepatocytes
- Role in recruitment of T-lymphocytes?
- Inverse association of IP-10 plasma levels with SVR after dual and triple therapy


Vijgen L, et al. EASL 2012 (abstract 1167)
HCV replication upregulates IP10 levels that tend to normalize after therapy. Baseline IP10 plus IL28B genotype improves prediction of treatment responses. IP-10 not an independent predictor.

Rallón et al. AASLD 2011
Predicted effect of direct acting antivirals in the current HIV–HCV-coinfected population in Spain

Eva Poveda¹, Eugenia Vispo¹, Pablo Barreiro¹, Carmen de Mendoza¹, Pablo Labarga¹, José Vicente Fernández-Montero¹, Luz Martin-Carbonero¹, Vincent Soriano¹*

¹Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain

Antiviral Therapy 2012; 17: 571-5.

IFN experience
- Yes: 41%
- No: 59%

HCV genotype
- G1a: 39%
- G1b: 22%
- G3: 11%
- G4: 8%
- Others: 20%

IL28B
- CC: 30%
- CT/TT: 70%

Advanced liver fibrosis
- No: 47%
- Yes: 53%

424 HIV/HCV-coinfected patients in 2011
Predicted Effect of DAA in HIV-HCV Coinfected Patients

- HCV subtype 1a
- IFN exposure
- IL28B nonCC
- Metavir F3-F4

Similar Response to DAA in Naïve Patients Despite HIV Infection

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir</th>
<th>Telaprevir</th>
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<tbody>
<tr>
<td>% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>w8 RVR</td>
<td>57%</td>
<td>42%</td>
</tr>
<tr>
<td>SVR</td>
<td>66%</td>
<td>62%</td>
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<tr>
<td>w4 RVR</td>
<td>68%</td>
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<tr>
<td>SVR</td>
<td>79%</td>
<td>74%</td>
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<table>
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<tr>
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<th>HIV neg</th>
<th>HIV pos</th>
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<tr>
<td>w8 RVR</td>
<td>208/368</td>
<td>27/64</td>
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<tr>
<td>SVR</td>
<td>243/368</td>
<td>40/64</td>
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<tr>
<td>w4 RVR</td>
<td>246/363</td>
<td>26/38</td>
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<tr>
<td>SVR</td>
<td>288/363</td>
<td>28/38</td>
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Mallolas J et al. EASL Barcelona-Spain. April, 2012
DT Dieterich et al., CROI 2012
## Too Favorable Factors in HIV-HCV Coinfected Patients Treated with DAA

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<thead>
<tr>
<th></th>
<th>Boceprevir</th>
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<tr>
<td><strong>Naive</strong></td>
<td>All</td>
<td>All</td>
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<tr>
<td><strong>HCV 1a</strong></td>
<td>66%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>High HCV-RNA</strong></td>
<td>88%</td>
<td>87%</td>
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<tr>
<td><strong>Cirrhosis</strong></td>
<td>6%</td>
<td>0%</td>
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<tr>
<td><strong>Median CD4 count (cells/uL)</strong></td>
<td>577</td>
<td>535</td>
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<tr>
<td><strong>IL28B nonCC</strong></td>
<td>NA</td>
<td>NA</td>
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Mallolas J, et al. EASL 2012
Sulkowski MS, et al. CROI 2012
# Aproach to DAA Therapy

## Treatment history

<table>
<thead>
<tr>
<th>Chances of response</th>
<th>Treatment history</th>
<th>Predictors</th>
<th>Treatment duration</th>
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<tbody>
<tr>
<td>Naive</td>
<td>Yes CC No</td>
<td>RVR, IL28B, F4</td>
<td>12 weeks?</td>
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<tr>
<td>Relapsers</td>
<td>Yes CT/TT No</td>
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<td>24 weeks</td>
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<tr>
<td>Partial responders</td>
<td>No Any Yes</td>
<td></td>
<td>48 weeks</td>
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<tr>
<td>Null responders</td>
<td>No Any No</td>
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<td>Defer</td>
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## Optimization of therapy

- **RVR** (rapid virological response)
- **IL28B**
- **F4**
- **CC**
- **CT/TT**
- **Any**
## Summary

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<thead>
<tr>
<th>HCV-genotype</th>
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<tr>
<td><strong>Therapy</strong></td>
<td>pIFN-RBV</td>
<td>pIFN-RBV-PI</td>
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<td>HCV-RNA level</td>
<td>++</td>
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<td>+</td>
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<tr>
<td>HCV-1 subtype</td>
<td>--</td>
<td>++</td>
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<tr>
<td>IL28B</td>
<td>-</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>RBV doses</td>
<td>++</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Liver fibrosis</td>
<td>+</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>RVR</td>
<td>++</td>
<td>+++</td>
<td>++ (R) / ++++ (F)</td>
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<tr>
<td>LIP</td>
<td>-</td>
<td>-</td>
<td>High VL / Nulls</td>
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<td>RAVs</td>
<td>-</td>
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<td>IFN resistance</td>
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<td>Prior pegIFN-RBV failure</td>
<td>Any</td>
<td>Any</td>
<td>Null / Partial response</td>
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## Acknowledgements

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<tr>
<th>Molecular Biology</th>
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<th>Computing and Administration</th>
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<td>Carmen de Mendoza</td>
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