Optimal Treatment with Boceprevir

Michael Manns

6th Paris Hepatitis Conference, 14th January 2013
Acknowledgements

Benjamin Maasoumy
Optimal Patient Selection
Defining the Ideal Candidate

- Treatment Urgency
- Chances for SVR
- Safety Profile

Maasoumy and Manns, Liver International 2013
In the real world there may even occur additional, nonmedical factors that interfere with aim to initiate treatment

i.e. professional drivers, social reasons, poor compliance, patient wish
# Optimal Patient Selection

## Real Life Safety of Triple Therapy

<table>
<thead>
<tr>
<th></th>
<th>CUPIC Week 16</th>
<th>MHH Week 12 (+/- Personalized lead-in)</th>
<th>EAP Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>497</td>
<td>86</td>
<td>609</td>
</tr>
<tr>
<td>SAEs (% of patients affected)</td>
<td>40%</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- due to Infection</td>
<td>6 (1.2%)</td>
<td>1 (1.2%)</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBV Dose reduction</td>
<td>12%</td>
<td>36%</td>
<td>28%</td>
</tr>
<tr>
<td>EPO</td>
<td>51%</td>
<td>0%</td>
<td>24%</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>12%</td>
<td>14%</td>
<td>12%</td>
</tr>
</tbody>
</table>

### Predictors for SAEs:

- **CUPIC**
  - Platelets <100,000/ml
  - Albumin <35g/l

- **MHH**
  - Platelets <110,000/ml (SAE rate 48%)
  - Child-Pugh Score >5 (SAE rate 45%)

**EAP:** Patients with advanced cirrhosis were not included – *may explain lower rate of SAEs*

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Colombo et al., AASLD 2012; Hezode et al., AASLD 2012;
Optimal Patient Selection
Defining the ideal Candidate

Treatment Urgency

Chances for SVR

Safety Profile

Ideal Candidate

(F2/)F3 fibrosis early cirrhosis

No significant Co-Morbidities

Previous Relapser Treatment naïve

Things may not be that easy in many cases!
208 patients with chronic HCV GT1 infection referred to hepatitis outpatient clinic of Hannover Medical School between June 1st and November 30th 2011 were evaluated for triple therapy Real Life ≠ Phase-3 trials:

- F3/F4: 64%; platelets <90/nl: 16%, treatment-experienced: 60%

Optimal Patient Selection
Real Life Eligibility for Triple Therapy

Almost 50% (n=103) not treated
# Optimal Patient Selection

**Telaprevir vs. Boceprevir**

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir</th>
<th>Boceprevir</th>
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<tbody>
<tr>
<td><strong>Treatment Duration</strong></td>
<td>RGT possible for Relapsers</td>
<td></td>
</tr>
<tr>
<td><strong>Co-Infections</strong></td>
<td>Some efficacy in GT2</td>
<td>Some efficacy in GT3</td>
</tr>
</tbody>
</table>
Telaprevir has some antiviral efficacy against HCV genotype 2 but not against genotype 3.
Boceprevir has some antiviral efficacy against HCV genotype 2 and genotype 3.

- 4 pts. Genotype 3
- 2 pts. Genotype 2
# Optimal Patient Selection
Telaprevir vs. Boceprevir

<table>
<thead>
<tr>
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<th>Telaprevir</th>
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<td>Some efficacy in GT3</td>
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<tr>
<td><strong>Lower PI Costs</strong></td>
<td>In Null Responders and Cirrhotics (if treatment is not discontinued)</td>
<td>Naïve patients In cases of treatment discontinuation</td>
</tr>
</tbody>
</table>
PI Treatment costs

- **Telaprevir**
- **Boceprevir**

<table>
<thead>
<tr>
<th>Naive</th>
<th>Naive_RGT</th>
<th>Relapser/PR</th>
<th>Cirrhotics/NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>€36 463</td>
<td>€31 894</td>
<td>€36 463</td>
<td>€36 463</td>
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<tr>
<td>€36 463</td>
<td>€23 920</td>
<td>€36 463</td>
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</tbody>
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Boceprevir PI treatment costs per month lower: 3.987€ vs. 12.154€

Boceprevir cheaper in cases of early treatment failure
Optimal Patient Selection
Ideal Candidate for Boceprevir

- Treatment-naïve
- Co-infected with HCV GT3
- and
- Patients that benefit from a Lead-In
Optimal Treatment Design
Lead-In – a controversial debate

Pro
Contra

No significant virological benefit
Optimal Treatment Design
Lead-In – Virological data

Zeuzem et al., NEJM 2011
Kwo et al., Lancet 2010
Optimal Treatment Design
Lead-In – a controversial debate

- Not every Patient requires a PI
- On-Treatment Risk/Benefit evaluation
- Uncertain Response to previous Therapy
- Uncertain IFN Tolerance

**Pro**
- Identify patients for dual therapy
- Use as Futility Rule
- Predict Virological Response
- Test Treatment Tolerance

**Contra**
- No significant virological benefit

Lead-In as a “test phase” important tool used to gain additional information
Lead-in in easy to treat patients
Not every patient benefits from a PI

Vierling et al., EASL 2011
Poordad et al., NEJM 2011
179 treatment-naïve patients with chronic HCV GT1 infection and a LVL (<600,000 IU/ml)
## P/R = P/R/PI?

### A randomized trial - Results

<table>
<thead>
<tr>
<th></th>
<th>P/R/BOC n=41</th>
<th>P/R n=38</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overall</td>
<td>90%</td>
<td>89%</td>
<td>0.8</td>
</tr>
<tr>
<td>- IL28B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>96%</td>
<td>96%</td>
<td>0.51</td>
</tr>
<tr>
<td>non-CC</td>
<td>79%</td>
<td>77%</td>
<td>0.72</td>
</tr>
<tr>
<td>- GT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>81%</td>
<td>85%</td>
<td>ns</td>
</tr>
<tr>
<td>1b</td>
<td>96%</td>
<td>92%</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Relapse rates</strong></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Dose reductions</strong></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td><strong>Discontinuations</strong></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
</tbody>
</table>
Optimal Patient Selection
Ideal Candidate for Boceprevir

- Treatment-naïve
- Co-infected with HCV GT3
- Patients that benefit from a Lead-In
  - “Easy-to-treat” patients
- Patients with uncertain virological outcome
- Patients with uncertain treatment tolerance

Lead-In also possible for Telparevir

…not well established!
Optimal treatment with boceprevir
Finding the optimal treatment design

- Lead-in?
- RGT vs. fixed duration
- Regimens for treatment-experienced patients
- Stopping criteria
Optimal Treatment Design
Response Guided Treatment

**SPRINT-2 study**: Phase 3 trial with 1097 treatment-naïve patients.
Optimal Treatment Design
Response Guided Treatment

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>63%</td>
<td>66%</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>F0-F2</td>
<td>67%</td>
<td>67%</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>eRVR</td>
<td>96%</td>
<td>96%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Decision by FDA and EMA: RGT for treatment-naïve, non-cirrhotic patients

Patients with eRVR
- End treatment after 28 weeks
- Just like in the SPRINT-2 trial

Those without eRVR
- not directly studied!!!
- Recommended regimen ≠ SPRINT-2
- Non-eRVR patients considered to be a mixture of PR and NR
  - Treated like non-eRVR patients in RESPOND-2 (4w P/R; 32 w P/R/BOC; 12w P/R)

Poordad et al., NEJM 2011
Optimal Treatment Design
Response Guided Treatment

**Respond-2 study**: Phase 3 trial with 403 IFN partial responders or relapsers. **Null responders excluded!!**
Optimal Treatment Design
Response Guided Treatment

**RESPOND-2**

<table>
<thead>
<tr>
<th>Category</th>
<th>RGT</th>
<th>Fixed 48w</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>59%</td>
<td>66%</td>
</tr>
<tr>
<td>F0-F2</td>
<td>66%</td>
<td>68%</td>
</tr>
<tr>
<td>F3/F4</td>
<td>44%</td>
<td>68%</td>
</tr>
<tr>
<td>Relapser</td>
<td>69%</td>
<td>75%</td>
</tr>
<tr>
<td>Partial Responder</td>
<td>40%</td>
<td>52%</td>
</tr>
<tr>
<td>eRVR</td>
<td>86%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Decision by:

**FDA**: no significant difference in non-cirrhotics with eRVR
RGT possible in non-cirrhotic Relapsers and PR
Same regimen like in the RESPOND-2 trial

**EMA**: no RGT!!! All non-cirrhotic Relapsers and PR should be treated for 48 weeks (4w L1; 32w P/R/BOC; 12w P/R)

Bacon et al., NEJM 2011
Optimal Treatment Design
RGT in Relapsers and PR – the EMA approach

<table>
<thead>
<tr>
<th></th>
<th>Patients with undetectable HCV RNA W8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 2: RGT</td>
</tr>
<tr>
<td>Relapse</td>
<td>*8/71 (11%)</td>
</tr>
<tr>
<td>SVR</td>
<td>64/74 (86%)</td>
</tr>
</tbody>
</table>

*In a few patients without FU24 data SVR12 data were used

**EMA Rationale:** Patients in both groups were treated the same way until week 36. Thus analysis should exclude those who dropped out before this stage !!!!!!

<table>
<thead>
<tr>
<th></th>
<th>Patients with undetectable HCV RNA W8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 2: RGT</td>
</tr>
<tr>
<td>Relapse</td>
<td>*7/69 (10%)</td>
</tr>
<tr>
<td>SVR</td>
<td>63/71 (89%)</td>
</tr>
</tbody>
</table>

No RGT due to **seven** Relapses in the RGT arm!
Optimal Treatment Design
Cirrhotics and null responders

Cirrhotics:
- Data on efficacy in cirrhotics are limited
  - RESPOND-2: 39 cirrhotic patients; SVR: 35% (RGT) vs. 77% (fixed)
  - SPRINT-2: 40 cirrhotic patients; SVR: 31% (RGT) vs. 42% (fixed)
- Overall, less favorable outcome
- **Recommendation:** 4 weeks lead-in and 44 weeks triple therapy if tolerated
  - If AEs i.e. anemia is challenging dual therapy (P/R) in the last 12 weeks can be considered

Null Responder:
- not studied in the pivotal trials!
- Indirect analysis by considering those with a poor lead-in response comparable to previous null responders
- **Recommendation:** difficult-to-treat cohort; 4 weeks lead-in and 44 weeks triple therapy
Boceprevir in null-responders
PROVIDE-Study - Efficacy

164 patients treated with P/R/BOC previously experienced a treatment failure with P/R in a BOC phase 2/3 control arm

SVR and Relapse Rates, by Prior Treatment Response

- SVR was also achieved in all 4 patients with ‘other’ prior non-response.
- Overall, 81 of 138 patients (59%) achieved SVR.
Optimal Treatment Design
Recommended Design

- Treatment-naïve
- Partial Responders/Relapsers
- Null Responders/Cirrhotics

Weeks 0 4 8 12 24 28 36 48

Peg-IFN RBV Peg-IFN/RBV/Boceprevir Peg-IFN/RBV

Peg-IFN RBV Peg-IFN/RBV/Boceprevir Peg-IFN/RBV

Peg-IFN RBV Peg-IFN/RBV/Boceprevir Peg-IFN/RBV

Peg-IFN RBV Peg-IFN/RBV/Boceprevir Peg-IFN/RBV

FDA

EMA

Victrelis Prescribing information EMA
Victrelis Prescribing information FDA
Based on the *risk/benefit* ratio **personalized approaches** may be applied i.e.

- Dual therapy for treatment-naïve patients with RVR
- PR and relapsers with eRVR: risk of AEs vs. small chance for a relapse (10%)
- Null Responders and cirrhotics with eRVR: Lack of data
Optimal Treatment Design – Some Personalized Approaches

- **Treatment-naïve**
  - FDA: Peg-IFN/RBV
  - EMA: Peg-IFN/RBV/Boceprevir

- **Partial Responders/Relapsers**
  - FDA: Peg-IFN/RBV
  - EMA: Peg-IFN/RBV/Boceprevir

- **Null Responders/Cirrhotics**
  - FDA: Peg-IFN/RBV
  - EMA: Peg-IFN/RBV/Boceprevir

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**EMA Decision based on seven patients**

**Lack of data for null responders/cirrhotics**

**Room for personalized approaches:**

*Personalized decision based on personalized risk/benefit ratio*
Optimal Treatment Design – Some Personalized Approaches

**Treatment-naïve**
- Peg-IFN RBV
- Peg-IFN RBV/Boceprevir
- Peg-IFN RBV

**Partial Responders/Relapsers**
- Peg-IFN RBV
- Peg-IFN RBV/Boceprevir
- Peg-IFN RBV

**Null Responders/Cirrhotics**
- Peg-IFN RBV
- Peg-IFN RBV/Boceprevir
- Peg-IFN RBV

**Weeks**
0 4 8 12 24 28 36 48

**Label**
- HCV-RNA ≥100 IU/ml
- HCV-RNA > LLD

**Futility Rules**
- <1log decline
- Null responder + cirrhotic
- <3log decline

*Personalized
- Shortening of treatment, if eRVR and poor P/R/BOC tolerability
- Shortening of treatment or P/R only, if poor (P/R)/BOC tolerability

*decision based on personalized risk/benefit ratio

Maasoumy and Manns, Liver International 2013
Optimal Treatment for Boceprevir
Every Single Step is essential!!

Optimal Patient Selection

Optimal Dosing

Optimal Treatment Design
- Lead-In
- Treatment Duration - RGT

Management of Adverse Events

Management of Drug-Drug-Interactions

Optimal Treatment
Thank you for your attention!!