Farmacogenética en el tratamiento de infecciones víricas en 2011: Hepatitis y VIH

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Hospital Carlos III, Madrid
The most prevalent chronic viral infections in humans

- HBV
- HCV
- HIV

Venn diagram showing the number of people infected with each virus and their overlaps:
- HBV: 400
- HCV: 200
- HIV: 35
- Overlap between HBV and HCV: 200
- Overlap between HBV and HIV: 400
- Overlap between HCV and HIV: 35
Hepatitis C

- 2-3% of the world population
- 1.5% in Spain (~700,000 persons) (~40% undiagnosed)
- Routes of infection: sporadic >50%
- Risk factors: transfusions <1990; IVDU
- 30% of chronic carriers will develop cirrhosis
- HCV is the primary reason for liver transplantation
- HCV is the major cause of liver cancer in the West
- No vaccine
- Only curable (eradication) chronic viral infection
Current algorithm for HCV therapy (peginterferon + ribavirin)

- **W4**
- **W12**
- **W24**
- **W48**
- **W72**

HCV-RNA neg

- G2/3
- G1/4

24 weeks therapy

HCV-RNA pos

- > 2 log drop in HCV-RNA

HCV-RNA neg

- G2/3
- G1/4

48 weeks therapy

HCV-RNA pos

- HCV-RNA pos

72 weeks therapy

- Stop

< 2 log drop in HCV-RNA

Stop

Predictors of response to HCV therapy

- HCV genotype
- Baseline serum HCV-RNA
- Liver fibrosis stage
- RVR
- EVR
- IL28b polymorphism
**IL28B polymorphisms & hepatitis C outcome**

IL28B gene

SNP: rs12979860 (CC, CT, TT)

Chromosome 19

Interferon λ3

Response to pegIFN+RBV

Spontaneous HCV clearance

IL28B polymorphisms, ethnicity & SVR

The graph illustrates the relationship between rs1297980 C-allele frequency and SVR (%) across different ethnic groups. The graph shows:

- **East Asians** with a higher SVR (%) compared to other groups.
- **Caucasians** and **Hispanics** have an intermediate SVR (%) between East Asians and **African-Americans**.
- **African-Americans** have the lowest SVR (%) among the groups depicted.

The x-axis represents the rs1297980 C-allele frequency, while the y-axis represents the SVR (%).
Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients

Norma I. Rallón, Susanna Naggie, José M. Benito, José Medrano, Clara Restrepo, David Goldstein, Kevin V. Shianna, Eugenia Vispo, Alex Thompson, John McHutchison and Vincent Soriano

AIDS 2010

SVR

p<0.0001

<table>
<thead>
<tr>
<th>CC</th>
<th>CT/TT</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>89</td>
<td>164</td>
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</table>

p=0.087

<table>
<thead>
<tr>
<th>CC</th>
<th>CT/TT</th>
<th>HCV-4</th>
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<tbody>
<tr>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>34</td>
<td>61</td>
<td>95</td>
</tr>
<tr>
<td>35</td>
<td>16</td>
<td>51</td>
</tr>
</tbody>
</table>

CC CT/TT CC CT/TT CC CT/TT CC CT/TT

34 61 35 16 37 67 30 25

SVR

p=0.001

<table>
<thead>
<tr>
<th>CC</th>
<th>CT/TT</th>
<th>HCV-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>61</td>
<td>95</td>
</tr>
<tr>
<td>35</td>
<td>16</td>
<td>51</td>
</tr>
</tbody>
</table>

All HCV-3 HCV-1 HCV-4

164 51 95 18
## Broader effect of IL28B SNPs on Hep C

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>IL28B</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous HCV clearance</td>
<td>24</td>
<td>CC</td>
<td>Enhanced in genotypes 1 and 4</td>
<td>Rallón et al. AIDS 2010</td>
</tr>
<tr>
<td>Response to pegIFNα-RBV</td>
<td>164</td>
<td>CC</td>
<td>Increased SVR mainly in G1 and G4</td>
<td></td>
</tr>
<tr>
<td>Early viral kinetics on therapy</td>
<td>196</td>
<td>CC</td>
<td>Increased RVR and EVR mainly in G1 and G4</td>
<td>Rallón et al. AIDS 2011</td>
</tr>
<tr>
<td>Response to pegIFNα-RBV in prior non-response or relapse patients</td>
<td>62</td>
<td>CC</td>
<td>Increased SVR only in G1 and G4 prior true non-responders</td>
<td>Labarga et al. AIDS 2011</td>
</tr>
<tr>
<td>Serum HCV-RNA levels</td>
<td>289</td>
<td>CC/CT</td>
<td>Greater viral load</td>
<td>Labarga et al. AIDS 2011</td>
</tr>
<tr>
<td>Liver fibrosis progression</td>
<td>304</td>
<td>CC</td>
<td>Greater rate of cirrhosis</td>
<td>Barreiro et al. J Infect Dis 2011</td>
</tr>
<tr>
<td>Liver enzymes elevation</td>
<td>304</td>
<td>CC</td>
<td>Increased ALT levels</td>
<td></td>
</tr>
<tr>
<td>Serum IFN λ3 levels</td>
<td>112</td>
<td>CC</td>
<td>No impact at baseline but greater increase during IFNα therapy</td>
<td>Rallon et al. CROI 2011</td>
</tr>
</tbody>
</table>
Chromosome 19

**IL28B gene**
*(CC, CT, TT)*

Interferon λ3

**Acute Hepatitis C**

HCV load

**Chronic hepatitis C**

Liver fibrosis progression

Spontaneous HCV clearance

IFNα therapy elimination
IL28B polymorphisms in HIV-HCV coinfection

HCV-RNA <600,000 IU/ml
- 11.9
- p<0.001

HCV genotype 3
- 8.0
- p<0.001

rs12979860 CC genotype
- 3.7
- p=0.002

Liver fibrosis stage F0-F2
- 3.5
- p=0.009

Odds ratio (95% confidence interval)

Rallon et al. AIDS 2010
Modeling the Probability of Sustained Virological Response to Therapy with Pegylated Interferon plus Ribavirin in Patients Coinfected with Hepatitis C Virus and HIV

Clinical Infectious Diseases 2010;51(10):1209–1216

Prometheus index

- HCV genotype
- Fibrosis stage (KPa)
- Serum HCV-RNA
- IL28B SNPs

http://www.fundacionies.com/prometheusindex.php
Prometheus Index

Prediction of Sustained Virological Response (SVR) after treatment of Hepatitis C with Pegylated Interferon plus weight adjusted Ribavirin

# A new era for hepatitis C – new diagnostic tools & new weapons

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non-invasive liver fibrosis methods</td>
<td>• Protease inhibitors</td>
</tr>
<tr>
<td>• IL28B alleles</td>
<td>• Polymerase inhibitors</td>
</tr>
<tr>
<td>• Drug resistance</td>
<td>• NS5A inhibitors</td>
</tr>
<tr>
<td>• Viral load</td>
<td>• Interferon lambda</td>
</tr>
<tr>
<td>• HCV geno/subtyping</td>
<td>• Alisporivir</td>
</tr>
</tbody>
</table>
### New Therapies for Hepatitis C Virus Infection

**Clinical Infectious Diseases** 2009;48:313–20

*Vincent Soriano,¹ Marion G. Peters,² and Stefan Zeuzem³*

¹Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain; ²Division of Gastroenterology, University of California, San Francisco; and ³Medizinische Klinik I, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany

<table>
<thead>
<tr>
<th>Protease inhibitors</th>
<th>Polymerase inhibitors</th>
<th>NS5A inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>Mericitabine</td>
<td>BMS-790052</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>PSI-7851</td>
<td>IDX-184</td>
</tr>
<tr>
<td>Danoprevir</td>
<td>PSI-7977</td>
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</tr>
<tr>
<td>BI-1335</td>
<td>Tegobuvir</td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Mericitabine</td>
<td></td>
</tr>
<tr>
<td>MK-5172</td>
<td>PSI-7977</td>
<td></td>
</tr>
<tr>
<td>GS-9256</td>
<td>Tegobuvir</td>
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<td>ABT-450</td>
<td>Filibuvir</td>
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<td></td>
<td>BI-7127</td>
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<td></td>
<td>ANA-598</td>
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<tr>
<td></td>
<td>VX-222</td>
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</tr>
<tr>
<td></td>
<td>VX-222</td>
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<td></td>
<td>VCH-759</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABT-072</td>
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</table>

**Polymerase inhibitors**

**Non-nucleoside analogues**

- Mericitabine
- Tegobuvir
- Filibuvir
- BI-7127
- ANA-598
- VX-222
- VCH-759
- ABT-072
The new hepatitis C treatment paradigm

- Test all
- Treat hard and short
- Cure most

but individualize treatment options!
# Tailoring HCV therapy

<table>
<thead>
<tr>
<th>IL28B CC</th>
<th>pegIFN +/-</th>
<th>PI</th>
<th>NA</th>
<th>NNA</th>
<th>NS5A</th>
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</thead>
<tbody>
<tr>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HCV genotypes</th>
<th>pegIFN +/-</th>
<th>PI</th>
<th>NA</th>
<th>NNA</th>
<th>NS5A</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
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<td>++</td>
<td>++</td>
<td>++</td>
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</tr>
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<td>1b</td>
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<td>++</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>
Main side effects of current HCV therapy

- **pegIFNα**: flu-like, mood changes, etc.
- **RBV**: anemia *

* RBV-induced hemolytic anemia is severe enough to require dose modification in 15% of patients.
Genetic variants leading to inosine triphosphatase (ITPA) deficiency protect against hemolytic anemia.
ITPA deficiency protects against clinically significant decline in Hb concentration induced by HCV anti-viral treatment.
ITPA Deficieny is Associated with Lower Risk of Ribavirin-Induced Anemia in HIV/HCV Co-Infected Patients Independently of Ribavirin Dose

Norma I. Rallón1, Judith Morello1, Pablo Labarga1, José M. Benito1, Sonia Rodriguez-Novoa1, Eugenia Vispo1, Clara Restrepo1, Lorena Cuenca1, Pablo Barreiro1, M. Ángeles Castro2, Koldo Aguirrebengoa3, Juan Antonio Pineda4, Pilar Miralles5, M. J. Tellez6, José Joaquín Portu7, Celia Miralles8, Antonio Ocampo8, Vincent Soriano1

On behalf of PERICO Study team

1Hospital Carlos III, Madrid, 2Hospital Juan Canalejo, A Coruña; 3Hospital Cruces, Bilbao; 4Hospital Universitario de Valme, Sevilla; 5Hospital Gregorio Marañón, Madrid; 6Hospital Clínico San Carlos, Madrid 7Hospital Txagorritxu, Vitoria; 8Hospital Xeral Cies, Vigo, Spain

Clinical Infectious Diseases (in press)

Rates of Hb decline ≥2 g/dl according to ITPA genotype

- rs1127354: protective genotype - 29% (p=0.043)
- rs7270101: protective genotype - 33% (p=0.002)

Rates of Hb decline ≥2 g/dl according to % of ITPase deficiency

- 0%: 80%
- 40%: 40%
- 70%: 25%
- >90%: 0%
• Overall 33% of this HIV/HCV coinfected cohort was predicted to have reduced ITPase activity.

• Reduced ITPase activity was associated with protection from anemia at week 4 of therapy.

• The role of the ITPA SNP in medical practice remains unclear. Patients with ITPase deficiency might tolerate higher RBV dosing, which previously has been associated with improved virological outcomes. This will require further investigation.
Introduction of Genomics in the HCV clinic

- **IL28B**: Enter routine clinical care
  - Surrogate of treatment efficacy
  - Baseline predictor of treatment response to IFN-based therapy
  - Cheap (30 euros)
  - Once in life
  - Easy interpretation

- **ITPA**: Remain as research tool
  - Surrogate of treatment tolerability
  - Predictor of risk of RBV-associated anemia
  - Less cheap (60 euros)
  - Once in life
  - More difficult interpretation
**Main genetic determinants of HCV natural history and treatment outcome**

- IL28B
- ITPA
- LDL-cholesterol receptor
- Others: IP-10, HCV core mutations 70/91, etc.
### Toxicogenética de los antirretrovirales

<table>
<thead>
<tr>
<th>Gen o proteína</th>
<th>Alelo o variante</th>
<th>Efecto</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B</td>
<td>HLA-B*5701</td>
<td>hipersensibilidad al Abacavir</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>CYP2B6 *6,*11,*18,*27,*28</td>
<td>pérdida de función asociada a toxicidad neurológica del EFV</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>*28</td>
<td>Síndrome de Gilbert, hiperbilirrubinemia en presencia de ATV o IDV.</td>
</tr>
<tr>
<td>MRP2; MRP4</td>
<td>24C&gt;T; 3463A&gt;G</td>
<td>riesgo de tubulopatía renal proximal asociada al uso de TDF</td>
</tr>
<tr>
<td>ADN mitocondrial</td>
<td>Haplotipo T del ADN mitocondrial</td>
<td>↑ susceptibility a neuropatía periférica. La depleción de ADNm se asocia a lipodistrofia.</td>
</tr>
<tr>
<td>HLA-C</td>
<td>HLA-Cw8</td>
<td>reacción de hipersensibilidad a nevirapina</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>HLA-DRB1*0101</td>
<td>alto VPN para reacción de hipersensibilidad a nevirapina</td>
</tr>
</tbody>
</table>
PGX de abacavir

Asociación del HLA-B*5701 con la reacción de hipersensibilidad al Abacavir.

Mallal S et al. PREDICT-1 study. NEJM 2008
Saag M et al. SHARPE study. CID 2008

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents
NIH - December 1, 2007

What’s new in the document?

HLA-B*5701 Testing – The Panel recommends HLA-B*5701 testing prior to initiating abacavir therapy to reduce the risk of hypersensitivity reaction (AI). HLA-B*5701-positive patients should not be prescribed abacavir (AI), and the positive status should be recorded as an abacavir allergy in the patient’s medical record (AII). When HLA-B*5701 screening is not readily available, it remains reasonable to initiate abacavir with appropriate clinical counseling and monitoring for any signs of abacavir-associated hypersensitivity reaction (CIII).
Toxicidad neurológica asociada a Efavirenz

PGX de efavirenz

CYP2B6-G516G (genotipo común)

CYP2B6-G516T (polimorfismo en homozigosis)

Rodríguez-Nóvoa et al. CID 2005
Interplay between bilirubin metabolism, Gilbert’s genotype and atazanavir

- Heme
- IDV, ATV
- Conjugated bilirubin
- UGT
- TA insertion
- Gilbert (5-10%)
- UGT gene
- Human DNA

Bar graph: Patients with severe hyperbilirubinemia
- UGT1A1 genotypes: TA6/TA6, TA6/TA7, TA7/TA7
- TA6/TA6: 18%
- TA6/TA7: 29%
- TA7/TA7: 80%

Rodríguez-Nóvoa et al, AIDS 2007
Toxicidad renal asociada a Tenofovir

Haplotipo CATC (-24, 1249, 3563, 3972): > riesgo KDT

*Izzedine H et al, 2006*

-24 CC: >% pacientes con KTD en -24 CC vs CT o TT (24% vs. 6%, \( p=0.020 \)).

*Rodríguez-Novoa et al, CID 2009*

MRP2

MRP7

MRP7 (rs9349256-intrón 4)- KTD

*Pushpakom S et al, CROI 2010*
Toxicidad renal asociada a Tenofovir

≥ 2 risk factors:
NPV: 94%
PPV: 39%

- age (>50)
- weight (<60 kg)
- genotype CC at ABCC2 -24 (MRP2)

Rodríguez-Nóvoa et al, CID 2009
Agradecimientos

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Eugenia Vispo
Pablo Barreiro
Inmaculada Jiménez-Nácher
I Reunión de la RIS sobre Coinfección VIH-Hepatitis

Miércoles 23 noviembre 2011, Salón de Actos, Hospital Carlos III, Madrid

Coordinadores:
Dr. Juan A Pineda (Sevilla), Dr. Juan Berenguer (Madrid), Dr. Bonaventura Clotet (Barcelona) y Dr. Vicente Soriano (Madrid)

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