RECENT ADVANCES IN THE TREATMENT OF HEPATITIS C

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HCV
The Discovery
HCV: the History

- 1968: Discovery of HBV (Blumberg)
- 1973: Discovery of HAV (Feinstone)
- 1975: Description of non-A, non-B hepatitis (Alter)
- DNA virus (HBV mutant) or RNA virus (Flavivirus)?
- 1989: Sequencing of the HCV RNA and production of specific anti-HCV antibodies (Houghton)
HCV: the History

- 1989: 70% of patients with NANB hepatitis are anti-HCV + (Alter, Marcellin)
- 1990: Screening of blood donors for anti-HCV (Alter)
- 1992: Sensitive anti-HCV assays (100%)
- 1994: First PCR assays (Xu)
- 1995: Genotypes and viral load as predictors of response to therapy (Martinot-Peignoux)
HCV: the History of Treatment

- 1986: IFN can induce a sustained biochemical response (Hoofnagle)
- 1989: Randomized controlled trials of IFN (Di Bisceglie, Marcellin)
- 1991: Ribavirin can induce a biochemical response (Reichard)
HCV: the History

- 1994: Ribavirin doubles the SVR rate of IFN
  (Brillanti)
- 1999: EASL Consensus Conference: IFN+RBV as the SOC of hepatitis C
- 2000: PEG IFN more effective than IFN (Zeuzem)
- 2001: PEG IFN+RBV more effective than IFN+RBV (Manns, Fried)
RESULTS OF THERAPY
(Sustained Virological Response)

6% IFN 6 m. 1989
16% IFN 12 m. 1994
41% IFN + RBV 1998
39% PEG IFN 2000
55% PEG IFN + RBV 2001
>60% Optimized 2010
IMPACT OF THERAPY?
Objectives of Therapy:

- Sustained virological response (SVR)
- Arrest progression of liver disease (fibrosis)
- Prevent cirrhosis
- Prevent complications of cirrhosis (HCC)
- Improve survival
SUSTAINED VIROLOGICAL RESPONSE = ERADICATION?
Sustained Virological Response = Viral Eradication

- 80 patients treated in 1987-1992 with SVR
- Follow-up (mean = 3 years)
- Normal ALT = 95%
- Undetectable serum HCV RNA = 97%
- Undetectable liver HCV RNA = 100%

Marcellin et al. Liver 1994
Sustained Virological Response = Viral Eradication

- 213 patients with SVR
- Most sensitive HCV RNA assay (TMA)
- Follow-up (1-18 years)
  - Normal ALT = 95%
  - Undetectable serum HCV RNA = 100%
  - Undetectable liver HCV RNA = 98%
  - Undetectable PBMC HCV RNA = 100%

Maylin et al. Gastroenterology 2008
Objectives of Therapy:

• Sustained virological response (SVR)
• Eradication of HCV
• Arrest progression of liver disease (fibrosis)?
• Prevent cirrhosis?
• Prevent complications of cirrhosis (HCC)?
• Improve survival?
80 responders; 1-8 years post treatment


103 responders; 0.5-14 years post treatment

Maylin et al. Gastroenterology 2008

Fibrosis (Metavir)

- Stable: 59%
- Improved: 27%
- Deteriorated: 14%
LS (Fibroscan) ACCORDING TO THE DELAY IN PATIENTS WITH AND WITHOUT SVR

With SVR (n=38)

- < 3 years (n=13) LS measurement: 10.9 kPa
- 3-6 years (n=14) LS measurement: 8.8 kPa
- > 6 years (n=11) LS measurement: 6.3 kPa

Without SVR (n=76)

- < 3 years (n=42) LS measurement: 16.4 kPa
- 3-6 years (n=27) LS measurement: 15.5 kPa
- > 6 years (n=7) LS measurement: 15.1 kPa

\( p=0.02 \)

\( p=0.57 \)

Cardoso et al. AASLD 2008
# Regression of Cirrhosis?

123 cirrhotics, 2 LBs with median interval of 4 years (1-17)

<table>
<thead>
<tr>
<th></th>
<th>F4</th>
<th>F3</th>
<th>F2</th>
<th>F1</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR+</td>
<td>54%</td>
<td>25%</td>
<td>13%</td>
<td>8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SVR-</td>
<td>84%</td>
<td>13%</td>
<td>3%</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Cardoso et al. J Hepatol 2010
HCC
SVR vs non SVR (in 300 cirrhotics)

Cumulative Incidence of HCC

SVR (-)
SVR (+)

p < 0.001

Cardoso et al. J Hepatol 2010
SURVIVAL WITHOUT LT
SVR vs non SVR (in 300 cirrhotics)

Cardoso et al. J Hepatol 2010
HOW TO PREDICT RESPONSE?
How to predict response:

- Before treatment

- During treatment
<table>
<thead>
<tr>
<th>VIRUS</th>
<th>HOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Genotype</td>
<td>o Ethnicity</td>
</tr>
<tr>
<td>o Viral load</td>
<td>o Age</td>
</tr>
<tr>
<td></td>
<td>o Gender</td>
</tr>
<tr>
<td></td>
<td>o Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>o Alcohol</td>
</tr>
<tr>
<td></td>
<td>o Weight</td>
</tr>
<tr>
<td></td>
<td>o Insulin-Résistance +++</td>
</tr>
<tr>
<td>Genotype</td>
<td>90%</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Genotype 2, low VL</td>
<td></td>
</tr>
<tr>
<td>Genotype 2, high VL</td>
<td></td>
</tr>
<tr>
<td>Genotype 3, low VL</td>
<td></td>
</tr>
<tr>
<td>Genotype 3, high VL</td>
<td></td>
</tr>
<tr>
<td>Genotype 4, VL (?)</td>
<td></td>
</tr>
<tr>
<td>Genotype 1, low VL</td>
<td></td>
</tr>
<tr>
<td>Genotype 1, high VL</td>
<td></td>
</tr>
</tbody>
</table>
PREDICTION OF SVR BEFORE TREATMENT

**Virus**
- Genotype
- Viral load

**HOST**
- Ethnicity
- Age
- Gender
- Cirrhosis
- Alcohol
- Weight
- Insulin-Résistance +++
SVR and Insulin-Resistance

113 Patients Genotype 1, PEG IFN + RBV 48 weeks

- SVR: 60%
- HOMA < 2: 40%
- HOMA 2-4: 20%

Romero-Gomez et al. Gastroenterology 2005
Genotypes 2 & 3

Genotypes 1 & 4

HOMA – IR

2.5

3.2

p = 0.01

Moucari et al. Gastroenterology 2008
HCV RNA LEVEL AND IR

- HCV RNA < 200,000: HOMA-IR 1.3
- HCV RNA 200-600,000: HOMA-IR 1.8
- HCV RNA ≥ 600,000: HOMA-IR 2.3

Moucari et al. Gastroenterology 2008
Insulin Resistance: HCV versus HBV

Moucari et al. Gastroenterology 2008
ROLE OF GEOGRAPHICAL ORIGIN IN HCV G4 PATIENTS?
Severe fibrosis according to geographical origin in G4

Geographical origin and IR are independent factors (p<0.001)

Moucari et al. GUT 2009
SVR ACCORDING TO GEOGRAPHICAL ORIGIN IN G4

Geographical origin and IR are independent factors of SVR (p<0.001)

Moucari et al. GUT 2009
How to predict response:

- Before treatment
- During treatment
PREDICTIVE VALUE OF EARLY VIRAL KINETIC
Predictive Value of Early Virological Response in HCV G1 patients

- Yes: 86% (n = 390) → SVR 65%
- No: 14% (n = 63) → SVR 3%

2 log reduction
W12 (n = 453)

Predictive value of Rapid Virological Response (RVR) = 4 weeks (N = 400 naive, NR, RR)

- PPV of HCV RNA - Week 4: 96%
- NPV of HCV RNA < 2 log - Week 12: 97%

Martinot et al. Antiviral Therapy 2009
HOW TO OPTIMIZE TREATMENT?

The concept of response guided therapy
THE « ACCORDION » CONCEPT

Rapid responders
Slow responders

Undetectable HCV RNA

Marcellin et al. J Hepatol 2007
### Definitions of on-treatment response

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RVR</strong>*</td>
<td>HCV RNA negative at week 4</td>
</tr>
<tr>
<td><strong>EVR</strong></td>
<td></td>
</tr>
<tr>
<td>Complete EVR</td>
<td>HCV RNA positive at week 4 but negative at week 12</td>
</tr>
<tr>
<td>Partial EVR</td>
<td>HCV RNA positive but $\geq 2 \log_{10}$ drop at week 12</td>
</tr>
<tr>
<td>Non-EVR</td>
<td>$&lt;2 \log_{10}$ drop from at week 12</td>
</tr>
</tbody>
</table>

* RVR = rapid virological response
** EVR = early virological response

Marcellin et al. APASL 2008
SVR rates in G 1 patients according to RVR or EVR

PEG IFN 180 µg/wk plus RBV 1000/1200 mg/day for 48 weeks; n=569

SVR: 5% (5/111)
SVR: 87% (78/90)
SVR: 27% (34/128)
SVR: 68% (162/240)

No EVR 20% (111/569)
RVR 16% (90/569)
cEVR 42% (240/569)
pEVR 22% (128/569)

Marcellin et al. APASL 2008
TREATMENT OF NON RESPONDERS
Induction dosing had less impact than treatment duration on rate of SVR

HCV RNA - at week 12 is a strong predictor of SVR with 72 weeks treatment.

All patients (n=942)

HCV RNA - at week 12:
- YES 17%
- NO 83%

Moucari et al. J Hepatol 2007

**Maintenance Therapy?**

"HALT-C" Study (PEG IFN a2a, 90)

Significant decrease of ALT, HCV RNA and liver necro-inflammation (p<0.0001)

Shiffman et al. NEJM 2009
PERSPECTIVES
PERSPECTIVES:

- Better predict the response and adjust therapy

- The new molecules
Prediction of SVR with Liver Gene Expression: Transcriptome

Table 3. List of the genes that differ between NR and SVR in Group A

<table>
<thead>
<tr>
<th>Gene</th>
<th>NR / normal</th>
<th>SVR / normal</th>
<th>NR / SVR</th>
<th>P-value*</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFI6</td>
<td>126.5 ± 84.3</td>
<td>35.6 ± 48.1</td>
<td>3.5</td>
<td>0.002</td>
<td>0.039</td>
</tr>
<tr>
<td>IFI27</td>
<td>141.1 ± 107.3</td>
<td>33.6 ± 40.7</td>
<td>4.2</td>
<td>0.002</td>
<td>0.039</td>
</tr>
<tr>
<td>ISG15</td>
<td>88.5 ± 80.3</td>
<td>24.1 ± 33.0</td>
<td>3.7</td>
<td>0.002</td>
<td>0.039</td>
</tr>
<tr>
<td>Mx1</td>
<td>40.1 ± 33.9</td>
<td>14.9 ± 19.2</td>
<td>2.7</td>
<td>0.006</td>
<td>0.059</td>
</tr>
<tr>
<td>HERC5</td>
<td>11.6 ± 9.1</td>
<td>5.4 ± 5.3</td>
<td>2.2</td>
<td>0.006</td>
<td>0.059</td>
</tr>
<tr>
<td>TGBF2</td>
<td>6.2 ± 7.6</td>
<td>2.3 ± 1.7</td>
<td>2.7</td>
<td>0.006</td>
<td>0.059</td>
</tr>
<tr>
<td>OAS2</td>
<td>27.0 ± 15.4</td>
<td>14.9 ± 16.0</td>
<td>1.8</td>
<td>0.016</td>
<td>0.118</td>
</tr>
<tr>
<td>VEGFD</td>
<td>5.5 ± 5.0</td>
<td>2.3 ± 2.9</td>
<td>2.4</td>
<td>0.020</td>
<td>0.118</td>
</tr>
<tr>
<td>IL8</td>
<td>49.2 ± 63.9</td>
<td>15.4 ± 15.5</td>
<td>3.2</td>
<td>0.020</td>
<td>0.118</td>
</tr>
<tr>
<td>IFI1</td>
<td>387.8 ± 1399.3</td>
<td>7.0 ± 8.2</td>
<td>55.3</td>
<td>0.020</td>
<td>0.118</td>
</tr>
</tbody>
</table>

Best signature: IFI27 et CXCL9

Accuracy: 78 %

Asselah et al. GUT 2008
Prediction of SVR by Genomic

Responders N=500

Non responders N=500

3 domains associated With SVR

Ge et al. Nature 2009
SVR According to T/C Polymorphism And Ethnicity

Figure 1 | Percentage of SVR by genotypes of rs12979860. Data are percentages ± s.e.m.
PREDICTION OF SVR WITH GENETIC POLYMORPHISM

- C/T polymorphism (chromosome19) associated with SVR
  C/C : 80%
  T/T : 25%
- Higher frequency of T/T in Africans might explain poor response
- Mécanisms implicated?
  Domain close to IL28 gene coding for lambda 3 IFN
<table>
<thead>
<tr>
<th>Cible</th>
<th>Molécule</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease</strong></td>
<td>Telaprevir/VX-950 <em>(Vertex/J&amp;J)</em></td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Boceprevir/SCH 503034 <em>(SP)</em></td>
<td>Phase III</td>
</tr>
<tr>
<td><strong>Protease</strong></td>
<td>R7227/ITMN-191 <em>(Roche/InterMune)</em></td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>TMC435350 <em>(Tibotec/Medivir)</em></td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Polymerase</strong></td>
<td>R1626 <em>(Roche)</em></td>
<td>Phase II</td>
</tr>
<tr>
<td><em>(Nucleoside)</em></td>
<td>R7128/PSI-6130 <em>(Roche/Pharmasset)</em></td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Polymerase</strong></td>
<td>A-837093 <em>(Abbott)</em></td>
<td>Phase II</td>
</tr>
<tr>
<td><em>(non-nuc)</em></td>
<td>BILB 1941 <em>(Böhringer-Ingelheim)</em></td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>GS 9190 <em>(Gilead)</em></td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>VCH 759 <em>(VircoChem)</em></td>
<td>Phase I</td>
</tr>
</tbody>
</table>
Telaprevir + PEG IFN + Ribavirine

HCV RNA (Log_{10} IU/mL) vs. Study Time (in Days)
Telaprevir + PEG IFN a2a + ribavirin in genotype 1, naive patients

- **PROVE11 (US)**
  - TVR + SOC 12 weeks, then SOC for 24-36 weeks: 67%
  - Standard of care (SOC) (48 weeks): 48%

- **PROVE12 (Europe)**
  - TVR + SOC 12 weeks, then SOC for 24-36 weeks: 41%
  - Standard of care (SOC) (48 weeks): 68%

*Figure showing the percentage of patients with an SVR (Sustained Viral Response) in the studies PROVE11 and PROVE12.*
TELAPREVIR + PEG IFN + RBV
according to posology and type of PEG IFN

Marcellin et al. AASLD 2009
Perspectives

- Triple therapy with Telaprevir or Boceprevir in 2011-2012:
  70-80% SVR rate
  24 weeks in the majority (RVR)
- Prot inhibitor + pol inhibitor without PEG IFN and RBV ?
ANTI-PROTEASE + ANTI-POLYMERASE
Inform 1

RG 7128 + RG 7227

Median Log_{10} HCV RNA (IU/mL)

Days 1 3 5 7 9 11 13

25% NRs

63% Naives

Gane et al. EASL 2009
COMBO ANTI-PROT + ANTI-POL vs TRIPLE THERAPIE TELAPREVRIR + IFN + RBV

Median log_{10} HCV RNA (IU/mL)

Days

Double therapy

Triple therapy
HCV antivirals as components of new treatment paradigm

IFN-based

PEG IFN + RBV (SOC)

1 Antiviral + SOC

2 Antivirals + PEG IFN

2 Antivirals + RBV ?

2 Antivirals ?

IFN-sparing

Today

Mid-term ~2012

Long-term 2020?
CONCLUSION

100% of Cure
Within 10 years
with oral combinations
Short duration and well tolerated?