Expert Perspectives

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Expert Perspectives Format

• We will review some top line data from EASL
• Majority of the time discussing how the data affects daily practice
Grazoprevir (GZR; MK-5172) + Elbasvir (EBR; MK-8742)

Future Treatment Option
New Fixed Dose Combination: GZR/EBR

- **Grazoprevir** (MK-5172)
  - HCV NS3/4A inhibitor
  - 100 mg once daily, oral

- **Elbasvir** (MK-8742)
  - HCV NS5A inhibitor
  - 50 mg once daily, oral

- Broad *in vitro* activity against most HCV genotypes
- Retains *in vitro* activity against many clinically relevant RAVs

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Abstract G07

The Phase 3 C-EDGE Treatment-Naïve Study of a 12-Week Oral Regimen of Grazoprevir (GZR; MK-5172)/Elbasvir (EBR; MK-8742) in Patients With Chronic HCV GT 1, 4 or 6 Infection

S. Zeuzem et al
# SVR12 – FULL ANALYSIS SET

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>GT1a</th>
<th>GT1b</th>
<th>GT4</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td>95%</td>
<td>92%</td>
<td>99%</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>95%</td>
<td>299/316</td>
<td>144/157</td>
<td>129/131</td>
<td>18/18</td>
<td>8/10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Non-virologic failure</th>
<th>Breakthrough</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
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<td></td>
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<td></td>
<td>0</td>
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<td>2</td>
</tr>
</tbody>
</table>

Zeuaem et al., Abstract #G07, EASL 2015
C-SALVAGE: Grazoprevir (GZR; MK-5172), Elbasvir (EBR; MK-8742) and Ribavirin (RBV) for Chronic HCV-Genotype 1 Infection After Failure of Direct Acting Antiviral (DAA) Therapy

X. Forns et al
## GZR + EBR + RBV x 12 Weeks: SVR12 By Subgroup

<table>
<thead>
<tr>
<th>All Subjects</th>
<th>N = 79</th>
<th>SVR12 76 (96.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td>3 (3.8%)</td>
</tr>
<tr>
<td>By Prior PI Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boceprevir</td>
<td></td>
<td>27/28 (96%)</td>
</tr>
<tr>
<td>Telaprevir</td>
<td></td>
<td>41/43 (95%)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td></td>
<td>8/8 (100%)</td>
</tr>
<tr>
<td>By Prior Failure Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment failure</td>
<td></td>
<td>38/40 (95%)</td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td>25/26 (96%)</td>
</tr>
<tr>
<td>Intolerance</td>
<td></td>
<td>13/13 (100%)</td>
</tr>
<tr>
<td>By Time Since Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.1 year</td>
<td></td>
<td>22/24 (92%)</td>
</tr>
<tr>
<td>≥1.1 year</td>
<td></td>
<td>46/46 (100%)</td>
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<tr>
<td>By Presence of NS3 RAVs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td>43/43 (100%)</td>
</tr>
<tr>
<td>Present</td>
<td></td>
<td>31/34 (91%)</td>
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<tr>
<td>By Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1a</td>
<td></td>
<td>28/30 (93%)</td>
</tr>
<tr>
<td>G1b</td>
<td></td>
<td>48/49 (98%)</td>
</tr>
<tr>
<td>By Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>32/34 (94%)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>44/45 (98%)</td>
</tr>
<tr>
<td>By Viral Load</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤800,000 IU/mL</td>
<td></td>
<td>27/29 (93%)</td>
</tr>
<tr>
<td>&gt;800,000 IU/mL</td>
<td></td>
<td>49/50 (98%)</td>
</tr>
</tbody>
</table>

- Highly efficacious in patients who failed first generation protease inhibitor/PEG/RBV treatment
Advanced Chronic Kidney Disease

Review of New Data
Safety of Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir for Treating HCV GT 1 Infection in Patients With Severe Renal Impairment or End-Stage Renal Disease: The RUBY-1 Study

P. Pockros et al
Background/Objectives

• 12 weeks of OBV/PTV/r + DSV
  – GT 1 treatment-naïve
    • Included RBV for GT 1a
    • No RBV for GT 1b
  – CKD stage 4/5, including 60% on hemodialysis
  – Excluded cirrhotics
Summary

• Regimen has been well tolerated, including those on hemodialysis, with or without RBV

• Hemoglobin reductions were managed with monitoring and RBV dose interruption (8/13) and erythropoietin use (4/13)

• No virologic failures to date and all 10 subjects who reached PTW4
Abstract LP-02

C-SURFER: Grazoprevir Plus Elbasvir in Treatment-naïve and Treatment-experienced Patients With HCV GT 1 Infection and Chronic Kidney Disease

D. Roth et al
Background/Objectives

• <1% of GZR and EBR is renally excreted

• This study evaluated GZR+EBR in HCV-infected patients with CrCl<30 mL/min, including patients on hemodialysis
  – GT 1 treatment-naïve or treatment-experienced
  – CKD stage 4/5
  – Included compensated cirrhotics
• GZR/EBR was generally safe and well tolerated.
How Do We Currently Manage HCV-infected Patients With CKD Stage 4/5?

Are We Concerned With Using RBV For GT 1a Patients?
Can We Simplify the AbbVie Regimen for GT 1b?
Abstract G13

Ombitasvir/Paritaprevir/Ritonavir for Treatment of HCV Genotype 1B in Japanese Patients With or Without Cirrhosis: Results from GIFT-1

K Chayama et al
Background/Patient Population

- 2 DAA regimen: ombitasvir/paritaprevir/ritonavir
  - No interferon, ribavirin or dasabuvir
  - 12 week treatment
- Patient population
  - GT 1b-infected Japanese patients
  - Included cirrhotics
  - Treatment naïve or IFN-experienced patients
GIFT-I: Secondary Efficacy Results-SVR12 Rates in ITT Subpopulations

Patients with SVR12 (%)

Primary Efficacy Population

All

Naive

Experienced

Arm A
DB OBV/PTV/r

Arm B
OL OBV/PTV/r

Arm C
OL OBV/PTV/r

Patients without cirrhosis

Patients with compensated cirrhosis

Error bars: 95% CI. DB, double-blind; OL, open-label; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir.

Chayama et al., Abstract #G13, EASL 2015
Does This Study Have Applicability For Countries Other Than Japan?
GT 3 Update
Abstract L-05

Sofosbuvir Plus Peg-IFN/RBV for 12 Weeks vs Sofosbuvir/RBV for 16 or 24 Weeks in Genotype 3 HCV-Infected Patients and Treatment-experienced Cirrhotic Patients With Genotype 2 HCV: The BOSON Study

G. Foster et al
Study Design

- Multicenter study, open-label, randomized (1:1:1) study at 80 sites in UK, Australia, USA, Canada, and New Zealand
- GT 2 patients: treatment experienced (TE) with cirrhosis
- GT 3 patients: TE or treatment naïve (TN), with or without cirrhosis
- Stratification
  - Cirrhosis
  - HCV Genotype
  - Prior HCV treatment
- Platelets ≥60,000 cells/mm³

Foster et al., Abstract #L-05, EASL 2015
Overall SVR12 (GT 2 and GT 3 Combined)

Error bars represent 95% confidence intervals.

Foster et al., Abstract #L-05, EASL 2015
SVR12: GT 2 vs GT 3

Error bars represent 95% confidence intervals.
SVR12 in GT 3 by Treatment History and Cirrhosis Status

- **SOF + RBV 16 weeks**
  - No Cirrhosis: Treatment Naïve - 83, Treatment Experienced - 58
  - Cirrhosis: Treatment Naïve - 96, Treatment Experienced - 70

- **SOF + RBV 24 weeks**
  - No Cirrhosis: Treatment Naïve - 90, Treatment Experienced - 65
  - Cirrhosis: Treatment Naïve - 82, Treatment Experienced - 68

- **SOF + PEG/RBV 12 weeks**
  - No Cirrhosis: Treatment Naïve - 91, Treatment Experienced - 12
  - Cirrhosis: Treatment Naïve - 82, Treatment Experienced - 18

Foster et al., Abstract #L-05, EASL 2015
Abstract LP-05

Daclatasvir Plus Sofosbuvir With or Without Ribavirin in Patients With HCV Genotype 3 Infection: Interim Analysis of a French Multicenter Compassionate Use Program

C. Hezode et al
SVR4: DCV/SOF ± RBV in GT 3 Patients (12 vs 24 Weeks)

EASL Recommendation: GT 3 cirrhotics should receive SOF/DCV + RBV for 24 weeks

Hezode et al., Abstract #LP-05, EASL 2015
Is SOF + PEG/RBV for 12 Weeks Standard of Care for GT 3?
Can We Shorten Treatment Duration of SMV/SOF?
SVR12: SMV/SOF in GT 1 Non-cirrhotics (8 vs 12 Weeks)

A) Proportion of patients (%)

- SMV+SOF 12 weeks:
  - Treatment-naïve: 112/115 (94.0;100)
  - Treatment-experienced: 38/40 (97;100)

- SMV+SOF 8 weeks:
  - Treatment-naïve: 88/103 (75.1;92.7)
  - Treatment-experienced: 40/52 (64.5;89.3)

B) Proportion of patients (%)

- GT1a:
  - 112/116 (97;100)

- GT1a with Q80K:
  - 44/46 (79;100)

- GT1a without Q80K:
  - 68/70 (79;100)

- GT1b:
  - 38/39 (92;100)

Kwo et al., Abstract #LP-14, EASL 2015
Can We Shorten Treatment Durations To <12 Weeks By Combining Potent DAAs from Different Classes?
Abstract O006

C-SWIFT: Grazoprevir/Elbasvir + Sofosbuvir in Cirrhotic and Noncirrhotic Treatment-naive Patients With Hepatitis C Virus GT 1 Infection, for Durations of 4, 6 or 8 Weeks and GT 3 Infection for Durations of 8 or 12 Weeks

F. Poordad et al
### SVR12 in GT 1 Treatment-naïve Patients

#### Breakthrough
- **4 weeks**: 0
- **6 weeks**: 0
- **6 weeks**: 0
- **8 weeks**: 0

#### Relapse
- **4 weeks**: 20
- **6 weeks**: 4
- **6 weeks**: 4
- **8 weeks**: 1

#### Excluded
- **4 weeks**: 1
- **6 weeks**: 0
- **6 weeks**: 0
- **8 weeks**: 3†

*Excluded patients who discontinued due to reasons other than virologic failure
† One of the 3 patients who discontinued had HCV G2 at discontinuation

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Poordad et al., Abstract #O006, EASL 2015
SVR12 in GT 3 Treatment-naïve Patients

mITT analysis excluded patients who discontinued early due to reasons other than virologic failure

Poordad et al., Abstract #006, EASL 2015
Are There Long-Term Consequences of Treating for Too Short?
Retreatment of Patients Who Failed 8 or 12 Weeks of Ledipasvir/Sofosbuvir-Based Regimens With Ledipasvir/Sofosbuvir for 24 Weeks

E. Lawitz et al
SVR12 by Subgroup

- Overall SVR12 = 71% (29/41)

- All 11 patients without NS5A RAVs received 8 weeks of prior treatment
How Do We Best Manage Patients With NS5A RAVs?

Should All Patients Have Baseline RAV Testing?

How Long Before Retreating a Patient with RAVs?
Advanced Cirrhosis/Post-OLT
Regimens With New Data

• **SOLAR 2: SOF/LDV/RBV (G02; Manns, et al)**
  - 12 vs 24 week treatment
  - GT 1 CPT B&C
  - SVR12: 88% (57/65) (12 wk arm) vs 89% (54/61) (24 wk arm)

• **UK EAP: SOF + LDV or DCV ± RBV (O002; Foster, et al)**
  - 12 week treatment
  - GT 1 and GT 3 CP-B and C patients (Mean MELD=11.9)
  - Virologically effective with >40% showing improvement in liver function
  - For patients <65 years if albumin is >35 g/L, improvement in liver function is more likely than harm
Regimens With New Data

**ALLY 1: DCV/SOF/RBV (L-08; Poordad, et al)**
- 12 week treatment
- Any genotype enrolled but predominantly GT 1
- Advanced cirrhosis (CPT A, B and C patients) and post-OLT
- SVR12: CPT A=92% (11/12), CPT B=94% (30/32), CPT C=56% (9/16) and post-OLT=94% (50/53)

**C-SALT: GZR/EBR (O008; Jacobson, et al)**
- 12 week treatment
- GT 1 CPT B patients (Mean MELD=9.9)
- SVR12: 90% (27/30)
Advantages vs Disadvantages of Treating Advanced Cirrhosis vs Post-OLT
“EASL Recommendations on Treatment of Hepatitis C 2015” issued this week (J Hep). Is there any impact on current practice?

Drug:drug interaction concerns?

Community/primary care vs specialized care setting?