HCV treatment with DAAs
Management of side effects

Roma, 31.05.2012

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Hôpital Cochin, Paris, France
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Treatment of chronic hepatitis C

Genotype 1

- Ribavirin 1000-1400 mg/d + PEG Interferon 180\(\mu\)g \(\alpha\)2a or 1.5\(\mu\)g \(\alpha\)2b /w 24*.
- + Protease inhibitor

SVR ~ 75%

*In IL28B CC, fibrosis F0-2, RVR and low baseline viral load corresponding to 15% of caucasian patients

SVR ~ 75%

AASLD or French guidelines 2011
Treatment of chronic hepatitis C

Genotype 1

RVR+

Ribavirin 1000-1400 mg/d + PEG Interferon 180µg α2a or 1.5µg α2b /w 24*.

SVR ~ 75%

but the safety/tolerance profile limits feasibility...

Ribavirin 1000-1400 mg/d + PEG Interferon 180µg α2a or 1.5µg α2b /w 24* or 48 w. + Protease inhibitor

SVR~75%

*In IL28B CC, fibrosis F0-2, RVR and low baseline viral load Post- FDA & -EMEA approval corresponding to 15% of caucasian patients

AASLD or French guidelines 2011
Peg-IFN/ribavirin/protease inhibitor for HCV treatment

Main side effects: pooled phase III

<table>
<thead>
<tr>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash (37%)</td>
<td>Anemia (49% vs. 29%)</td>
</tr>
<tr>
<td>Pruritus (50% vs. 36%)</td>
<td>Dysgeusia (40% vs. 18%)</td>
</tr>
<tr>
<td>Anemia (37% vs. 19%)</td>
<td></td>
</tr>
<tr>
<td>Nausea (43% vs. 31%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea (28% vs. 22%)</td>
<td></td>
</tr>
</tbody>
</table>
# Telaprevir: week 16 safety findings

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir n = 295</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (% patients with at least one event)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>535 in 160 patients (54.2%)</td>
</tr>
<tr>
<td>Premature discontinuation / due to SAEs</td>
<td>139 (47.1%) / 63 (21.3%)</td>
</tr>
<tr>
<td>Death</td>
<td>7 (2.4%)</td>
</tr>
<tr>
<td>Infection (Grade 3/4)</td>
<td>27 (9.1%)</td>
</tr>
<tr>
<td>Hepatic decompensation (Grade 3/4)</td>
<td>15 (5.1%)</td>
</tr>
<tr>
<td>Rash (grade 3/SCAR)</td>
<td>16 (5.4%) / 2 (0.6%)</td>
</tr>
<tr>
<td>Anemia (Grade 3/4: Hb &lt;8 g/dL)</td>
<td>38 (12.9%)</td>
</tr>
<tr>
<td>EPO use / blood transfusion</td>
<td>168 (56.9%) / 53 (18.0%)</td>
</tr>
<tr>
<td>GCSF use</td>
<td>8 (2.7%)</td>
</tr>
<tr>
<td>TPO use</td>
<td>6 (2.0%)</td>
</tr>
</tbody>
</table>

SCAR: severe cutaneous adverse reaction

Hezode C et al. J Hepatol 2013
### Boceprevir: week 16 safety findings

<table>
<thead>
<tr>
<th>Patients, n (% patients with at least one event)</th>
<th>Boceprevir n = 190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>321 in 97 patients (51.0%)</td>
</tr>
<tr>
<td>Premature discontinuation / due to SAEs</td>
<td>80 (42.1%) / 27 (14.2%)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>(1 pneumonia, 1 septicemia, 1 anevrysmal bleeding,)</td>
<td></td>
</tr>
<tr>
<td>Infection (Grade 3/4)</td>
<td>8 (4.2%)</td>
</tr>
<tr>
<td>Hepatic decompensation (Grade 3/4)</td>
<td>9 (4.7%)</td>
</tr>
<tr>
<td>Rash (grade 3/SCAR)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Anemia (Grade 3/4: Hb &lt;8 g/dL)</td>
<td>19 (10.0%)</td>
</tr>
<tr>
<td>EPO use / blood transfusion</td>
<td>119 (62.6%) / 26 (13.7%)</td>
</tr>
<tr>
<td>GCSF use</td>
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<td>TPO use</td>
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SCAR: severe cutaneous adverse reaction

Hezode C et al. J Hepatol 2013
HCV treatment with DAAs
Management of side effects

• « General » severe side effects
• Cutaneous events
• Anemia
HCV treatment with DAAs
Management of side effects

- « General » severe side effects
- Cutaneous events
- Anemia
Multivariate analysis: baseline predictors of severe complications*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin Time</td>
<td>1.03</td>
<td>1.01-1.06</td>
<td>0.038</td>
</tr>
<tr>
<td>(per unit decrease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.01-1.11</td>
<td>0.025</td>
</tr>
<tr>
<td>(per year increase)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count ≤100,000/mm³</td>
<td>3.19</td>
<td>1.32-7.73</td>
<td>0.0098</td>
</tr>
<tr>
<td>Albumin level &lt;35 g/L</td>
<td>4.95</td>
<td>2.04-12.01</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

* Death, severe infection and hepatic decompensation, n=32

Hezode C et al. J Hepatol 2013
Baseline predictors of severe complications*

<table>
<thead>
<tr>
<th></th>
<th>≤100,000/mm³</th>
<th>&gt;100,000/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelet count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 g/L</td>
<td>44%</td>
<td>7%</td>
</tr>
<tr>
<td>≥35 g/L</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Death, severe infection and hepatic decompensation, n=32

Hezode C et al. J Hepatol 2013
Prevention of severe complications

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>≤100,000/mm³</th>
<th>&gt;100,000/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin level</td>
<td>&lt;35 g/L</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>≥35 g/L</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>&lt;35 g/L</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>≥35 g/L</td>
<td>3%</td>
</tr>
</tbody>
</table>

1. Do not treat F4 patients with baseline low platelets count and low albumin levels (risk/benefit ratio)

2. Discuss pre-emptive antibiotics
HCV treatment with DAAs
Management of side effects

• "General" severe side effects
• Cutaneous events
• Anemia
Skin eruption and DAAs

Dermatological side effects of hepatitis C and its treatment: Patient management in the era of direct-acting antivirals

Patrice Cacoub1, Marc Bourlière2, Jann Lübbe3, Nicolas Dupin4, Peter Buggisch5, Geoffrey Dusheiko6, Christophe Hézode7, Odile Picard8, Ramon Pujol9, Siegfried Segaert10, Bing Thio11, Jean-Claude Roujeau12

1Department of Internal Medicine, Assistance Publique-Hôpitaux de Paris, Groupe Hospitalier Pité-Salpêtrière, and Université Pierre et Marie Curie, Paris, France; 2Service d’Hépatologie-Gastroentérologie, Hôpital Saint-Joseph, Marseille, France; 3Faculté de Médecine, Université de Genève, Geneva, Switzerland; 4Service de Dermatologie, Hôpital Tarnier-Cochin, Université Paris Descartes, Assistance Publique-Hôpitaux de Paris, Paris, France; 5Liver Center Hamburg, IF, Asklepios Klinik St. Georg, Hamburg, Germany; 6Centre for Hepatology, Royal Free and University College School of Medicine and Royal Free Hospital, Hampstead, London, UK; 7Service d’Hépatologie et de Gastroentérologie, Hôpital Henri-Mondor, Assistance Publique-Hôpitaux de Paris, Université Paris Est, Créteil, France; 8Hôpital Saint-Antoine, Paris, France; 9Department of Dermatology, Hospital del Mar IMAS, Barcelona, Spain; 10Department of Dermatology, University Hospital Leuven, Belgium; 11Department of Dermatology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; 12Université Paris-Est Créteil, Créteil, France

Cacoub P et al. J Hepatol 2012
Skin eruption and DAAs
Boceprevir
SPRINT 1, SPRINT 2, RESPOND 2

<table>
<thead>
<tr>
<th></th>
<th>BOC/PR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1548</td>
<td>N = 547</td>
</tr>
<tr>
<td>rash/skin reaction</td>
<td>32% (490)</td>
<td>27% (150)</td>
</tr>
<tr>
<td>rash</td>
<td>17% (262)</td>
<td>17% (95)</td>
</tr>
</tbody>
</table>

No Stevens-Johnson syndrome/ no DRESS syndrome

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000MedR.pdf
Skin eruption and DAAs
Telaprevir (pooled phase 2 & 3 studies)

Aspect
- > 90% mild or moderate
- Pruritus or eczema-like lesion <30% body surface
- Grade increase, rare (<10%)

Starting point
- 50% within the first month
## Skin eruption and DAAs

### Classification of Skin Lesion

<table>
<thead>
<tr>
<th>Grades</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1 (mild)</strong></td>
<td>• Localized, w/wo pruritus</td>
</tr>
<tr>
<td><strong>Grade 2 (moderate)</strong></td>
<td>• Diffuse ≤ 50 % BSA</td>
</tr>
</tbody>
</table>
| **Grade 3 (severe)**   | • > 50% BSA or  
                        • Mucous superficial ulcerations  
                        • DRESS signs                  |
| **Grade 4 (SCAR)**    | • Drug Reaction with Hypereosinophilia Sd (DRESS)  
                        • Stevens Johnson Syndrome (SJS)  
                        • Toxic epidermic necrolysis (TEN, Lyell) |

BSA = body surface area; SCAR = severe cutaneous adverse reaction
Skin eruption and DAAs

Skin Eruption: Body Surface Evaluation

<table>
<thead>
<tr>
<th>Adult</th>
<th>Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>9 %</td>
</tr>
<tr>
<td>Head</td>
<td>9 %</td>
</tr>
<tr>
<td>Neck</td>
<td>1 %</td>
</tr>
<tr>
<td>Leg</td>
<td>18 %</td>
</tr>
<tr>
<td>Trunk (anterior)</td>
<td>18 %</td>
</tr>
<tr>
<td>Trunk (posterior)</td>
<td>18 %</td>
</tr>
</tbody>
</table>

1 hand palm = 1 %

Skin eruption and DAAs

Grade 2 Skin Eruption with Telaprevir

Grade 2 eruption
W5 TPR

Grade 2 eruption
W2 TPR

Courtesy, N. Dupin
Skin eruption and DAAs

Skin Eruption with Telaprevir

Grade 1 & 2: management by the hepatologist or the HCV-physician

- **Rash**
  - Grade 1: Local treatment
  - Grade 2: Local treatment, plus dermatology advice within 7 days

GRADE 1 & 2: management by the hepatologist or the HCV-physician

- Do not stop HCV treatment, including PI
- Anti-histaminics (H1-blockers)
- Topic steroids
- No sun exposure
- **Follow-up** of skin manifestations
Skin eruption and DAAs

Grade 3 or 4 skin eruption with Telaprevir

- **Rash**: Grade 3
  - Dermatology advice: urgent (24.00 hrs.)

- **SCARs**: Immediate hospitalization in a dermatology unit

GRADE 3 & 4: management by a dermatologist
Skin eruption and DAAs

Grade 3 (severe) skin eruption with Telaprevir
Skin eruption and DAAs

Grade 3 (severe) skin eruption with Telaprevir
Skin eruption and DAAs

- Grade 3 skin eruption
- PegIFN/ribavirin/Telaprevir
- Stop Telaprevir

Courtesy, N. Dupin
Skin eruption and DAAs

SCAR: Severe Cutaneous Adverse Reaction

SCAR encompasses several conditions

Acute generalized exanthematous pustulosis (AGEP) and Erythema Multiforme Major (EMM)

Drug rash/reaction with eosinophilia and systemic symptoms (DRESS)

Toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)

DRESS also called drug-induced hypersensitivity syndrome (DIHS); SJS and TEN may be considered as variants of single disorder

Skin eruption and DAAs

SCAR: Severe Cutaneous Adverse Reaction

Week 9
TPR

Courtesy N. Dupin
Skin eruption and DAAs

SCAR: Severe Cutaneous Adverse Reaction

- Week 9 Telaprevir
- Body surface >40%
- Facial edema
- T° > 38°7 C
- Eosinophilia = 913/mL
- DRESS possible
- Stop all treatments
Skin eruption and Telaprevir

Take Home Messages

Rash

Grade 1

Do NOT stop Telaprevir
**Skin eruption and Telaprevir**

**Take Home Messages**

- **Grade 1**: Do NOT stop Telaprevir

- **Grade 2**: Do NOT stop Telaprevir
  - Stop only if progression of skin lesions

- Stop ribavirin if not better 7 days after stopping Telaprevir
Skin eruption and Telaprevir

Take Home Messages

- **Rash**
  - **Grade 1**
    - Do NOT stop Telaprevir
  - **Grade 2**
    - Do NOT stop Telaprevir
      - Stop only if progression of skin lesions
    - Stop ribavirin if not better 7 days after stopping Telaprevir
  - **Grade 3**
    - Stop Telaprevir
    - Stop ribavirin if not better 7 days after stopping Telaprevir
Rash

Grade 1
Do NOT stop Telaprevir

Grade 2
Do NOT stop Telaprevir
• Stop only if progression of skin lesions

Grade 3
Stop ribavirin if not better 7 days after stopping Telaprevir

Grade 4
Stop Telaprevir
Stop ribavirin if not better 7 days after stopping Telaprevir

Stop ALL treatments

Take Home Messages

Skin eruption and Telaprevir
HCV treatment with DAAs
Management of side effects

• « General » severe side effects

• Cutaneous events

• Anemia
Anemia and DAAs

Hemoglobin nadir
Boceprevir & Telaprevir

Boceprevir

Telaprevir

Hb < 10 g/dL  Hb < 8.5 g/dL

Hb < 10 g/dL  Hb < 8.5 g/dL

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000MedR.pdf; Sprint 2, Respond 2 pooled
FDA advisory committee briefing document
Anemia and DAAs

Peg-IFN/ribavirin/Telaprevir for HCV treatment

Hemoglobin levels: pooled phase III

http://www.fda.gov/downloads/AdvisoryCommittees/Committees/MeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf
Anemia and DAAs
Peg-IFN/ribavirin/Boceprevir for HCV treatment
Hemoglobin levels: pooled phase III
Anemia and DAAs
Treatment options

**EPO**
- Not reimbursed in many countries
- Overcost
- Side effects?

**Ribavirin dose reduction (RDR)**
- Impact on SVR rates?

**Blood transfusions**
- Rejected by patients
- Risk of infection and immunisation
Anemia and DAAs
Impact of ribavirin dose reduction (RDR) in Telaprevir phase 3 studies

Treatment naïve patients

- HCV RNA Undetectable
  - RBV dose reduction: 89% (40/45)
  - No RBV dose reduction: 86% (347/405)

- HCV RNA Detectable
  - RBV dose reduction: 68% (120/176)
  - No RBV dose reduction: 65% (168/259)

Anemia and DAAs
Impact of ribavirin dose reduction (RDR) in Telaprevir phase 3 studies

Treatment-experienced patients

Anemia and DAAs
Impact of ribavirin dose reduction (RDR) in Telaprevir phase 3 studies

Prior partial responders

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
<th>T12/PR48</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never reduced</td>
<td>66</td>
<td>20</td>
<td>1/2</td>
</tr>
<tr>
<td>800–1000 mg</td>
<td>50</td>
<td>0</td>
<td>0/13</td>
</tr>
<tr>
<td>≤ 600 mg</td>
<td>62</td>
<td></td>
<td>0/5</td>
</tr>
</tbody>
</table>

Prior null responders

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
<th>T12/PR48</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never reduced</td>
<td>31</td>
<td>3</td>
<td>2/3</td>
</tr>
<tr>
<td>800–1000 mg</td>
<td>67</td>
<td></td>
<td>2/3</td>
</tr>
<tr>
<td>≤ 600 mg</td>
<td>25</td>
<td>25</td>
<td>2/8</td>
</tr>
</tbody>
</table>
Anemia and DAAs
Impact of ribavirin dose reduction (RDR) in Boceprevir phase 3 studies

Sulkowski M., EASL 2011, Abstract 476
Anemia and DAAs

Anemia and DAA/Boceprevir: A Prospective Randomized Trial
EPO vs. RDR

- Multicenter international (n = 687)

BOC in all patients after 4week-lead in (n = 687) → Hemoglobin < 10 g/dl* (n = 500) (72.8%) → R → RDR (n = 249) → Hemoglobin < 8.5 g/dl: Second strategy (EPO, RDR, transfusion) → EPO (40 000 UI/w) (n = 251)

* Patients might be randomized with Hb level 10 to 11 g/dL, if rapid decline

Poordad F, EASL 2012, Abs. 1419
**Anemia and DAAs**

Anemia and DAA/Boceprevir: A Prospective Randomized Trial

**EPO vs. RDR**

- A second strategy was used in:
  - 18% of patients in the RBV reduction group
  - 38% of patients in the EPO group

⇒ RBV dose decrease had no impact on SVR

---

EPO, érythropoïétine ; RBV, ribavirin ; SVR sustained virological response. Adjusted difference

Poordad F, EASL 2012, Abs. 1419
# Anemia and DAAs

**Anemia and DAA/Boceprevir: A Prospective Randomized Trial**  
**EPO vs. RDR**

<table>
<thead>
<tr>
<th></th>
<th>RBV reduct.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 249</td>
</tr>
<tr>
<td></td>
<td>EPO n = 251</td>
</tr>
<tr>
<td><strong>Race, n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>24/45 (53)</td>
</tr>
<tr>
<td>Non-black</td>
<td>154/204 (75)</td>
</tr>
<tr>
<td><strong>Gender, n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>60/78 (77)</td>
</tr>
<tr>
<td>Women</td>
<td>118/171 (69)</td>
</tr>
<tr>
<td><strong>Weight, n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 75 kg</td>
<td>76/106 (72)</td>
</tr>
<tr>
<td>≥ 75 kg</td>
<td>102/143 (71)</td>
</tr>
<tr>
<td><strong>Fibrosis, n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>F0/1/2</td>
<td>156/211 (74)</td>
</tr>
<tr>
<td>F3/4</td>
<td>19/33 (58)</td>
</tr>
<tr>
<td><strong>IL28B genotype, n/N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>61/78 (78)</td>
</tr>
<tr>
<td>CT</td>
<td>86/123 (70)</td>
</tr>
<tr>
<td>TT</td>
<td>30/46 (65)</td>
</tr>
</tbody>
</table>

*Central pathologist.  
Poordad F, EASL 2012, Abs. 1419
DAA and Anemia: Take Home Messages

- PegIFN/RBV plus BOC/TVR increase the rates of anemia (+20%) compared to PegIFN/RBV.

- In naive/relapser patients, non cirrhotics:
  - First line strategy: RBV dose reduction (even when HCV RNA+)
  - EPO: discussed on a case by case analysis

- In null responders or cirrhotics:
  - Need more data ....
  - If HCV RNA+, try to maintain RBV dose and add EPO until HCV RNA negativation

- Permanent RBV discontinuation has a negative impact on SVR

V. Leroy et al. Liver International 2012
HCV treatment with DAAs
Management of side effects: summary

• Treatment of F3-4 patients and F2 with co-morbidities is cost-effective (waiting the highly efficient oral combinations)

  Deuffic-Burban S et al. EASL 2013

• Adverse events are frequent but an early diagnosis and management of rash or anemia allows to maintain an efficient treatment and should not discourage physicians to treat patients who need to be treated.
HCV treatment with DAAs

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- Treatment of F3-4 patients and F2 with co-morbidities is cost-effective (waiting the highly efficient oral combinations)

  Deuffic-Burban S et al. EASL 2013

- Adverse events are frequent but an early diagnosis and management of infection, rash or anemia allows to maintain an efficient treatment and should not discourage physicians to treat patients who need to be treated.

p < 0.001 for comparison among three groups
p < 0.001 for HCV RNA detectable vs undetectable

Liver cancer

REVEAL-HCV study in mono-infected patients

HCV treatment with DAAs
Management of side effects: summary

- Treatment of F3-4 patients and F2 with co-morbidities is cost-effective waiting highly efficient oral combinations

- Adverse events are frequent but an early diagnosis and management of infection, rash or anemia allows to maintain an efficient treatment and should not discourage physicians to treat patients who need to be treated.

Deuffic-Burban S et al. EASL 2013

Berenguer M et al. CID 2012