Eligibility, Safety and Efficacy of New Triple Therapy: Lessons learned from the first experiences

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New treatment options since 2011

**BOCEPREVIR**
- 4 x 200 mg every 8h

**TELAPREVIR**
- 2 x 3 every 8h
- or
- 3 x 2 every 12h
Improvement of SVR with HCV protease inhibitor in naïve CHC G1-patients

Phase 3 Trials – Real World?

Phase III Trials

Age 49-51
F3/F4 fibrosis 7-50%
platelets 217-250 *10^3/ul

„Real World“
MHH clinic

Zeuzem et al, NEJM 2011
Hezode et al, EASL 2012
Poordad et al, NEJM 2011

208 patients with chronic HCV GT1 infection

- Currently not on antiviral treatment

**Triple Therapy?**
# Experiences from the MHH hepatitis clinic

## Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52.9 (+/- 12)</td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>115 (55%)</td>
<td></td>
</tr>
<tr>
<td>- Female</td>
<td>93 (45%)</td>
<td></td>
</tr>
<tr>
<td>- HCV-1a</td>
<td>75 (36%)</td>
<td></td>
</tr>
<tr>
<td>- HCV-1b</td>
<td>128 (62%)</td>
<td></td>
</tr>
<tr>
<td>- n.d.</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>- Il28B CC</td>
<td>38 (24%)</td>
<td></td>
</tr>
<tr>
<td>- Il28B non-CC</td>
<td>121 (58%)</td>
<td></td>
</tr>
<tr>
<td>- treatment-naïve</td>
<td>84 (40%)</td>
<td></td>
</tr>
<tr>
<td>- treatment-experienced</td>
<td>124 (60%)</td>
<td></td>
</tr>
<tr>
<td>Platelets (/nl)</td>
<td>&lt; 90</td>
<td>169 (+/- 77.6)</td>
</tr>
<tr>
<td>- &lt; 90</td>
<td>35 (17%)</td>
<td></td>
</tr>
<tr>
<td>Liver fibrosis (METAVIR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- F0-F2</td>
<td>72 (35%)</td>
<td></td>
</tr>
<tr>
<td>- F3/F4</td>
<td>133 (64%)</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh Score</td>
<td>&gt;6</td>
<td>9 (4%)</td>
</tr>
</tbody>
</table>

Maasoumy et al, PLoS one 2013
Phase 3 Studien – Real World?

Phase III Trials

Age: 49-51
F3/F4 fibrosis: 7-50%
Platelets: 217-250 *10^3/ul

„Real World“ MHH clinic

Age: 52.9
F3/F4 fibrosis: 64%
Platelets: 169 *10^3/ul

Zeuzem et al, NEJM 2011
Hezode et al, EASL 2012
Poordad et al, NEJM 2011
Maasoumy et al, PLoS one 2013
Phase 3 Studien – Real World?

Phase III Trials

Pre-Selected for Triple Therapy

Age 49-51
F3/F4 fibrosis 7-50%
Platelets 217-250 *10^3/ul

„Real World“ MHH clinic

52.9
64%
169 *10^3/ul

No every patient eligible for Tripel Therapy

Zeuzem et al, NEJM 2011  Hezode et al, EASL 2012
Experiences from the MHH hepatitis clinic
Evaluation of patients – Who is treated?

- Depression?
- Ascites?
- Young and healthy? “Wait for better options”

Hepatitis-clinic
MHH

Evaluation
Experiences from the MHH hepatitis clinic
Evaluation of patients

Maasoumy et al, PLoS one 2013
Experiences from the MHH hepatitis clinic
Evaluation of patients

11 randomized into phase 2/3 trials

Out of 197 patients treatment was not initiated in 103 (> 50%)
Experiences from the MHH hepatitis clinic Evaluation of patients

Therapy-associated Safety Concerns

Low Treatment Urgency: Wait for better Options

Decision: No Triple Therapy n=103/197

Regularly multiple reasons influenced the final decision

Poor Chance for SVR

Nonmedical Patient related Reasons: i.e. Patients Wish

Maasoumy et al, PLoS one 2013
Reasons not to treat

<table>
<thead>
<tr>
<th>Factor</th>
<th>Frequency n (% of 86 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment associated safety concerns</td>
<td>66 (64%)*</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>48 (47%)</td>
</tr>
<tr>
<td>Autoimmune exacerbation</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>Neuro-psychiatric diseases</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>8 (7.8%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (6.8%)</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>9 (8.7%)</td>
</tr>
<tr>
<td>Risk of hepatic decompensation</td>
<td>10 (9.7%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Age</td>
<td>8 (7.8%)</td>
</tr>
<tr>
<td>Intolerance to previous P/R treatment</td>
<td>6 (5.8%)</td>
</tr>
<tr>
<td>Need for other urgent procedures</td>
<td>6 (5.8%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Nonmedical patient related reasons</td>
<td>32 (31%)*</td>
</tr>
<tr>
<td>Patient wish</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>Poor compliance/LTFU</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Social reasons (i.e. bus driver)</td>
<td>7 (6.8%)</td>
</tr>
</tbody>
</table>

*More than factor could have influenced treatment decision.
1Eleven patients with platelets <60/μl; one patient with a platelet count of 89/μl and several other risk factors.
2Based on individual risk for disease progression and current stage of liver fibrosis (majority F0/F1:71%; remaining patients with Fibroscan result <9 kPa and one patient with F2 in liver biopsy)
Experiences from the MHH hepatitis clinic
Evaluation of patients

11 randomized into phase 2/3 trials

Out of 197 patients treatment was not initiated in 103 (> 50%)

8 treated by local physicians

86 patients treated with a triple therapy concept in our clinic
Phase 3 Trials – Real World?

Phase III Studien

„Real World“
MHH clinic
Treated

CUPIC

86 patients

Age
49-51

53.5

56.8

F3/F4 fibrosis
7-50%

86%

100%

Platelets
217-250 \( \times 10^3/\text{ul} \)

158 \( \times 10^3/\text{ul} \)

150 \( \times 10^3/\text{ul} \)

Zeuzem et al, NEJM 2011
Hezode et al, EASL 2012
Poordad et al, NEJM 2011
Maasoumy et al, PLoS one 2013
Experiences from the MHH hepatitis clinic

Treatment concepts

<table>
<thead>
<tr>
<th>PEG-IFN/RBV/Boceprevir</th>
<th>PEG-IFN/RBV/Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN/RBV</td>
<td></td>
</tr>
</tbody>
</table>

Lead-In as test period
- Uncertain treatment tolerability
- Uncertain compliance
- Not well-documented response to previous therapy
- Poor chance for SVR

Maasoumy et al, PLoS one 2013
Experiences from the MHH hepatitis clinic
Interim-Analysis Week 12 - Outcome

Patients Treated
N=86
Experiences from the MHH hepatitis clinic
Interim-Analysis Week 12 - Outcome

Patients Treated
N=86

N=20
Discontinued
-10 Virological failure
- 8 Intolerance/AEs
- 1 Death
-2 Both

N=5
Discontinued
-4 Virological failure
-1 Intolerance/AEs

N=25
Treatment Failure

Week 12
N=66 (77%)

At week 12
29% Treatment Failure
128 (62%) of all 208 patients not cured

Continued after
week 12
N=61 (71%)

Maasoumy et al, PLoS one 2013
Factors associated with Treatment Failure

<table>
<thead>
<tr>
<th>Factor</th>
<th>RR</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin &gt; 20 μmol/l</td>
<td>1.53</td>
<td>1.07 – 2.18</td>
</tr>
<tr>
<td>Albumin &lt; 40 g/l</td>
<td>1.65</td>
<td>1.19 – 2.28</td>
</tr>
<tr>
<td>Child-Pugh &gt; 5</td>
<td>1.74</td>
<td>1.29 – 2.34</td>
</tr>
<tr>
<td>Platelets &lt; 110/nl</td>
<td>1.83</td>
<td>1.33 – 2.52</td>
</tr>
<tr>
<td>IL28B CC</td>
<td>0.35</td>
<td>0.1 – 1.21</td>
</tr>
<tr>
<td>Treatment naive</td>
<td>0.6</td>
<td>0.34 – 1.07</td>
</tr>
<tr>
<td>Genotype 1a</td>
<td>1.55</td>
<td>1.1 – 2.18</td>
</tr>
</tbody>
</table>

Maasoumy et al, AASLD 2013
Overall Effectiveness of Triple Therapy

- **Screening:** 100%
- **Baseline of Antiviral Therapy:** 50% Not cured with triple therapy, 41% Possible curable with triple therapy
- **After Lead-In:** 55% Not cured with triple therapy, 36% Possible curable with triple therapy
- **Week 12 of Triple Therapy:** 62% Not cured with triple therapy, 29% Possible curable with triple therapy
- **End of Triple Therapy:** 67% Not cured with triple therapy, 24% Possible curable with triple therapy
- **SVR 12:** 74% Cured with triple therapy, 17% Included into clinical trials or treated elsewhere, (19%) Possible curable with triple therapy

Maasoumy et al, AASLD 2013
Experiences from the MHH hepatitis clinic - Safety

<table>
<thead>
<tr>
<th>Hematological adverse event/ applied management</th>
<th>Number until week 12 (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 g/dl</td>
<td>32 (37%)</td>
</tr>
<tr>
<td>&lt; 8.5 g/dl</td>
<td>12 (14%)</td>
</tr>
<tr>
<td><strong>Thrombopenia</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 50/nl</td>
<td>17 (20%)</td>
</tr>
<tr>
<td>&lt; 25/nl</td>
<td>4 (5%)</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.75/nl</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>&lt; 0.5/nl</td>
<td>2 (2%)</td>
</tr>
<tr>
<td><strong>Ribavirin</strong></td>
<td></td>
</tr>
<tr>
<td>- Dose reduction</td>
<td>31 (36%)</td>
</tr>
<tr>
<td>- Discontinuation</td>
<td>11 (13%)</td>
</tr>
<tr>
<td><strong>Blood transfusion</strong></td>
<td>11 (13%)</td>
</tr>
<tr>
<td><strong>Interferon</strong></td>
<td></td>
</tr>
<tr>
<td>- Dose reduction</td>
<td>20 (23%)</td>
</tr>
<tr>
<td>- Discontinuation</td>
<td>6 (7%)</td>
</tr>
</tbody>
</table>

Maasoumy et al, PLoS one 2013 and AASLD 2013
Factors associated with SAEs

- **Bilirubin > 20 μmol/l**: RR 2.59, CI (95%) 1.37 – 4.9
- **FibroScan > 30 kPa**: RR 2.56, CI (95%) 1.26 – 5.21
- **Albumin < 40 g/l**: RR 3.55, CI (95%) 1.88 – 6.68
- **Child-Pugh > 5**: RR 3.38, CI (95%) 1.87 – 6.08
- **Platelets < 110/μl**: RR 3.49, CI (95%) 1.98 – 6.25
- **Female Gender**: RR 2.13, CI (95%) 1.09 – 4.15

Maasoumy et al, AASLD 2013
## Safety and Efficacy stratified by Risk Profile in Patients with Cirrhosis

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt;110/nl and Child-Pugh Score &gt;5</td>
<td>Platelets &lt;110/nl or Child-Pugh Score &gt;5</td>
<td>Platelets ≥110/nl and Child-Pugh Score 5</td>
</tr>
<tr>
<td>n=7</td>
<td>n=16</td>
<td>n=20#</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failure</td>
<td>100% (n=7/7)</td>
<td>69% (n=11/16)</td>
<td>30% (n=6/20)</td>
</tr>
<tr>
<td>SAE</td>
<td>57% (n=4/7)</td>
<td>63% (n=10/16)</td>
<td>25% (n=5/20)</td>
</tr>
<tr>
<td>Either SAE or Treatment Failure</td>
<td>100%</td>
<td>94%</td>
<td>50%</td>
</tr>
</tbody>
</table>

#Five patients with platelets ≥110/nl but no accessible Child-Pugh Score as well as one patient with no available platelet count were excluded.

In the whole cohort platelets <110/nl and a Child-Pugh Score >5 associated with early treatment failure and SAEs until week 12
Risk factors for treatment failure and SAEs in different real-world cohorts

French CUPIC Study: Platelets <100/nl and Albumin <35g/l

Hamburg cohort: Platelets <100/nl, Albumin <39g/l, Age >65y

Austrian cohort: Albumin <35g/l and HVPG ≥10

Cost/Efficacy ratio of triple therapy
The Hannover Score

1 point per criteria

Maasoumy et al, AASLD 2013
### Cost/Efficacy ratio of triple therapy
#### The Hannover Score

<table>
<thead>
<tr>
<th>Hannover Score</th>
<th>Patients</th>
<th>SAE</th>
<th>SVR</th>
<th>SAE per PTY</th>
<th>SAE per SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52</td>
<td>5</td>
<td>28 (54%)</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>18</td>
<td>7 (39%)</td>
<td>1.46</td>
<td>2.57</td>
</tr>
<tr>
<td>2-3</td>
<td>15</td>
<td>14</td>
<td>1 (7%)</td>
<td>2.69</td>
<td>14</td>
</tr>
</tbody>
</table>

SAE: Serious Adverse Event
SVR: Sustained Virological Response (HCV RNA undetectable 12 weeks after end of treatment)
PTY: Patient Treatment Year = 48 weeks of antiviral therapy
PTW: Patient Treatment Week = one week of antiviral therapy

Maasoumy et al, AASLD 2013
Experiences from the MHH hepatitis clinic

Closing Remarks – Conclusions for patient selection

Stage of liver disease
Experiences from the MHH hepatitis clinic

Closing Remarks – Conclusions for patient selection

Stage of liver disease

Group A/Hannover Score 1
Experiences from the MHH hepatitis clinic

Closing Remarks – Conclusions for patient selection

Stage of liver disease

Group A/Hannover Score 1

- Naive, IL28B-CC
- LI-Response
- Relapse
Experiences from the MHH hepatitis clinic

Closing Remarks

- Tripel Therapy has a good efficacy in “Real World” for those who remain on treatment (PP: SVR 56%), **But: Efficacy ≠ Effectiveness**

- Not all patients are eligible

- SAEs and AEs appear more often in “real-world”-patients, in particular in “advanced” compensated cirrhotics might haven been ineligible for the pivotal trials

- Treating patients with advanced liver disease is associated with a high risk and poor treatment outcome (Hannover Score 2/3; low platelets and albumin)

- Current IFN and PI-based treatment options are “uncomfortable” and therefore do not attract many “healthy” patients who are able to wait for better (IFN-free) treatment options
Experiences from the MHH hepatitis clinic

Closing Remarks

- Tripel Therapy has good efficacy in “Real World” for those who remain on treatment (PP: SVR 56%), **But: Efficacy ≠ Effectiveness**

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- Current IFN and PI-based treatment options are “uncomfortable” and therefore do not attract many “healthy” patients who are able to wait for better (IFN-free) treatment options

- **A wise selection of patients for treatment is crucial to achieve an acceptable risk/benefit-ratio and ensure an optimal use of limited resources**
Challenges in Hepatitis Research
“Networking in Hepatology”

German Center for Infection Research: DZIF

Thank you for your attention