Expert Perspectives

Saeed Hamid, MD
Alex Thompson, MD, PhD
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

- HCV NS3/4A inhibitor
- 100 mg once daily, oral

- HCV NS5A inhibitor
- 50 mg once daily, oral

- Broad \textit{in vitro} activity against most HCV genotypes \textsuperscript{1-3}
- Retains \textit{in vitro} activity against many clinically relevant RAVs\textsuperscript{1-3}

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

- **All Patients**: 95% (299/316)
- **GT1a**: 92% (144/157)
- **GT1b**: 99% (129/131)
- **GT4**: 100% (18/18)
- **GT6**: 80% (8/10)

<table>
<thead>
<tr>
<th>Category</th>
<th>All Patients</th>
<th>GT1a</th>
<th>GT1b</th>
<th>GT4</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>299/316</td>
<td>144/157</td>
<td>129/131</td>
<td>18/18</td>
<td>8/10</td>
</tr>
<tr>
<td>Non-virologic failure</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>0</td>
<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>SVR12</th>
<th>76</th>
<th>(96.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 79</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Relapse</th>
<th>3</th>
<th>(3.8%)</th>
</tr>
</thead>
</table>

**By Prior PI Therapy**
- Boceprevir: 27/28 (96%)
- Telaprevir: 41/43 (95%)
- Simeprevir: 8/8 (100%)

**By Prior Failure Category**
- On treatment failure: 38/40 (95%)
- Relapse: 25/26 (96%)
- Intolerance: 13/13 (100%)

**By Time Since Therapy**
- <1.1 year: 22/24 (92%)
- ≥1.1 year: 46/46 (100%)

**By Presence of NS3 RAVs**
- Absent: 43/43 (100%)
- Present: 31/34 (91%)

**By Genotype**
- G1a: 28/30 (93%)
- G1b: 48/49 (98%)

**By Cirrhosis**
- Yes: 32/34 (94%)
- No: 44/45 (98%)

**By Viral Load**
- ≤800,000 IU/mL: 27/29 (93%)
- >800,000 IU/mL: 49/50 (98%)

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

Review of New Data
Abstract L-01

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

Pockros, et al. Abstract #LP-01, EASL 2015
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?
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
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 $\geq 60,000$ cells/mm$^3$
Overall SVR12 (GT 2 and GT 3 Combined)

- **SOF + RBV 16 Weeks**: 72%, 141/196
- **SOF + RBV 24 Weeks**: 85%, 170/199
- **SOF + PEG/RBV 12 Weeks**: 93%, 183/197

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.

SOF + RBV 16 weeks
SOF + RBV 24 weeks
SOF + PEG/RBV 12 weeks

GT 2

SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>GT 2</th>
<th>GT 3</th>
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</thead>
<tbody>
<tr>
<td>16 weeks</td>
<td>87/15</td>
<td>17/17</td>
</tr>
<tr>
<td>24 weeks</td>
<td>100/16</td>
<td>71/17</td>
</tr>
<tr>
<td>12 weeks</td>
<td>94/16</td>
<td>84/17</td>
</tr>
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</table>

GT 3

SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>GT 2</th>
<th>GT 3</th>
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</thead>
<tbody>
<tr>
<td>16 weeks</td>
<td>128/181</td>
<td>153/182</td>
</tr>
<tr>
<td>24 weeks</td>
<td>153/182</td>
<td>168/181</td>
</tr>
<tr>
<td>12 weeks</td>
<td>168/181</td>
<td>168/181</td>
</tr>
</tbody>
</table>

Foster et al., Abstract #L-05, EASL 2015
SVR12 in GT 3 by Treatment History and Cirrhosis Status

- SOF + RBV 16 weeks
- SOF + RBV 24 weeks
- SOF + PEG/RBV 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
<th>Treatment Naïve</th>
<th>Treatment Experienced</th>
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</thead>
<tbody>
<tr>
<td>Treatment Naïve</td>
<td>58/70</td>
<td>65/72</td>
<td>12/21</td>
<td>17/36</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>68/71</td>
<td>68/71</td>
<td>21/23</td>
<td>26/34</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td></td>
<td></td>
<td>41/54</td>
<td>47/35</td>
</tr>
<tr>
<td>No Cirrhosis</td>
<td>83/90</td>
<td>90/96</td>
<td>82/91</td>
<td>77/86</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>83/57</td>
<td>76/21</td>
<td>82/44</td>
<td>47/36</td>
</tr>
<tr>
<td>No Cirrhosis</td>
<td>94/47</td>
<td>94/47</td>
<td>49/52</td>
<td>30/35</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>82/77</td>
<td>72/34</td>
<td>54/34</td>
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</tbody>
</table>
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 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 (%)

<table>
<thead>
<tr>
<th>Primary Efficacy Population</th>
<th>All</th>
<th>Naive</th>
<th>Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>94.6</td>
<td>94.9</td>
<td>94.2</td>
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<tr>
<td>Arm B</td>
<td>96.1</td>
<td>98.1</td>
<td>98.5</td>
</tr>
<tr>
<td>Arm C</td>
<td>97.4</td>
<td>90.5</td>
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</table>

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?
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

<table>
<thead>
<tr>
<th></th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
</tr>
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<tbody>
<tr>
<td>Breakthrough</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>20</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Excluded*</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3†</td>
</tr>
</tbody>
</table>

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

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

HCV RNA <15 IU/mL (%, 95% CI)

- Non-cirrhotic
- Cirrhotic

8 weeks: 93%
- Non-cirrhotic: 14/15
- Cirrhotic: 100%
- Non-cirrhotic: 14/14
- Cirrhotic: 10/11

12 weeks: 91%

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

Poordad et al., Abstract #0006, 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

Lawitz et al., Abstract #0005, EASL 2015
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?