Management of Chronic Hepatitis C: In the New Era of DAA

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Prevalence of HCV in Asia-Pacific countries

Prevalence of HCV (%)

- Australia: 1.1%
- New Zealand: 0.3%
- China: 2.2%
- Japan: 2.4%
- North Korea: 1.0%
- South Korea: 1.7%
- Mongolia: 10.7%
- Pakistan: 5.9%
- India: 1.5%
- Indonesia: 3.9%
- Thailand: 2.2%
- Vietnam: 1.0%
- Singapore: 1.0%
- Cambodia: 4.1%
- Malaysia: 1.5%

~75% unaware they are infected until they have symptoms of cirrhosis/HCC

Bangladesh: 0.88%

- Prevalence = % anti-HCV (2010);
- HCC = hepatocellular carcinoma.


Anti-HCV positivity

Estimated anti-HCV positivity in Mainland China : 29,791,212

Lavanchy et al Clin Microbiol Infect 2011
Wei et al Gastroenterology 2014
HCV Genotype Affects Natural History?

Seto WK et al J Hepatol 2010

HCV: Natural History

HCV exposure → Chronic 85% → Cirrhosis 10–15% → Decompensation 6.4%/yr → HCC 3.4%/yr → Transplant/death 4.6%/yr

Resolved 15%

Alcohol use, obesity, co-infection with HIV or HBV accelerate HCV progression

% = percent of previous group; ESLD, End-Stage Liver Disease.
HCV: The Options?
Treatment paradigm will change with all oral DAAs.

SVR (%)

- **1989**
  - IFN monotherapy: 6–19%
  - IFN + ribavirin: 31–44%
  - PegIFN: 18–39%
  - PegIFN + ribavirin: 42–46%

- **2012**
  - PegIFN + ribavirin: 66–75%
  - BOC + P/R: 80–90%

- **2014**
  - All oral DAAs: 80–100%


BOC, BOCEPREVIR; SMV, SIMEPREVIR; SOF, SOFOSBUVIR; P/R, PEGIFN + RIBAVIRIN; DAA, DIRECT ACTING ANTIVIRALS
The HCV Genome

Seto WK et al. (2013) Hepatitis viruses and hepatocellular carcinoma. In Cancer and Inflammation Mechanism: Chemical, Biological and Clinical Aspects
The difference between HBV and HCV

**HBV**
- Host cell
- cccDNA
- Host DNA
- Nucleus
- Integrated DNA
- Require long-term viral suppression

**HCV**
- Host cell
- HCV RNA
- Host DNA
- Nucleus
- Definitive viral clearance
Available DAA

- Daclatasvir
- Asunaprevir
- Sofosbuvir
  - Harvoni (Sofosbuvir / Ledipasvir)
  - Epclusa (Sofosbuvir / Velpatasvir)
- Viekira Pak (Ombitasvir / Paritaprevir / Ritonavir and Dasabuvir)
- Technivie (Ombitasvir / Paritaprevir / Ritonavir)
- Zepatier (Grazoprevir / Elbasvir)
Treatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin

Jordan J. Feld, M.D., M.P.H., Kris V. Kowdley, M.D., Eoin Coakley, M.D., Samuel Sigal, M.D., David R. Nelson, M.D., Darrell Crawford, M.D., Ola Weiland, M.D., Humberto Aguilar, M.D., Junyuan Xiong, M.S., Tami Pilot-Matias, Ph.D., Barbara DaSilva-Tillmann, M.D., Lois Larsen, Ph.D., Thomas Podsadecki, M.D., and Barry Bernstein, M.D.

Ombitasvir (NS5A)
Paritaprevir (NS3/4A)
Ritonavir

Dasabuvir (NS5B)

Noncirrhotic treatment-naïve and experienced: PEARL II and III
ITT SVR12 rates for treatment with viekira pak ± RBV for HCV-1B

PEARL II
viekira pak for 12 weeks
treatment-experienced*, non-cirrhotic

PEARL III
viekira pak for 12 weeks
treatment-naïve, non-cirrhotic

*Prior pegIFN/ RBV treatment
#Two patients data was missing at post-treatment week 12

viekira pak: three direct-acting antivirals, ombitasvir/paritaprevir/ritonavir and dasabuvir
error bars: 95% CI
TURQUOISE-III phase IIIb, in cirrhotic patients with GT1b HCV

Feld J et al J Hepatol 2016

Recommended Regimen: viekira pak 12 Weeks
GT1b Cirrhotic Patients
Viekira Pak recommendations

- Genotype 1B
  - 12 weeks

- Genotype 1A
  - Without cirrhosis: 12 weeks, add ribavirin
  - Cirrhosis: 24 weeks, add ribavirin
Harvoni: Sofosbuvir and Ledipasvir
Genotype 1, 4, 5, 6

- **Ledipasvir**
  - Picomolar potency against HCV GT 1a and 1b\(^1\)
  - Effective against NS5B RAV S282T\(^2\)
  - Once-daily, oral, 90 mg

- **Sofosbuvir**
  - Potent antiviral activity against HCV GT 1–6
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet

- **Ledipasvir/Sofosbuvir STR**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet
  - No food effect
  - >2000 patients treated
ION-1 treatment naïve: N = 865
ION-2 treatment experienced: N = 440
ION-3 treatment naïve: N = 647

N=1952 total patients
All four treatment arms met the primary endpoint of superiority over the historical response rate of 60% ($P < 0.001$ for all comparisons)

- 16% had NS5A RAVs at baseline, with 96% achieving SVR

Error bars represent 95% confidence intervals.

ION-1 (LDV/SOF±RBV x 12 or 24 weeks)

Cirrhosis vs No cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Absence of Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12 Weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>100/179 (97%)</td>
<td>32/33</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>100/178 (100%)</td>
<td>33/33</td>
</tr>
<tr>
<td><strong>24 Weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>99/181 (97%)</td>
<td>31/32</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>100/179 (100%)</td>
<td>36/36</td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals

All four treatment arms met the primary endpoint of superiority over the historical response rate of 25% ($P<0.001$ for all comparisons)

14% had NS5A RAVs at baseline, with 89% achieving SVR

Error bars represent 95% confidence intervals

Cirrhosis vs No cirrhosis

ION-2 (LDV/SOF±RBV x 12 or 24 weeks)

Error bars represent 95% confidence intervals

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>83/87</td>
<td>89/89</td>
</tr>
<tr>
<td>LDV/SOF + RBV</td>
<td>19/22</td>
<td>18/22</td>
</tr>
</tbody>
</table>

8 weeks of LDV/SOF was non-inferior to 8 weeks of LDV/SOF + RBV and 12 weeks LDV/SOF.

18% had NS5A RAVs at baseline, with 90% achieving SVR.

Error bars represent 95% confidence intervals.
Sofosbuvir and Ledipasvir recommendations – Genotype 1A and 1B

- **12 weeks**
  - Treatment-naive
  - Treatment-experienced without cirrhosis
  - Treatment-experienced cirrhosis (with ribavirin)
- **24 weeks**
  - Treatment-experienced cirrhosis
- **8 weeks (at discretion of physician)**
  - Non-cirrhosis with HCVRNA <6,000,000 IU/mL
Prospective, multicenter study of 12 or 24 weeks of LDV/SOF + RBV in TN and TE HCV GT 1 and 4 subjects with CTP B (N=59) or CTP C (N=49) clinically decompensated cirrhosis

- 108 subjects randomized 1:1 to 12 or 24 weeks of treatment
- Stratified by CTP class B [7-9] or C [score 10–12]*
- Broad inclusion criteria:
  - No history of major organ transplant, including liver
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤10 mg/dL, Hemoglobin ≥ 10 g/dL
  - CrCl≥ 40 mL/min, Platelets > 30,000
- RBV dosing: dose escalation, 600–1200 mg/d

*Subjects with CTP scores 13-15 were excluded
Charlton M et al Gastroenterology 2015
Results: SVR12

SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Error bars represent 90% confidence intervals.

Charlon M et al. Gastroenterology 2015
Sofosbuvir and ribavirin for genotypes 2/3

FUSION Treatment Experienced
- SOF 400mg QD + RBV, n=103
- PBO

GT 2/3†
- SOF 400mg QD + RBV, n=98
- SVR12

FISSION Treatment Naïve
- SOF 400mg QD + RBV, n=256
- PEG-IFN+RBV, n=243
- SVR12

POSITRON PEG-IFN-unable
- SOF 400mg QD + RBV, n=207
- PBO, n=71
- SVR12

*PEG-IFN 180 μg/wk, RBV 1000-1200 mg/d; †PEG-IFN 180 μg/wk, RBV 1000-1200 mg/d for SOF+RBV arms and 800 mg/d for PEG-IFN+RBV arm
## HCV-2/3 results

### Efficacy Endpoints: SVR 12

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Status</th>
<th>Overall</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FISSION – Treatment Naive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF + RBV x 12 weeks</td>
<td></td>
<td>67%</td>
<td>97%</td>
<td>56%</td>
</tr>
<tr>
<td><strong>FUSION – Treatment Experienced</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF + RBV x 12 weeks</td>
<td></td>
<td>50%*</td>
<td>86%</td>
<td>30%</td>
</tr>
<tr>
<td>SOF + RBV x 16 weeks</td>
<td></td>
<td>73%*</td>
<td>94%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>POSITRON – IFN Unable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF + RBV x 12 weeks</td>
<td></td>
<td>78%</td>
<td>93%</td>
<td>61%</td>
</tr>
</tbody>
</table>

HCV-3: Need 24 weeks

- Higher SVR12 rates with SOF+PegIFN+RBV compared to SOF+RBV for 16 or 24 weeks
  - 86% SVR12 in GT 3 TE with cirrhosis treated with SOF+PegIFN+RBV
  - >80% in all other subgroups treated with 24 weeks SOF+RBV; consistent with earlier Phase 3 studies

Error bars represent 95% confidence intervals.

Sofosbuvir and Velpatasvir (Epclusa)

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection


Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection


Genotype 1, 2, 4, 5, 6
98-99%

Genotype 3
95%

Child’s B
94% (with ribavirin)

Sofosbuvir and Velpatasvir recommendations

- Genotype 3 without cirrhosis
  - 12 weeks

- Genotype 3 with cirrhosis
  - 12 weeks
The Future: Sofosbuvir, Velpatasvir, Voxilaprevir

Error bars represent 95% confidence intervals.

- One patient relapsed at post-treatment week 8

Including cirrhotics
Including prior exposure other DAAs

Lawitz et al Gastroenterology 2016
**HCV-4 LDV/SOF**

Multicenter study in TN/TE GT 4 patients in France

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=44</strong></td>
<td>LDV/SOF</td>
<td>SVR12</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Naïve n=22</th>
<th>Experienced n=22</th>
</tr>
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<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>52 (21–69)</td>
<td>50 (30–62)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>11 (50)</td>
<td>17 (77)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>19 (86)</td>
<td>17 (77)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>1 (5)</td>
<td>9 (41)</td>
</tr>
<tr>
<td>IL28B non-CC, n (%)</td>
<td>15 (68)</td>
<td>21 (95)</td>
</tr>
<tr>
<td>Mean HCV RNA, log_{10} IU/mL (range)</td>
<td>6.0 (5.1–6.8)</td>
<td>6.3 (5.6–7.5)</td>
</tr>
<tr>
<td>GT 4a, n (%)</td>
<td>13 (59)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>GT 4d, n (%)</td>
<td>5 (23)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>GT 4b, 4f, 4m, 4o, 4r, n (%)</td>
<td>4 (18)</td>
<td>5 (23)</td>
</tr>
</tbody>
</table>

No subjects D/C study due to AEs

Abergel, EASL, 2015, O056
HCV-6: LDV/SOF

CLINICAL—LIVER

Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin, for 12 Weeks in Patients With HCV Genotype 3 or 6 Infection

Edward J. Gane,¹ Robert H. Hyland,² Di An,² Evguenia Svarovskaia,² Phillip S. Pang,² Diana Brainard,² and Catherine A. Stedman³

¹Auckland Clinical Studies Ltd., Auckland, New Zealand; ²Gilead Sciences, Inc., Foster City, California; and ³Christchurch Hospital and University of Otago, Christchurch, New Zealand

SVR 96%
Grazoprevir (MK-5172) | Elbasvir (MK-8742)

Grazoprevir (NS3/4A)
Elbasvir (NS5A)
Efficacy in Chronic Kidney Disease 4 or 5

122 Subjects Enrolled

116 (95%) Primary Efficacy Pop’n

SVR_{12}: 115/116 (99.1%)

1 failure: Non-cirrhotic, Relapse (GT1b)

6 (5%) Early Non-Virology Stop

- 2 pts: Loss to follow-up
- 2 pts: Withdrawal by Subject or Physician
- 1 pt: Non-drug-related death
- 1 pt: Non-compliance

SVR_{12} (FAS): 115/122 (94.3%)

Roth D et al Lancet 2015
Drug Interactions: Beware
Example of protein-pump inhibitors

**HCV-Target**
- PPI use at baseline was independent predictor of SVR
- OR=0.41 (95% CI: 0.25-0.67)

**TRIO Propensity-Matched Cohorts**

<table>
<thead>
<tr>
<th>Group</th>
<th>All N=887</th>
<th>Cirrhosis N=337</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PPI</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>High dose PPI</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>BID PPI</td>
<td>91%</td>
<td>77%*</td>
</tr>
<tr>
<td>Any PPI</td>
<td>98%</td>
<td>96%</td>
</tr>
</tbody>
</table>

*P=0.05

- Only twice daily PPI at baseline associated with lower SVR
- Effect most marked in cirrhotics

Terrault N, Gastroenterology 2016

Tapper E, Hepatology 2016
Drug interaction: use your smartphone

Liverpool HEP iChart
Providing summary data of hepatitis drug interactions. Full details available at
www.hep-druginteractions.org

Search for Drug Interactions
Sponsors Privacy Disclaimer
Drug interactions
Protein-pump inhibitors

Coadministration has not been studied, but data with omeprazole show only a small decrease in ledipasvir exposure. Proton pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with ledipasvir/sofosbuvir. Proton pump inhibitors should not be taken before ledipasvir/sofosbuvir.

Pantoprazole exposure may decrease when administered with by ombitasvir/paritaprevir/ritonavir + dasabuvir. Pantoprazole is a substrate of CYP2C19, CYP3A4 and CYP2C9, and is also metabolised by sulfotranseferases. Exposure of omeprazole, a model CYP2C19 substrate, decreased by 40-50% when administered with ombitasvir/paritaprevir/ritonavir + dasabuvir, but exposure of the DAA was not affected. An interaction of similar magnitude is expected with other CYP2C19 substrates. Use higher doses of pantoprazole, if clinically indicated.
Drug interactions
Always check never assume

Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Warfarin is metabolised by CYP2C19, CYP2C9 and CYP3A4 but ledipasvir is only a weak inhibitor of intestinal CYP3A4 in vitro.

Potential Interaction

Ledipasvir/Sofosbuvir

Dabigatran

Coadministration has not been studied but may increase dabigatran concentrations due to inhibition of P-gp by ledipasvir. No effect on ledipasvir/sofosbuvir concentrations is expected. Clinical monitoring (for signs of bleeding and anaemia) is recommended.
HCV DAA Treatment Improves Quality of Life
(Pooled analysis of ION studies)

- Work productivity
- Fatigue
- Bodily pain
- Social functioning
- Emotion
- Mental health

Younossi ZM et al J Hepatol 2015
LDV / SOF: Cost-effectiveness in USA

LDV / SOF: Cost-effectiveness in USA

ICER:
USD 55,400 per QALY


Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold
Peter J. Neumann, Sc.D., Joshua T. Cohen, Ph.D., and Milton C. Weinstein, Ph.D.

For more than two decades, the ratio of $50,000 per quality-adjusted life-year (QALY) gained by using a given health care intervention has played an important if enigmatic role in health policy circles as a benchmark for the value of care. Researchers have summoned this cost-effectiveness ratio in order to champion or denounce particular investments in medical technologies and health programs. Critics, meanwhile, have argued that the ratio murky origins. It is often attributed to the U.S. decision to mandate Medicare coverage for patients with end-stage renal disease (ESRD) in the 1970s: because the cost-effectiveness ratio for dialysis at the time was roughly $50,000 per QALY, the government’s decision arguably endorsed that cutoff point implicitly. However, the link to dialysis is inexact — and even something of an urban legend, given that the cost-effectiveness ratio for dialysis was assured in similar terms and ranked by the favorability of their incremental cost-effectiveness ratios, decision makers with a fixed budget could maximize health gains by choosing interventions with the lowest (most favorable) ratios and working their way down the list until the available resources were consumed. The cost-effectiveness of the last (least favorable) technology covered would represent society’s willingness-to-pay threshold — the highest

USD 100,000 more appropriate?

Cost-effectiveness by Years: Treat Early!

- 10 years: USD 148,500
- 20 years: USD 82,100
- 30 years: USD 66,800

High sustained virological response rates using generic direct antiviral treatment for Hepatitis C

REDEMPTION-1

James Freeman¹, Richard Sallie², Adam Kennedy³, Pham Thi Ngoc Nieu¹, John Freeman⁴, Greg Jeffreys⁵, Andrew M. Hill⁶

¹GP2U Telehealth, Hobart, ²Hepatology, Nedlands, ³Kingswood Pharmacy, ⁴Nephrology, Sandy Bay, ⁵University of Tasmania, Hobart, Australia, ⁶St Stephens AIDS Trust, Chelsea and Westminster Hospital, London, United Kingdom

International Liver Congress 2016 13-18 April, Barcelona, Spain
High sustained virological response rates using generic direct antiviral treatment for Hepatitis C REDEMNPTION-1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
<th>Count (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF+RBV</td>
<td>0.9%</td>
<td>4 (4/448)</td>
</tr>
<tr>
<td>SOF+LDV</td>
<td>45.8%</td>
<td>205 (205/448)</td>
</tr>
<tr>
<td>SOF+LDV+RBV</td>
<td>4.7%</td>
<td>21 (21/448)</td>
</tr>
<tr>
<td>SOF+DCV</td>
<td>42.6%</td>
<td>191 (191/448)</td>
</tr>
<tr>
<td>SOF+DCV+RBV</td>
<td>6.0%</td>
<td>27 (27/448)</td>
</tr>
<tr>
<td>Naïve</td>
<td>51.6%</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>31.3%</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54.2%</td>
<td></td>
</tr>
<tr>
<td>Mean Age</td>
<td>54.4 years</td>
<td></td>
</tr>
<tr>
<td>Mean HCV RNA</td>
<td>6.46 log IU/ml, 2878793 IU/ml</td>
<td></td>
</tr>
</tbody>
</table>
Sofosbuvir and Daclatasvir HCV GT 1, 2 or 3
Phase 2: Study AI444-040 Virologic Response

- **Phase 2**, parallel-group, randomized, open-label study of SOF + DCV ± RBV for 12 or 24 weeks in treatment-naïve HCV GT 1, 2 or 3, and PI-failure (TVR, BOC) HCV GT 1 patients with no evidence of cirrhosis.

**SVR12**

- **TN, GT 1 (n = 126)**
  - SOF
  - SOF + DCV
  - SOF + DCV
  - SOF + DCV + RBV
  - SOF + DCV + RBV
  - 100% (15/15)
  - 100% (14/14)
  - 100% (15/15)
  - 100% (41/41)
  - 95% (39/41)

- **PI-Failure, GT 1 (n = 41)**
  - SOF + DCV
  - SOF + DCV + RBV
  - 100% (21/21)
  - 95% (19/20)

- **TN, GT 2 or 3 (n = 44)**
  - SOF
  - SOF + DCV
  - SOF + DCV
  - SOF + DCV + RBV
  - 100% (14/14)
  - 100% (14/14)
  - 100% (14/14)
  - 88% (14/16)
  - 86% (12/14)

- SVR12 was achieved in 98% of GT 1 patients, 92% of GT 2 patients, and 89% GT 3 patients.
Recommendations for HCV Genotype 3

- Sofosbuvir and velpatasvir for 12 weeks
  - Add ribavirin for decompensated cirrhosis

- Sofosbuvir and daclatasvir for 12-24 weeks
  - Add ribavirin for decompensated cirrhosis

- Sofosbuvir and ribavirin for 24 weeks
EASL Recommendations on Treatment of Hepatitis C 2016

European Association for the Study of the Liver*
HCV.....the end is nigh?

NO...
Many With Hepatitis C Missing Out on Treatment, Study Finds

Without proper care, infection can lead to liver failure

Many hepatitis C patients get "lost" in the U.S. health care system, a new study suggests.

Researchers looked at data from about 13,600 people in Philadelphia who tested positive for hepatitis C virus between January 2010 and December 2013. During that time, just 27 percent of the patients were in care and 15 percent had been treated or were receiving treatment, the study authors found.

The study was recently published in the journal Hepatology.

"Our findings show that many [hepatitis C] patients..."
Screening for HCV....what you can do

SCREEN THEM!!!

THANK YOU!