Current standards in the management of hepatitis C (inherited bleeding disorders)

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Hepatitis C in bleeding disorders

• **Background**
  – High rates of hepatitis C in hereditary bleeding disorders
  – Prevalence up to 100% patients treated with concentrates before 1985

• **Disease progression**
  – Important co-morbidity in patients
  – HIV infection: faster disease progression
  – Screening, viral inactivation and recombinant factor replacement have prevented transfusion-transmitted viral pathogens
Mortality and causes of death in Italian persons with haemophilia, 1990–2007

Life expectancy - All hemophilia

Life expectancy - HA severe

Life expectancy - HB severe
Antiviral therapy for chronic hepatitis C in patients with inherited bleeding disorders: an international, multicenter cohort study

Cumulative incidence of end stage liver disease

No response to IFN ($n = 148$)

SVR after IFN ($n = 147$)

Time since end of IFN-based therapy (years)
Approved or Investigational DAAs hepatitis C

NS3/4A protease inhibitors
- ABT-493
- Asunaprevir
- Boceprevir
- Grazoprevir
- GS-9857
- Paritaprevir
- Simeprevir
- Sovaprevir
- Telaprevir
- Vedroprevir

NS5B polymerase inhibitors
- MK-3682
- Sofosbuvir
- Beclabuvir
- Dasabuvir
- PPI-383
- TMC647055

NS5A inhibitors
- ABT-530
- ACH-3102
- BMS-824393
- Daclatasvir
- Elbasvir
- Velpatasvir (GS-5816)
- GSK2336805
- Ledipasvir
- Ombitasvir
- Samatasvir
- MK-8408

NS5A protein
Component of the HCV replication complex

Note: selected approved and investigational DAAs; list not exhaustive.
Efficacy of LDV + SOF + RBV in more advanced disease (SOLAR-1)

Charlton et al. Gastroenterology 149 (3) 649—659 2015

Decompensated cirrhosis¹

CTP B

- 12 weeks: 86/30
- 24 weeks: 90/27

CTP C

- 12 weeks: 87/24
- 24 weeks: 90/22

Post transplant²

F0–F3

- 12 weeks: 96/53/55
- 24 weeks: 98/55/56

CTP A

- 12 weeks: 96/25/26
- 24 weeks: 96/24/25

CTP B

- 12 weeks: 8/22/26
- 24 weeks: 83/15/18

CTP C

- 12 weeks: 60/3/5
- 24 weeks: 67/2/3

Charlton et al. Gastroenterology 149 (3) 649—659 2015
Real-World Cohorts Support ION-3 Clinical Trial Data

**GT 1: LDV/SOF 8 weeks**

97% (692/713) overall SVR for LDV/SOF 8 weeks

<table>
<thead>
<tr>
<th>Cohort</th>
<th>SVR12 (%)</th>
<th>Populations included</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-3</td>
<td>97%</td>
<td>TN, NC GT1 with baseline HCV RNA &lt; 6 million IU/mL</td>
</tr>
<tr>
<td>TRIO Cohort</td>
<td>95%</td>
<td>TN, NC GT 1; HCV-TARGET: primarily TN, NC GT1</td>
</tr>
<tr>
<td>HCV-TARGET</td>
<td>97%</td>
<td>primarily TN, NC GT1 with baseline HCV RNA &lt; 6 million IU/mL</td>
</tr>
<tr>
<td>IFI</td>
<td>100%</td>
<td>GECCO: primarily TN, NC GT1</td>
</tr>
<tr>
<td>GECCO</td>
<td>99%</td>
<td></td>
</tr>
</tbody>
</table>

Populations included in graph: ION-3: TN, NC GT1 with baseline HCV RNA < 6 million IU/mL; TRIO cohort: TN, NC GT 1; HCV-TARGET: primarily TN, NC GT1; IFI: primarily TN, NC GT1 with baseline HCV RNA < 6 million IU/mL; GECCO: primarily TN, NC GT1

# SOF LDV Real World TRIO treatment experienced SVR Cirrhosis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Duration</th>
<th>Regimen</th>
<th>Stage</th>
<th>Number</th>
<th>% SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a 1b</td>
<td>12</td>
<td>SOF LDV</td>
<td>F4</td>
<td>102/121</td>
<td>84</td>
</tr>
<tr>
<td>1b</td>
<td>12</td>
<td>SOF LDV</td>
<td>F4</td>
<td>35/41</td>
<td>85</td>
</tr>
<tr>
<td>1a</td>
<td>12</td>
<td>SOF LDV</td>
<td>F4</td>
<td>62/75</td>
<td>83</td>
</tr>
<tr>
<td>1a 1b</td>
<td>24</td>
<td>SOF LDV</td>
<td>F4</td>
<td>303/329</td>
<td>92</td>
</tr>
<tr>
<td>1a 1b</td>
<td>12</td>
<td>SOF LDV ± RBV</td>
<td>F4</td>
<td>25/26</td>
<td>96</td>
</tr>
<tr>
<td>1a</td>
<td>24</td>
<td>SOF LDV</td>
<td>F4</td>
<td>206/226</td>
<td>91</td>
</tr>
<tr>
<td>1a</td>
<td>12</td>
<td>SOF LDV + RBV</td>
<td>F4</td>
<td>17/18</td>
<td>94</td>
</tr>
<tr>
<td>1b</td>
<td>12</td>
<td>SOF LDV + RBV</td>
<td>F4</td>
<td>7/7</td>
<td>100</td>
</tr>
<tr>
<td>1b</td>
<td>24</td>
<td>SOF LDV</td>
<td>F4</td>
<td>78/82</td>
<td>95</td>
</tr>
<tr>
<td>1a 1b</td>
<td>12</td>
<td>SOF LDV ± RBV</td>
<td>F3</td>
<td>144/151</td>
<td>95</td>
</tr>
</tbody>
</table>

Curry et al AASLD 2015 poster 1108
Phase 3 evaluation of SOF+ VEL FDC for 12 weeks in Tx-naive and -experienced G1, 2, 4, 5, and 6 patients with and without cirrhosis: ASTRAL-1 study

Feld JJ, et al. AASLD 2015, San Francisco. #LB-2
Introduction: Genotype 3 infection

• Altered biology of genotype 3 infection
• New NS5A inhibitors show activity particularly daclatasvir
  – Recommended by most guidelines
• Sofobuvir plus ledipasvir or daclatasvir most effective before onset of cirrhosis
• Efficacy restricted with more advanced disease
High rates of SVR12 were observed in treatment-experienced patients without cirrhosis or the presence of baseline NS5A-Y93H resistance-associated variant (RAV) and in those with F0–3 fibrosis (Fibrotest), among other subgroups.

Individual baseline characteristics do not explain the lower SVR12 rates in patients with cirrhosis.

No NS5A-L31 RAVs nor NS5B SOF RAVs (analyzed by next-generation sequencing) were observed at baseline.

Nelson DR, et al. EASL 2015; Poster O782.
DCV + SOF ± RBV in G3 patients from a large French multicenter compassionate use program

Hezode C, et al. AASLD 2015, San Francisco. #206
DCV + SOF ± RBV in G3 patients from a large French multicenter compassionate use program

Hezode C, et al. AASLD 2015, San Francisco. #206
ASTRAL-3 Phase 3 study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 patients

**SVR12 by cirrhosis and treatment history**

- **Cirrhosis**
  - No
    - Treatment-naive: 98% SVR12 (160/163)
    - Treatment-experienced: 90% SVR12 (141/156)
  - Yes
    - Treatment-naive: 93% SVR12 (40/43)
    - Treatment-experienced: 73% SVR12 (33/45)
- **8 relapses**
  - No BL NS5A RAVs: 84% SVR12 (225/231)
  - BL NS5A RAVs: 16% SVR12 (38/43)

**Resistance analysis**

- **SOF/VEL**
  - Pts (%)
    - Treatment-naive: 88% SVR12
    - Treatment-experienced: 88% SVR12

Acknowledgement: IHEP group

Mangia A, et al. AASLD 2015, San Francisco. #249
ABT-493 and ABT-530 ± RBV in treatment-naive HCV G3 patients with cirrhosis

**Aim:** Evaluate ABT-493 + ABT-530 in difficult-to-treat treatment-naive G3-infected patients with cirrhosis and whether RBV improves response rates (SURVEYOR-II)

- **Day 1**
  - Treatment period
  - ABT-493 200 mg + ABT-530 120 mg
  - n=24
  - ABT-493 200 mg + ABT-530 120 mg + RBV 800 mg OD
  - n=24

**Safety (AEs and lab abnormalities)**

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>ABT-493 + ABT-530</th>
<th>ABT-493 + ABT-530 + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>21 (88)</td>
<td>20 (83)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (4)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>AE leading to study d/c</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALT/AST &gt;3 × ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bili &gt;1.5-3x ULN</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Bili &gt;3x ULN</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hb 8–10g/dL</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hb &lt;8 g/dL</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Efficacy (SVR12, %)**

- ABT-493 + ABT-530 for 12 weeks achieved SVR12 in 48/48 G3 TN cirrhotic patients
- No impact of RBV or BL RAVs
- Well tolerated with no ALT elevations

**Acknowledgement:** IHEP group

Kwo P, et al. EASL 2016, Barcelona. #LB01
HCV and HIV coinfection

High SVR genotype reported with several DAA regimens

Phase 3 ASTRAL-5: SOF/VEL FDC for 12 weeks in patients co-infected with HCV and HIV-1

- Phase 3 study of 12 weeks SOF/VEL in HCV/HIV coinfected patients (n=106)
- HCV G1–6, TN and TE
- Stable ART for ≥8 weeks, CD4 cell count ≥100 cells/mm³, HIV RNA ≤50 copies/mL
- Diverse range of ARVs:
  - TDF with boosting agent (RTV or COBI) (n=56)
  - TDF without boosting agent (n=35)
  - ABC/3TC (n=14)
  - No EFV permitted

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Mean age, y (range) 54 (25–72)
Male, n (%) 91 (86)
Black, n (%) 48 (45)
Mean BMI, kg/m² 27 (19–43)
Cirrhosis, n (%) 19 (18)
Treatment experienced, n (%) 31 (29)
IL28B CC, n (%) 24 (23)
Mean HCV RNA, log₁₀ IU/mL (range) 6.3 (5.0–7.4)
G1a / 1b 66 (62) / 12 (11)
G2 11 (10)
G3 12 (11)
G4 5 (5)

**SVR12 by HCV genotype**

*Two patients with relapse: Black women, non-cirrhotic; one with prior Tx

Acknowledgement: IHEP group
New data in inherited bleeding disorders (EASL April 2016)

Sofosbuvir based

Grazoprevir + elbasvir

Hezode et al EASL 2016 Sat-128; Reddy et al EASL 2016 Sat-188
SVR is associated with a reduced mortality, HCC and transplant

Meta-analysis of 129 studies of IFN-based therapy in 34,563 HCV patients

- Achieving SVR was associated with:
  - 62–84% reduction in all-cause mortality
  - 68–79% reduction in risk of HCC
  - 90% reduction in risk of liver transplant

Saleem J, et al. AASLD 2014; Poster# 44
Watershed moment for treatment of hepatitis C

- New therapies 90% -95% effective
- Powerful tools for eliminating HCV in those with inherited bleeding disorders
- Need to identify funding streams
- Some drawbacks: DAA therapy remain
  - Cost and disparities
  - Need for stratification/distribution moderate versus severe disease
  - Drug-drug interactions
  - Resistance (in some)
  - Clinician capacity
  - Need for HCC surveillance post SVR cirrhosis
  - Advanced cirrhosis may not respond
Therapy of hepatitis C

“We had come so far from where we started and weren't nearly approaching where we had to be but we were on the road to becoming better”

Maya Angelou 1928-2014. *I Know Why the Caged Bird Sings*