AASLD 2017 Viral Hepatitis Debrief

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Hepatitis C at the Liver Meeting
• New Therapies approved 2017
  – Sofosbuvir/Velpatasvir/Voxilaprevir in US for DAA failures
  – Glecaprevir/Pibrentasvir
• Refinement of existing therapies
• Hepatitis C, DAAs, and HCC: How can we interpret more mature data
• Therapies that will not move forward
  – Ruzasvir/Uprifosbuvir
  – AL-335/Odalasvir/Simeprevir
• Treatment of Hepatitis C: We are seeing the fruits of efforts
POLARIS Program

Regimens:

<table>
<thead>
<tr>
<th>DAA-Experienced</th>
<th>DAA-Naïve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLARIS-1</strong></td>
<td><strong>POLARIS-2</strong></td>
</tr>
<tr>
<td>N = 415</td>
<td>N = 941</td>
</tr>
<tr>
<td>GT 1 2 3 4 5 6</td>
<td>GT 1 2 3 4 5 6</td>
</tr>
<tr>
<td>NS5A-experienced</td>
<td>Non-NS5A-experienced</td>
</tr>
<tr>
<td>12 weeks</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

| **POLARIS-4**   | **POLARIS-3** |
| N = 333         | N = 219 Cirrhosis |
| GT 1 2 3 4 5 6 | GT 1 2 3 4 5 6 |
| Non-NS5A-experienced | |
| 12 weeks        | 8 weeks |

**Placebo**

12 weeks
SOF/VEL/VOX for 12 Weeks in NS5A-Inhibitor–Experienced HCV-Infected Patients: Results of the Deferred Treatment Group in the Phase 3 POLARIS-1 Study

Of the 4 patients who relapsed, 2 developed treatment-emergent resistance
1 had treatment-emergent NS3 Y56H, D168A/V, and NS5A L31L/M
1 had treatment-emergent NS3 V36V/A
GLECAPREVIR/PIBRENTASVIR Phase 2/3 program

ENDURANCE Trials
GT1 non-cirrhotic including HIV co-infection: 8 vs 12 weeks
GT2 placebo-controlled: 12 weeks
GT3 active comparator: 12 weeks
GT4-6: 12 weeks

MAGELLAN Trials
GT1,4-6 prior DAA failures: 12 vs 16 weeks

EXPEDITION Trials
GT1, 2, 4-6 cirrhotic
GT1-6 all stages of renal impairment

SURVEYOR Trials
GT2, 4-6 non-cirrhotic: 8 weeks
GT3 cirrhotic: 12 vs 16 weeks
Efficacy, Safety, and Pharmacokinetics of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1-6 Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis

- GLE was approximately 2.2-fold of exposure in patients without cirrhosis
- frequency and severity of AEs in patients with cirrhosis was similar to patients without cirrhosis
- PIB exposure in patients with compensated cirrhosis was similar to that previously reported in patients without cirrhosis

Gane et al HEPATOLOGY. 2017 66(1). #74
Efficacy and Safety of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Treatment-naïve Patients with Chronic HCV Genotype 3: An Integrated Phase II/III Analysis

Flamm et al HEPATOLOGY. 2017 66(1). #62
Refinement of existing therapies
100% SVR with 8 weeks of ledipasvir/sofosbuvir in HIV-infected Men with Acute HCV Infection: Results from the SWIFT-C Trial (Sofosbuvir- Containing Regimens Without Interferon For Treatment of Acute HCV in HIV-1 Infected Individuals)

- Acute HCV infection (<24 weeks), or re-infection after clearance: New + HCV RNA AND
  - ALT ≥ 5XULN (>250 U/L) if normal ALT <12 mo OR
  - ALT≥ 10XULN (>500 U/L) no ALT baseline OR
  - Serologic or virologic conversion evidence <6 mo

- Limited to GT1 or 4

Naggle et al HEPATOLOGY. 2017 66(1). #196
Safety and Efficacy of Treatment With Once-Daily Ledipasvir/Sofosbuvir (90/400 mg) for 12 Weeks in Genotype 1 HCV-Infected Patients With Severe Renal Impairment

There was no clinically meaningful change in eGFR: there was a 1.2-mL/min/1.73m² decrease from baseline to end of treatment.

Similar results #1180: Sofosbuvir with NS5A Inhibitors in Hepatitis C Virus Infected Patients with Severe Renal Insufficiency

Lawitz et al. HEPATOLOGY. 2017 66(1). #1587
Sofosbuvir/Velpatasvir for 12 Weeks in Genotype 1–4 HCV-Infected Liver Transplant Recipients

No changes in immunosuppression were needed for rejection or suspected drug-drug interactions

Agarwal et al HEPATOLOGY. 2017 66(1). #1069
EFFECTIVENESS OF ELBASVIR/GRAZOPREVIR IN PATIENTS WITH CHRONIC HEPATITIS C AND CHRONIC KIDNEY DISEASE: RESULTS FROM THE VETERANS AFFAIRS SYSTEM

HCV-infected patients initiated EBR/GZR from Feb. 1–Dec. 31, 2016, ≥18 years, positive HCV RNA, ≥1 inpatient or outpatient visit within 1 year prior to treatment (n=5845)

Had ≥2 eGFR values, at least 90 days apart (N=5709)

On-treatment HCV RNA or SVR data unavailable (n=506)
Prescribed >17 weeks, or had RBV added >1 month after treatment initiation (n=39)
Received EBR/GZR <11 weeks of Treatment (n=471)

Per protocol population (PP)
N=4693

CKD stage 3-5 (PP)
N=1528

Kramer et al HEPATOLOGY. 2017 66(1). #1113
High Efficacy and Safety of the combination HCV Regimen Grazoprevir and Elbasvir for 8 Weeks in Treatment-Naive, non-severe fibrosis HCV GT1b-Infected Patients: Interim Results of the STREAGER study.

Patients were treatment-naïve, GT1b, without HIV/HBV co-infection and without severe fibrosis. Non-severe fibrosis (F ≤ 2) was diagnosed according to a combination of two tests (J Boursier database, Angers):

- Fibroscan® lower than 9.5 kPa AND Fibrotest® lower than 0.59
- Fibroscan® lower than 9.5 kPa AND Fibrometer® lower than 0.63

Abergel et al. HEPATOLOGY. 2017 66(1). LB5
Implementing a hepatitis C treatment program: Hepatitis C Care in the VA system: (Hepatitis Innovation Teams) HIT Process Improvement Program by Streamlining Care Process

To treat large backlog of HCV-Infected individuals

Of ~168,000 Veterans who needed HCV treatment, only ~45,000 remain!
We can treat high risk populations and achieve SVR with low rates of relapse

• If you are not having re-infection cases, you are not treating high risk populations
HEPATITIS C VIRUS REINFECTION AND INJECTING RISK BEHAVIOR FOLLOWING ELBASVIR/GRAZOPREVIR TREATMENT IN PARTICIPANTS ON OPIATE AGONIST THERAPY: C-EDGE CO-STAR PART B

Open to all participants who received ≥1 dose of EBR/GZR in Part A
- Assessments every 6 months
  - HCV RNA
- Comparison of viral sequences at baseline and virologic recurrence to determine reinfection
  - Urine drug screen
  - Participant-reported behaviors
- Behavioral questionnaire: self-reported drug use

Reinfection rate was 2.3/100 person-years, with a persistent reinfection rate of 1.6/100 person-years

Dore et al HEPATOLOGY. 2017 66(1). 195
Reinfection rates remain low in at risk populations

• Wyles et al: Similar rates of HCV recurrence in HCV/HIV and HCV infected participants who achieved SVR after DAA treatment
  – Interim report
  median time since completion of HCV therapy was 121.9 weeks and 101.1 weeks for HCV/HIV and HCV participants, respectively
• Sylvestre et al: No Evidence of 1-Year Reinfection after Treating HCV at a Methadone Program

Effective treatment of opiate addiction appears to lower risk of reinfection

Wyles et al HEPATOLOGY. 2017 66(1).978
Sylvestre et al HEPATOLOGY. 2017 66(1). LB18
Treatment of HCV: It benefits those with decompensated liver disease
Survival Benefit of Direct-Acting Antiviral Therapy in Patients with Decompensated Cirrhosis

- Observed incidence of deaths in patients with hepatic decompensation in the SOLAR studies was compared with mortality predicted by survival models derived from HCV patients with hepatic decompensation in the pre-DAA era.

- DAA therapy is associated with significant decrease in mortality risk in patients with decompensated HCV cirrhosis, by as much as 60% within the first year of therapy.

Kim et al HEPATOLOGY. 2017 66(1). LB27
Eradication of HCV induced by DAAs is associated with a 71% reduction in HCC risk VA Retrospective Cohort study

Patients with SVR had lower HCC incidence

- Receipt of DAAs is not associated with increased HCC risk compared to receipt of IFN

Ioannou et al HEPATOLOGY. 2017 66(1). #142
Impact of SVR with DAA treatment on mortality and HCC

- SVR was associated with statistically significantly reduced all-cause mortality compared to No SVR (p<0.001).
- SVR was strongly associated with delayed time until development of HCC.

Compared UNOS listing of HCV+ adults for liver transplantation in the 3 years before (2011-2013) and the 3 years (2014-2016) after approval of DAAs.
Increase in the Incidence of HCC and increase in MELD HCC exceptions Among Liver Transplant Registrants with Hepatitis C Virus Infection

Incidence of de novo HCC among Candidates listed for OLT in US over time

Competing risks suggests higher LT/death rate explains observed increased incidence of HCC among HCV patients on WL

Listing during the DAA era increased the risk of applying for exception points by 44% after adjusting for demographics and listing MELD.

Kwong et al HEPATOLOGY. 2017 66(1)8
Rizvi et al HEPATOLOGY. 2017 66(1)1040.
Unexpected Hepatocellular Carcinoma (HCC) following treatment-induced HCV clearance in a VA cohort: A possible explanation for early recurrence

- Retrospective review of HCV cohort of 500 patients, 46 developed HCC after SVR
- 9 developed HCC after initiation of 2nd gen DAAs
- KIR (killer cell immunoglobulin–like receptor)/HLA typing was performed to assess innate inhibitory or activation of NK cells that are important in NK tumor surveillance
- Early HCC recurrence was associated with presence strong NK cell inhibitory genes (weak tumor surveillance)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Race</th>
<th>Tumor Type</th>
<th>Time DAA start to Liver Tumor (mos)</th>
<th>HLA-B</th>
<th>HLA-C</th>
<th>HLA-B inhibitory type</th>
<th>HLA-C inhibitory type</th>
<th>KIR Haplo-type</th>
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<tr>
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<td>HCC</td>
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<td>C1C2(C*04)</td>
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New Therapies That Will Not Move Forward
Evaluation of the efficacy and tolerability of JNJ-4178 (AL-335, odalasvir, and simeprevir) in hepatitis C virus-infected patients without cirrhosis: The Phase IIb OMEGA-1 study

Zeuzem et al HEPATOLOGY. 2017 66(1#65).
C-BREEZE-2: Efficacy and Safety of a Two-Drug Direct-Acting Antiviral Agent Regimen Ruzasvir 180 mg and Uprifosbuvir 450 mg for 12 Weeks in Adults With Chronic Hepatitis C Virus Genotype 1, 2, 3, 4, 5, or 6

- Ruzasvir (RZR, MK-8408) is a potent HCV NS5A complex inhibitor
- Uprifosbuvir (UPR, MK-3682) is a potent HCV NS5B nucleotide polymerase inhibitor
Hepatitis B and D at the Liver Meeting

• We have the tools to suppress hepatitis B
  – Tenofovir/entecavir highly effective therapies
    • More data on tenofovir alafenamide

• Novel therapies for hepatitis B
  – ARB-1467 LNP siRNA
  – JNJ-56136379 HBV Capsid Assembly Modulator
  – SB 9200 RIG-1 Activator

• Novel therapies for hepatitis D
  – Myrcludex B entry inhibitor blocks NTCP
  – Pegylated Interferon Lambda Monotherapy

Similar % in each group qualified for testing, including virologic breakthrough (VB) patients (TAF 3%; TDF 3%) – majority of VB due to nonadherence

Overall, majority of patients had no change or were unable to be sequenced

Only 1 conserved site mutation was seen in >1 patient (rtA181T; n=2)

No increase in HBV DNA when sequenced; rtA181T shown to be sensitive to TFV

Improved Bone and Renal Safety at 1 Year after Switching from Tenofovir Disoproxil Fumarate (TDF) to Tenofovir Alafenamide (TAF):

Pan et alal HEPATOLOGY. 2017 66(1)904
New Targets for HBV

Immunodulators
TLR agonists
T-cell vaccines
PD-1/PD-L1 blockade

Entry Inhibitors
Myrcludex

cccDNA silencing
Inhibit protein translation by siRNA
Arrowhead
Arbutus
Alnylam
GSK

Core inhibitors
Novira
Bayer
Assembly
Gilead
Janssen
Roche

RT Pol Inhibitors
Nucleotide analogues
Non-Nuc analogues
RNAseH inhibitors

HBsAg release Inhibitor
NAP

Fabien Zoulim, and David Durantel
Cold Spring Harb Perspect Med 2015;5:a021501
Interim results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection

- first-in-class entry inhibitor exerting its antiviral function by blocking the jointly used HBV/HDV receptor sodium taurocholate co-transporter NTCP
  - ALT levels improve
  - HBsAg does not change
  - Bile acids increase without pruritus
HBcrAg, HBV-RNA Declines in A Phase 2a Study Evaluating the Multi-Dose Activity of ARB-1467 in HBeAg-Positive and Negative Virally Suppressed With Hepatitis B

- Unique 3-trigger design inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens

- No apparent correlation was observed between declines in HBV-RNA or HBcrAg and declines in HBsAg
- Baseline HBsAg and IL28b genotype CC were significantly associated with response

Agarwal et al HEPATOLOGY. 2017 66(1). #40, LB-17
SB 9200 (Inarigivir), an oral selective immunomodulator is safe and efficacious in treatment-naïve, non-cirrhotic HBV patients: RIG-1 Activator

- RIG-I counteracts the interaction of HBV polymerase with pgRNA to suppress viral replication
- Induction of type I and III IFNs

Anti-viral efficacy on HBV DNA, HBsAg and HBV RNA at 12 weeks - more prominent in HBeAg –ve patients
A Phase 2 Randomized Clinical Trial to Evaluate the Safety and Efficacy of Pegylated Interferon Lambda Lambda Monotherapy in Patients with Chronic Hepatitis Delta Virus Infection. Interim Results From the LIMT HDV Study

- A novel first in class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells

![Graph showing treatment and follow-up periods](image)

<table>
<thead>
<tr>
<th>Week</th>
<th>N</th>
<th>≥ 2 log decline</th>
<th>PCR-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>33</td>
<td>7 (21.2%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>12 (36.4%)</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>9 (39.1%)</td>
<td>4 (17.4%)</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
<td>6 (60.0%)</td>
<td>4 (40.0%)</td>
</tr>
</tbody>
</table>
Safety, Tolerability, Pharmacokinetics and Antiviral Activity of JNJ-56136379, a Novel HBV Capsid Assembly Modulator, in Non-cirrhotic, Treatment-naïve Subjects with Chronic Hepatitis B.

- JNJ-56136379 (JNJ-379): potent capsid assembly modulator (CAM)
- JNJ-379 binds to the HBV core protein and interferes with the HBV capsid assembly, and prevents cccDNA formation during de novo infection, by interfering with capsid disassembly
- Dosed in chronic hepatitis B patients, treatment naive

Three patients with HBV DNA <LLOQ of the HBV DNA assay.
Summary

• We have the tools to cure virtually everyone with hepatitis C infection
• We need to learn from best practices how to identify and treat large numbers of individuals with hepatitis C
• High risk populations can be treated successfully with low relapse rates
• HCV/HCC/DAAs: The evidence points to a marked reduction in risk of HCC with SVR, but
  – vigilance is required to detect early recurrences and more data are required to better identify these individuals
• Hepatitis B: We can suppress, we need to better
• It is early in the field of HBV therapeutics: Both inhibition of replication and immunomodulation are going to be important