Update on Hepatitis C Therapy

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VM Liver Center of Excellence
Key Questions

• Who should be treated and why
• What information is required prior to starting treatment
• What are the treatment options
• Important Clinical trials
• Future options
HCV TREATMENT
WHY??
Benefits of HCV Therapy

Eradication of HCV virus confers:

- Halted progression of liver disease and prevent hepatic decompensation
- Potential reversal of fibrosis
- Lower but not eliminate risk of HCC
- Enhance quality of life *
- Reduce liver-related morbidity and mortality
- Reduce all-cause mortality

SVR Was Associated with a Reduction in HCC, Liver-Related Mortality, and All-Cause Mortality

This was an international, multicenter, long-term follow-up study of 530 consecutive CHC patients with advanced hepatic fibrosis or cirrhosis (Ishak score 4-6), who started interferon-based treatment regimen between 1990 and 2003, from 5 large tertiary care hospitals in Europe and Canada. Complete follow-up ranged between January 2010 and October 2011. Median follow-up duration was 8.4 years.

*SVR = sustained virologic response; defined as lack of detection of HCV RNA at 24 weeks after cessation of treatment. All $P<.001$.

Declining HCV incidence US Cirrhosis And HCC However Projected to Peak in the Coming Decades

Hepatitis C Incidence in United States, 1982-2010

Cirrhosis And HCC Is Projected to Peak

WHO SHOULD BE TREATED?
**Highest Priority for Treatment**

- Advanced fibrosis (F3) or compensated cirrhosis (F4)
- Liver transplant recipients
- Severe extrahepatic manifestation eg cryoglobulinemia, nephrotic syndrome, membranoproliferative glomerulonephritis

**Individuals At Risk of Transmitting HCV**

- MSM with high-risk sexual practices
- Active IVDU
- Incarcerated persons
- Women wishing to get pregnant

**High Risk of Fibrosis Progression**

- Stage 2 or more fibrosis
- HIV or HBV coinfection
- Coexisting liver disease and/or Diabetes
What Data is Necessary to Prescribe Therapy?

- HCV genotype; subtype
- Baseline viral load
- Details of previous HCV treatment
  - Exposure to IFN or DAA? Non-response, partial response, or relapse?
- Basic workup – CBC, CMR, INR, US liver, urine pregnancy test in young women, Hepatitis A and B serology, HIV
- Disease staging
- Identification of associated symptoms and conditions
- Patient interest and motivation
HCV Staging – Important Prior to Treatment

FIBROSCAN vs LIVER BIOPSY

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HCV Disease Staging

Staging is the most critical aspect of clinical evaluation

**Liver biopsy** has long been the gold standard, but has many disadvantages:
- Invasive and expensive ($3,000)
- Complication risk: pain (20%), bleeding (1%) which may require hospitalization, and 1/10,000 risk of death
- Potential for incorrect staging given small sample size, sampling error (25-30% risk)

**FibroScan**  FDA approved in 2013 for “use in measurement of shear wave speed in the liver to classify patients in terms of severity of liver fibrosis.”
- Has significant advantages
  - Performed in 15 minutes, point of care
  - Significantly less expensive than liver biopsy
  - Non-invasive, painless, and without side effects.
  - Instantaneous results allows for decision making during clinical visits

**And some limitations…**
- Less reliable accuracy in assessing lower degrees of liver fibrosis (F1-F2)
- Often not possible in patients with ascites, and/or morbid obesity
- Currently not covered by all insurances

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HCV Treatment

APPROVED TREATMENT OPTIONS
HCV – GENOTYPE 1
A History of HCV Therapy

Timeline


Sustained Virologic Response (%)

IFN 6m 16 IFN + RBV 6m IFN + RBV 12m PEG 12m PEG + RBV 12m PEG + RBV + PI 6-12m Multiple DAAs 3m

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## Treatment Options: Genotype 1

<table>
<thead>
<tr>
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<td>24 weeks for cirrhotic treatment experienced</td>
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<td>Consider 8 weeks non-cirrhotic, treatment naïve, with HCV PCR &lt; 6 million IU/ml</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir/ dasabuvir</td>
<td>12 weeks for GT1b non-cirrhotic</td>
</tr>
<tr>
<td>(Viekira Pak or ‘3 D’)</td>
<td>12 weeks + RBV for GT1a non-cirrhotic</td>
</tr>
<tr>
<td></td>
<td>12 weeks + RBV for GT1b with cirrhosis</td>
</tr>
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<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>12 - 24 weeks depending on presence/absence cirrhosis</td>
</tr>
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</table>
Ledipasvir-Sofosbuvir
(*Harvoni™* fixed dose 90 mg/400 mg)

- FDA approved October 10, 2014 for the treatment of chronic HCV GT 1 adults
- One pill, once a day formulation
- Overall SVR rates of 94-99%
- Drug target

Cost of 8-week course of therapy = $63,000
Cost of 12-week course of therapy = $94,500
Cost of 24-week course of therapy = $189,000
ION 1, 2, and 3: Sofosbuvir/Ledipasvir ± RBV in Treatment Naive and Previous Treatment Failures

- 8 wks adequate for noncirrhotic treatment-naive pts
- RBV provides no benefit
- No SOF resistance observed; most virologic failures have LDV resistance

SOFOSBUVIR/SIMEPREVIR

- FDA Approved 11/2014
- Two pills once a day; SVR 93%
- Should not be used in patients previously treated with simeprevir or other PI
- Side effects - Nausea, headache, rash
- Drug target
COSMOS: Sofosbuvir + Simeprevir ± RBV in Tx-Naive and Tx-Experienced GT1 Pts

- RBV provided no additional benefit
- 12 wks in noncirrhotos, 24 wks for cirrhotos

Viekira™ PAK or 3 ‘D’
Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir

- FDA approved Dec 2014 for genotype 1
- Taken as 2 FDC ombitasvir (12.5 mg)/paritaprevir (75 mg)/ritonavir (50 mg) tablets QD and 1 dasabuvir tablet (250 mg) BID
- 3 pills in the morning + RBV, 1 pill in the evening + RBV
- Weight-based ribavirin - GT1a subtype and in patients with cirrhosis
- Drug Target

Cost: $83,319 for 12 weeks (vs $94,500 for Harvoni)
Clinical use:
- GT 1 patients
- Approved for Child A cirrhosis, HIV co-infection, and post-transplant
- NOT indicated for Child B/C and renal failure
- NOT studied in DAA-experienced
- HCV/HIV coinfection: Coinfected patients should be receiving suppressive ART
SAPPHIRE I & II: OMV/PTV/RTV+ DSV + RBV for 12 Wks in Noncirrhotic Pts

Very well tolerated (vs placebo), few virologic failures but usually with multiclass resistance

TURQUOISE II: 12 vs 24 Wks of OMV/PTV/RTV + DSV + RBV in Cirrhotics

Ribavirin-Free Therapy in GT1b

PEARL-II[1]
- GT1b Tx Experienced
  - 3 DAAs (n = 95): Wk 12 SVR12, % = 100
  - 3 DAAs + RBV (n = 91): Wk 12 SVR12, % = 97

PEARL-III[2]
- GT1b Tx Naive
  - 3 DAAs (n = 209): Wk 12 SVR12, % = 99
  - 3 DAAs + RBV (n = 210): Wk 12 SVR12, % = 99

PEARL-IV[2]
- GT1a Tx Naive
  - 3 DAAs (n = 205): Wk 12 SVR12, % = 90
  - 3 DAAs + RBV (n = 100): Wk 12 SVR12, % = 97

RBV needed for GT1a, not necessary for GT1b noncirrhotics

Phase 2, ‘3 D’ with RBV 24 weeks, no cirrhosis

**Bar Chart: HCV RNA < 25 IU/ml(%)**

- **Week 4:** 100
- **Week 24:** 100
- **SVR4:** 97
- **SVR12:** 97
- **SVR24:** 97

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# Recommended Regimen

<table>
<thead>
<tr>
<th>Population</th>
<th>Regimen</th>
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<tr>
<td>GT1a, TN or TE, noncirrhotic</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12 wks</td>
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<tr>
<td>GT1a, TN or TE, cirrhotic</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>24 wks</td>
</tr>
<tr>
<td>GT1b, TN or TE, noncirrhotic</td>
<td>OMV/PTV/RTV + DSV</td>
<td>12 wks</td>
</tr>
<tr>
<td>GT1b, TN or TE, cirrhotic</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12 wks</td>
</tr>
<tr>
<td>GT1, post-OLT (Metavir ≤ 2)</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>24 wks</td>
</tr>
</tbody>
</table>

**NO RBV – GT1b noncirrhotics**
## Approved Treatment Options: Genotype 1

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<td><strong>Sofosbuvir/Ledipasvir (Harvoni)</strong></td>
<td>12 weeks for treatment naïve</td>
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<tr>
<td><strong>Sofosbuvir +Simeprevir</strong></td>
<td>12 - 24 weeks</td>
<td>93</td>
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</table>
Genotype 2/3
HCV – Genotype 2 and 3

GENOTYPE 2

2 factors to consider:
• Treatment Naïve or Experienced
• Presence/Absence of cirrhosis

GENOTYPE 3

Prior to treatment
• Treatment Naïve or Experienced
• Interferon eligible or not
• Presence/Absence of cirrhosis

Faster rate of fibrosis progression
Higher prevalence of severe steatosis
Higher incidence of HCC
# Genotype 2/3 – Treatment Options

## GENOTYPE 2

<table>
<thead>
<tr>
<th>Naive/Experienced AND No Cirrhosis</th>
<th>Sofosbuvir/ ribavirin 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive AND Cirrhosis</td>
<td>Sofosbuvir / ribavirin 16 weeks</td>
</tr>
<tr>
<td>Experienced AND Cirrhosis</td>
<td>Sofosbuvir / ribavirin 16 weeks Peg-INF/Riba/Sofosbuvir 12 weeks</td>
</tr>
</tbody>
</table>

## GENOTYPE 3

| Naïve AND EXPERIENCED             | Sofosbuvir/ribavirin 24 weeks Peg-INF/Riba/Sofosbuvir 12 weeks |
Genotype 2/3 Clinical Trials

FISSION G2/3 naïve; 20% cirrhosis
Sof/riba 12wks vs Peg/Riba 24 wks

VALANCE G2/3 naïve and experienced; 20% cirrhosis
Sof/Riba - G2 12 wks; G3 24 wks

FUSION - G2/G3 treatment experienced; 30% cirrhosis
Sof/Riba 12 vs 16 wks

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Genotype 2/3 – LONESTAR 2

- Phase 2, open label
- Genotype 2/3 treatment experienced; Cirrhosis 55%
- Sofosbuvir + PEG-INF + RBV – 12 weeks

![Bar chart showing SVR12 for Genotype 2 and 3 patients with and without cirrhosis.]

**Genotype 3**
- 12 weeks
- Sof/Peg-INF/Riba high
- SVR irrespective of cirrhosis status
## Genotype 2/3 - Treatment

<table>
<thead>
<tr>
<th>GENOTYPE 2</th>
<th>SVR %</th>
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<tr>
<td>NAÏVE AND NO CIRRHOSIS</td>
<td>Sofosbuvir/ ribavirin 12 weeks</td>
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<td>Peg-INF/Riba/Sofosbuvir 12 weeks</td>
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HCV Genotype 4,5,6
Genotype 4

- 1 to 2% in the US. Dominant in Egypt, North Africa
- 70% have moderate to severe steatosis
- Excellent SVR with DAA’s
  - Sofosbuvir/Ledipasvir x 12 weeks - SVR 95%
  - Ombitasvir/paritaprevir/ritonavir x 12 weeks
    + RBV - Overall 100% SVR
    No RBV – Overall 91% SVR (no cirrhosis in this study)
Treatment Options for GT4 HCV

SYNERGY: SOF/LDV x 12 Wks\textsuperscript{[1]}

- SVR12
  - Naive Pts: 100\% (95/95)
  - P/R Failure: < LLOQ (19/20)

PEARL-I: Paritaprevir/RTV/Ombitasvir ± RBV x 12 Wks\textsuperscript{[2]} (No Dasabuvir)

- 2 DAAs
  - Naive Pts: 40/44 (91\%)
  - P/R Failure: 42/42 (100\%)

- 2 DAAs + RBV
  - Naive Pts: 42/42 (100\%)
  - P/R Failure: 49/49 (100\%)

# Approved Treatment Options: Genotype 4

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</thead>
<tbody>
<tr>
<td><strong>Genotype 4</strong></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/Ledipasvir</td>
<td>12 weeks for treatment naïve and experienced</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Ribavarin</td>
<td>12 weeks for naïve and treatment experienced</td>
</tr>
<tr>
<td><strong>NOTE:</strong> No dasabuvir</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir + Ribavarin</td>
<td>24 weeks naïve and experienced</td>
</tr>
<tr>
<td>Sofosbuvir + IFN / RBV</td>
<td>12 weeks for naïve and experienced</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>12 weeks for naïve</td>
</tr>
</tbody>
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HCV Genotype 5/6

• Very limited data with DAA’s
• Peg-INF and Ribavarin 48 weeks 60-80% SVR
• Genotype 5
  – Peg-INF/Ribavarin/Sofosbuvir – 12 weeks
  – Peg-INF/Ribavarin – 48 weeks
• Genotype 6
  – Ledipasvir/Sofosbuvir – 12 weeks - SVR 96%
  – Peg-INF/Ribavarin/Sofosbuvir – 12 weeks - SVR 100%
**Real World Use of Sofosbuvir**

**HCV-TARGET**: Longitudinal observational cohort study of the safety and efficacy of Sofosbuvir-containing regimens in the real-world setting

- Intention to treat analysis of 2,330 subjects
- 48% with cirrhosis; 43% w/ history of decompensation
- 20% failed prior PI therapy (excluded from primary analysis)
- High rates of off-label use
TARGET Cohort

- Simeprevir + Sofosbuvir ± RBV (>1,000 patients)
  - 89% overall SVR: 92% for non-cirrhotic vs 82% for cirrhosis vs 75% for decompensated cirrhosis
  - 95% for GT 1b vs 86% for GT1a
  - SVR only 81% for prior protease inhibitor failures
  - Addition of RBV did not improve response rates

- 6% rates of significant adverse events; 12 deaths

- Summary: Post-marketing use of SOF-containing regimens roughly comparable to clinical trials but absolute SVR rates lower in ‘real world’ data

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D Jensen, et al, AASLD 2014
HCV Treatment
Awaiting Approval
Phase 2, 155 patients with GT1
Treatment experienced (previous PI) with compensated cirrhosis
LDV/SOF /RBV 12 weeks vs LDV/SOF for 24 weeks

Emerging data – decompensated cirrhosis, post liver transplant

Phase 2 (prelim results); LED/SOF/RBV for 12 or 24 weeks in naïve and treatment experience with G1 and 4

Decompensated cirrhosis awaiting transplant

Post Transplant (inc small # decomp pts)

FlammSL, al. 65th AASLD. 2014: Abstract 239

**Sofosbuvir + GS-5816**

**GS-5816** (pan-genotypic NS5A inhibitor) + **Sofosbuvir ± RBV**

Phase 2, - GT 1 Treatment Experienced (PI failures)
  - GT 3 +/- cirrhosis

Sofosbuvir + GS 5816 (25mg vs 100mg) +/- RBV x 12 weeks

GT 1 PI failures - 100% SVR
GT 3 - no cirrhosis 100% SVR, cirrhosis 88% vs 96% with RBV

→ 25 mgs GS 5816 was not effective
→ RBV was not needed in GT1 patients and GT3 without cirrhosis
Three studies of the all-oral regimen of **grazoprevir** (MK-5172, NS3/4A PI) + **elbasvir** (MK-8742, NS5A inh) ± RBV

- C-WORTHY (Sulkowski et al): Non-cirrhotics with and w/o HIV co-infection
- C-WORTHY (Lawitz et al): Naive Cirrhotics and prior null responders with and without cirrhosis
- C-SWIFT: Minimum treatment duration
C-WORTHY

Grazoprevir (NS3/4A PI) + Elbasvir (NS5A inhibitor)

Phase 2 trial of 218 total HCV mono-infected or stable HIV co-infected patients without cirrhosis (90% with stage <F2) for 12 or 8 weeks

- 92% SVR overall for GT1a (vs 95% with RBV)
- 95% SVR for GT1b (vs 92% with RBV)

Mono-infected:

- 98% SVR for 12 weeks of treatment without RBV
- Among GT1a treated for just 8 weeks, SVR fell to 80%

HIV co-infected (all on raltegravir-based HAART):

- 97% SVR for those treated 12 wks + RBV vs 87% without RBV
- No patients experienced HIV breakthrough or ↓ CD4 counts
• Grazoprevir + Elbasvir +/- Ribavirin

• Phase 2 trial of 253 GT1 patients; naïve with cirrhosis or previous null responders with or without cirrhosis (‘hard-to-treat’ subgroups) treated for 12 or 18 weeks
  – Overall, SVR 99% for 1b vs 93% for 1a
  – Overall, SVR 95% for both cirrhotic and non-cirrhotic
  – Overall, SVR 94% for treatment-naïve vs 95% for experienced
  – Lowest cure rate 92% for null-responders + cirrhosis treated for 12 weeks – but still high for such difficult to treat population

• “High efficacy was achieved regardless of presence or absence of RBV or extended treatment duration to 18 weeks”

Lawitz E, et al. Abstract #196, AASLD 2014
C-SWIFT

• Grazoprevir + Elbasvir + Sofosbuvir for 4, 6, 8 weeks in GT1
• Phase 2 trial, 102 patients
  ➢ noncirrhotics received 4 or 6 weeks
  ➢ cirrhotics received 6 to 8 weeks
• Overall, SVR4/8 weeks following therapy - 80 to 94.7% depending on presence or absence of cirrhosis following six and eight weeks of treatment.
• The four-week regimen resulted in sub-optimal efficacy
Ledipasvir-sofosbuvir alone vs with either GS-9669 (non-nuc NS5B inhibitor) or GS-9451 (NS3/4A PI) in treatment-naïve GT 1

- Phase 2, 60 patients
- LDV/SOF – all stages of fibrosis – 12 weeks treatment – SVR12 100%
- LDV/SOF + GS-9669 – No cirrhosis – 6 weeks treatment – SVR12 95%
- LDV/SOF + GS 9451 – No cirrhosis – 6 weeks treatment - SVR12 95%

“In this small proof-of-concept study, two different three-drug regimens that were given for 6 weeks resulted in high cure rates for HCV infection with excellent tolerability. Addition of a third potent direct-acting antiviral drug can reduce the duration of treatment required to achieve sustained viral response in patients with chronic HCV genotype 1 infection without cirrhosis.”

**TRIO Regimen (BMS)**

**Daclatasvir** (NS5A inhibitor) + **Asunaprevir** (NS3/4A PI) + **Beclabuvir** (non-nuc NS5B inhibitor) (twice daily FDC)

**UNITY-1**

- 12 week TRIO regimen *without* RBV
- 312 treatment-naïve and 103 experienced HCV GT1 patients *without* cirrhosis
- Overall SVR 91% (92% naïve vs 89% experienced)
- Nearly 100% for GT1b
- Patients with low baseline viral load did better (96% vs 90%)
- Well-tolerated overall; fatigue, headache, nausea, and diarrhea most common SE

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UNITY-2

- 202 treatment naïve or experienced GT1 patients with cirrhosis randomized to TRIO (twice daily FDC) +/- RBV
- Overall, 90% on TRIO alone and 96% on TRIO+RBV achieved SVR
  - Naïve: 93% vs 98% with RBV
  - Experienced: 87% vs 93% with RBV
  - 1b faired better than 1a (RBV likely not req 1b)
  - 3 on-treatment failures; 10 relapsed (9 not on RBV)
  - SAEs only occurred in RBV arm

Sofosbuvir and Daclatasvir (DCV pangenotypic NS5A inhibitor) in Genotype 3

Phase 3 trial of 152 patients GT3. Included naïve, treatment experienced and patients with cirrhosis (21%). Treated 12 weeks

Overall, SVR 90% for naïve vs 86% treatment experienced
Overall, SVR 96% noncirrhotics vs 63% cirrhosis

Further options for optimizing treatment outcome with DCV + SOF in GT 3-infected patients with cirrhosis are currently being evaluated
DCV in combination is approved in Japan and Europe; currently under regulatory review in the US

Ledipasvir-Sofosbuvir +/- RBV x 12 weeks

- Total 90 patients – 2 groups of GT1, one gp prior SOF failures (LDV/SOF/RBV 12 weeks) and other group with decompensated cirrhosis CPT – B (LDV/SOF 12 wks)
  - SOF failures - SVR 100%; Decomp pts – SVR 65%

- 3rd group - 51 treatment-naive with/out cirrhosis (15% cirrhosis) LDV/SOF +/-RBV 12 weeks
  - Overall, SVR RBV arm 100% vs 64% without ribavirin
  - In a separate study, 12-week course of ledipasvir-sofosbuvir plus RBV for 50 GT 3 treatment-experienced patients, including cirrhosis, overall SVR12 82% (noncirrhotics vs cirrhotics 89% vs 73%)

Summary

• All oral direct acting antiviral regimens are now the standard of care for most patients
• The new benchmark for sustained virologic response rates is 90% or greater.
• The major barrier to treatment with new therapies is the high cost of treatment.
• With the new DAA’s, genotype 3 has emerged as the most difficult genotype to treat.
• The most promising investigational agent daclatasvir, grazoprevir-elbasvir
• Combining multiple drug classes minimizes risk of virologic breakthrough
• Most treatment failures result from relapse
• Still a role of ribavirin in certain subgroup of patients
  – RBV appears to decrease relapse rate
• Still NO approved therapy for decompensated cirrhosis or advanced renal failure