Best of HCV from AASLD

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Ankara, Turkey
Abstract #82

An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with Ledipasvir/ Sofosbuvir with or without Ribavirin

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Methods

- 513 patients with GT 1, compensated cirrhosis
- Pooled data from Phase 2 and 3 LDV/SOF ± RBV studies
  - LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS
Baseline Demographics

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Treatment Naïve (n=161)</th>
<th>Treatment Experienced (n=352)</th>
<th>Total (n=513)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>63%</td>
<td>68%</td>
<td>67%</td>
</tr>
<tr>
<td>Black</td>
<td>8%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Asian</td>
<td>17%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>GT 1a</td>
<td>53%</td>
<td>63%</td>
<td>60%</td>
</tr>
<tr>
<td>Prior PI Failure</td>
<td>NA</td>
<td>68%</td>
<td>47%</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>50%</td>
<td>31%</td>
<td>37%</td>
</tr>
<tr>
<td>Ex-US</td>
<td>50%</td>
<td>69%</td>
<td>63%</td>
</tr>
</tbody>
</table>

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SVR12: LDV/SOF for 12 vs 24 Weeks in Compensated Cirrhotics

- Overall: 96% (493/513)
- 12 Weeks: 95% (305/322)
- 24 Weeks: 98% (188/191)

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Subgroup Observations

• Among treatment-experienced patients, 12 weeks of LDV/SOF resulted in a 90% SVR rate
  – Adding RBV or extending treatment duration increased this rate to ≥96%

• Platelet count <75 x 10^3/uL was associated with a lower SVR rate among treatment-experienced patients with cirrhosis

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Abstract #1948

High Rates of SVR in Patients with Genotype 1 HCV Infection and Cirrhosis After Treatment with Ledipasvir/ Sofosbuvir+Ribavirin or Ledipasvir/ Sofosbuvir+ GS-9669 for 8 Weeks

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Objectives

- Evaluate whether LDV/SOF together with RBV or GS-9669 (non-nucleotide NS5B inhibitor) would allow patients with cirrhosis to achieve high SVR12 rates when administered for 8 weeks
- Evaluate the safety and tolerability of LDV/SOF together with RBV or GS-9669

SVR12: LDV/SOF + RBV or GS-9669 in GT 1 Cirrhotics Treated for 8 Weeks

Conclusions

- LDV/SOF together with RBV or GS-9669 was effective in treating HCV
- Coadministration of GS-9669 did not appear to provide additional efficacy compared to RBV
- Shortening therapy further or achieving higher SVR12 rates may require either:
  - A third more potent agent; or
  - A third drug with a complementary mechanism of action
- All regimens were safe and well tolerated
Abstract #81

TURQUOISE-II: Regimens of ABT-450/r/Ombitasvir and Dasabuvir With Ribavirin Achieve High SVR12 Rates in HCV Genotype 1-Infected Patients with Cirrhosis, Regardless of Baseline Characteristics

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Summary

• This multi-targeted, IFN-free regimen of ABT-450/r/ombitasvir and dasabuvir with RBV achieves high SVR12 rates across a broad range of treatment-naïve and treatment-experienced GT1 patients with cirrhosis, irrespective of most host, viral, or disease characteristics
  - 91.6% (239/261) GT1a patients achieved SVR12
  - 99.2% (118/119) GT1b patients achieved SVR12

• In a logistic regression, the only factors associated with a lower likelihood of SVR included GT1a, prior null response to PEG/RBV, and IL28B TT genotype

• Importantly, demographics (eg, age, gender, race, BMI, diabetes), viral factors (baseline HCV RNA), disease related factors (albumin, platelets) were not associated with lower SVR rates
Abstract #LB-2

All-oral fixed-dose combination therapy with daclatasvir/asunaprevir/BMS-791325, ± ribavirin, for patients with chronic HCV genotype 1 infection and compensated cirrhosis: UNITY-2 Phase 3 SVR12 results

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Background

• All-oral DCV-TRIO regimen
  - Daclatasvir (DCV)
    • NS5A inhibitor
    • Approved in Europe and Japan; under review in US
  - Asunaprevir (ASV)
    • NS3 protease inhibitor
    • Clinical data in GT 1 and GT 4
  - Beclabuvir (BCV, BMS-791325)
    • Non-nucleoside NS5B polymerase inhibitor
    • Clinical data in GT 1 and GT 4

• UNITY-2 Study
  - DCV/ASV/BCV twice daily, fixed dose combo ± RBV in GT 1 treatment naïve and treatment experienced compensated cirrhotics

DCV-TRIO +/- RBV for 12 Weeks: SVR12 in GT 1 Treatment Naïve and Treatment Experienced Cirrhotic Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DCV TRIO</th>
<th>DCV TRIO + RBV</th>
<th>DCV TRIO</th>
<th>DCV TRIO + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Naïve</td>
<td>93/57</td>
<td>98/55</td>
<td>87/45</td>
<td>93/45</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td>54/55</td>
<td>39/45</td>
<td>42/45</td>
<td></td>
</tr>
</tbody>
</table>

DCV-TRIO +/- RBV for 12 Weeks: SVR12 in GT 1a vs GT 1b

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>GT 1a</th>
<th>GT 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCV TRIO</td>
<td>90/40</td>
<td>36/40</td>
<td>38/39</td>
</tr>
<tr>
<td>DCV TRIO + RBV</td>
<td>97/100</td>
<td>97/100</td>
<td>97/100</td>
</tr>
<tr>
<td>DCV TRIO</td>
<td>86/35</td>
<td>30/35</td>
<td>30/35</td>
</tr>
<tr>
<td>DCV TRIO + RBV</td>
<td>91/100</td>
<td>91/100</td>
<td>91/100</td>
</tr>
</tbody>
</table>

Conclusion

• DCV-TRIO ± RBV was safe and well tolerated with low rates of SAEs and AE discontinuations

• Most commonly observed AEs with DCV-TRIO were headache, nausea, diarrhea, and fatigue
Abstract #196

Efficacy and safety of MK-5172 and MK-8742 ± ribavirin in hepatitis C genotype 1 infected patients with cirrhosis or previous null response: Final results of the C-WORTHY Study (Parts A and B)

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7. CHU Purpan, Digest Dept., UMR 152, Toulouse 3 University, Toulouse, France
8. INSERM U954, Centre Hospitalier Universitaire de Nancy, Université de Lorraine, Vandoeuvre-les-Nancy, France
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15. Merck & Co., Inc., Whitehouse Station, NJ
Background

- Grazoprevir (MK-5172) is a highly potent HCV-specific NS3/4A protease inhibitor
- Elbasvir (MK-8742) is a highly potent HCV-specific NS5A inhibitor

Treatment- naive, non-cirrhotic
12 weeks ± RBV
(n = 65) Pt. A

- Treatment-naive Non-cirrhotic
  8-12 weeks ± RBV
  (n = 94) Pt.B

- HIV/HCV Co-infected Non-cirrhotic
  12 weeks ± RBV
  (n = 59) Pt.B

- Treatment-naive Cirrhotic
  12-18 weeks ± RBV
  (n = 123) Pt.B

- Null Responders Cirrhotic / Non-cirrhotic
  12-18 weeks ± RBV
  (n = 130) Pt.B

Lawitz E, et al. Abstract #196, AASLD 2014
SVR12 Rates in Cirrhotic Treatment-naïve and Null Responder GT 1 Patients

<table>
<thead>
<tr>
<th></th>
<th>Treatment-naïve patients with cirrhosis</th>
<th>PR-Nulls with or without cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Weeks</td>
<td>+ RBV (90%)</td>
<td>+ RBV (100%)</td>
</tr>
<tr>
<td>18 Weeks</td>
<td>No RBV (97%)</td>
<td>No RBV (97%)</td>
</tr>
</tbody>
</table>

Lawitz E, et al. Abstract #196, AASLD 2014
Summary

- SVR12 was 92% (23/25) in null responders with cirrhosis treated for 12 weeks with grazoprevir + elbasvir ± RBV

- High efficacy was achieved regardless of the presence or absence of RBV or extended treatment duration from 12 to 18 weeks

- Grazoprevir + elbasvir were generally safe and well tolerated

Lawitz E, et al. Abstract #196, AASLD 2014
Abstract #198

High Sustained Virologic Response Rates in Liver Transplant Recipients With Recurrent HCV Genotype 1 Infection Receiving ABT-450/r/Ombitasvir+Dasabuvir Plus Ribavirin

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CORAL-I: Summary

• In this ongoing study of 24 weeks of therapy with ABT-450/r/ombitasvir, dasabuvir, and RBV
  – 100% of patients achieved RVR (34/34) and EOTR (34/34)
  – 97.1% (33/34) achieved SVR4, SVR12, and SVR24

• The regimen was generally well tolerated:
  – Only 1 patient prematurely discontinued study drug at week 18 because of AEs; however, the patient subsequently achieved SVR12
  – No deaths, graft losses, or episodes of rejection were observed
  – All patients who required RBV dose reduction achieved SVR12

• Calcineurin inhibitor dosing was manageable over the study period using pharmacokinetic guidance established in a prior DDI study in volunteers

Multicenter Experience using Sofosbuvir and Simeprevir with/without Ribavirin to Treat HCV Genotype 1 after Liver Transplantation

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RBV Does Not Increase SVR 12 Rates in GT 1 Liver Transplant Recipients

Pungapong S, et al. Abstract #9, AASLD 2014
GT 1a Patients with Advanced Fibrosis Have Lower SVR 12 Rates

Pungapong S, et al. Abstract #9, AASLD 2014
Abstract #239

Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

Steven L. Flamm¹; Gregory T. Everson²; Michael Charlton³; Jill M. Denning⁴; Sarah Arterburn⁴; Theo Brandt-Sarif⁴; Phillip S. Pang⁴; John G. McHutchison⁴; K. Rajender Reddy⁵; Nezam H. Afdhal⁶

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3. Intermountain Medical Center, Murray, UT
4. Gilead Sciences, Raleigh, NC
5. University of Pennsylvania School of Medicine, Philadelphia, PA
6. Beth Israel Deaconess Medical Center, Boston, MA
Study Design

• 108 GT 1 or 4 treatment naïve or treatment experienced patients with decompensated cirrhosis (CPT class B[7-9]) or C[10-12])

• Inclusion/exclusion
  - No history of major organ transplant, including liver
  - No HCC
  - Total bilirubin ≤10 mg/dL, hemoglobin ≥10 g/dL
  - $\text{CL}_{\text{cr}}$ ≥40 mL/min, platelets >30,000 x 10$^3$/uL

• Stratified by CPT class B or C

• LDV/SOF + RBV for 12 or 24 weeks
LDV/SOF + RBV in Decompensated Cirrhosis: SVR12

Overall: 87/89
CPT B: 87/89
CPT C: 86/90

12 Weeks: 45/52, 26/30, 19/22
24 Weeks: 42/47, 24/27, 18/20

Flamm S, et al. Abstract #239, AASLD 2014
## Overall Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>CPT B</th>
<th>CPT C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients, %</strong></td>
<td>12 Weeks (n=30)</td>
<td>24 Weeks (n=29)</td>
</tr>
<tr>
<td>Adverse Events (AE)</td>
<td>97%</td>
<td>93%</td>
</tr>
<tr>
<td>Grade 3-4 AE</td>
<td>7%</td>
<td>28%</td>
</tr>
<tr>
<td>Serious AE</td>
<td>10%</td>
<td>34%</td>
</tr>
<tr>
<td>Serious and Related AEs</td>
<td>7%</td>
<td>0</td>
</tr>
<tr>
<td>Treatment discontinuation due to AE</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>Death</td>
<td>3%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Related SAEs:** Anemia, hepatic encephalopathy, peritoneal hemorrhage

Flamm S, et al. Abstract #239, AASLD 2014
Conclusions

• Extending treatment duration to 24 weeks did not increase SVR rate

• LDV/SOF + RBV for 12-24 weeks was generally safe and well tolerated in CPT class B and C patients
Serious Adverse Events and Hepatic Decompensation in Hepatitis C Virus Infected Patients on Sofosbuvir- and/or Simeprevir-based Therapies

Ponni Perumalswami; Kian Bichoupan; Rachana Yalamanchili; Alyson Harty; Donald Gardenier; Michel Ng; David B. Motamed; Viktoriya Khaitova; Nancy Bach; Charissa Y. Chang; Gene Y. Im; Jennifer Leong; Lawrence Ku; Thomas D. Schiano; Douglas Dieterich; Andrea D. Branch

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Methods

• Identify patients who experienced an SAE and/or hepatic decompensation during or up to one month following the end of treatment

• Two cohorts for analysis
  – Cohort 1: Did not undergo liver transplant
  – Cohort 2: Underwent liver transplant
Non LT Cohort: Cumulative Incidence of Hepatic Decompensation/SAE was 4.1%

- Average of 6.5 weeks passed until 1st episode of decompensation/SAE
- Average of 2 episodes per case

LT Cohort: Cumulative Incidence of Hepatic Decompensation/SAE was 28.4%

- Average of 4.3 weeks passed until 1\textsuperscript{st} episode of decompensation/SAE
- Average of 2 episodes per case

Conclusions

• Rather than the stage of fibrosis, low hepatic reserve may have increased risk in the non-LT patients

• Based on past and current data, SMV should not be used in Child Pugh Class C patients

• The underlying mechanisms leading to life-threatening adverse events or decompensation from SOF- and/or SMV-containing regimens need to be investigated further
SONUÇ

• KVC fibrozis derecesi artınca azalma eğiliminde
• Bu durumda çözüm tedavi suresini uzatmak veya ribavirin eklemek
• Fakat genelde sirozda tedavi basarisi çok yüksek, yeni çok potent antiviral kombinasyonları ile 12 haftada sonuç alma ihtimali yüksek
• Siroz almayanlarda tedavi suresi 8 haftaya inebilir. Daha kısa tedavi suresi mümkün, ama daha erken
• Dekompanse sirozda tedavi basarili, MELD skor, albumin düzeliyor, transplantasyon listesinden çıkan hastalar olacak. AMA gene de dikkatli olmalı