Management of Hepatitis C

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Medical School, University of Zagreb

ESCMID Summer School
LIVERPOOL, July 2019
Learning objective

• to gain the key understanding in pathogenesis, current therapies, guidelines and clinical outcomes in hepatitis C
Key discoveries in the basic science of HCV

1989: The HCV genome is cloned

1996: Crystal structure of the HCV NS3/4A protease

1999: JFH-1 HCV virus (Japanese fulminant hepatitis 1)

2005: Full HCV life cycle is replicated in vitro

2011: First HCV protease inhibitors approved
SVR ≈ 80%

2014: First all oral regimens approved
SVR <95%

2015: PEG-IFNα+RBV Treatment
SVR ≈ 45%

IFNα treatment
SVR <10%

Adapted from: Papić N, PhD thesis, Medical School Zagreb, 2015
SVR= sustained viral response; viral clearance

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Epidemiology of HCV

- **71.1 million** (62.5–79.4) viraemic infections$^{1,2}$
- ~**399,000** deaths each year, mostly from cirrhosis and HCC$^2$
- GT 1 and 3 are the most common causes of infection (44% and 25%, respectively)$^1$

Pathogenesis of the disease

- Serious chronic disease that affects liver and can lead to liver cirrhosis and hepatocellular carcinoma and extrahepatic manifestations
  - Increased risk for liver failure, HCC and liver-related mortality
  - Overall estimated annual risk for liver failure of 2.9%, HCC 3.2% and liver-related death 2.7% in patients with advanced fibrosis

Figure adapted from Asselah T, et al. J Hepatol 2014;61:193–5
Viral proteins: targets for direct acting antiviral agents (DAAs)

Requirements of DAAs

✓ Efficacy >95%
✓ Safety
✓ Tolerability
  ✓ Pangenotypic
  ✓ High barrier to resistance
  ✓ Short duration of treatment
  ✓ Minimal drug-drug interactions
  ✓ Low pill burden
  ✓ Equally efficent in HIV+ patients
Real-life data with different DAAs

Real-life data: SVR in patients with cHC treated at the University Hospital of Infectious Diseases Zagreb 2015-2018)
Goals and end points of HCV therapy

- To eradicate the virus
- Improve health-related outcomes and overall survival (fibrosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death)
- Reduce transmission of HCV
- Improve quality of life

- End point of therapy:
  - HCV RNA undetectable at 12 or 24 weeks after the end of treatment by a sensitive test (LLD < 15 IU/mL)
Is SVR 12 the final cure?

- Among persons who achieve an SVR12 with direct-acting antiviral (DAA) therapy, more than 99% go on to achieve an SVR24.
- Several large studies have shown a minimal relapse rate, between 0 to 1% at 5 years.
- An undetectable HCV RNA 12 or 24 weeks after antiviral therapy can be considered a virologic cure.
Impact of HCV treatment on clinical outcomes

- Impact on hepatic fibrosis
- Impact on hepatocellular carcinoma
- Impact on extrahepatic manifestation
- Impact on survival
De novo HCC after DAAs

- Overall relative risk reduction for de novo HCC of 73%
- Risk remained high in patients with advanced fibrosis, thus demanding continuous surveillance strategies in this population
- No HCC n F1-F2
Impact of HCV treatment on HCC

- Contradictory results on HCC recurrence after DAAs
- A larger prospective study with longer follow-up and risk stratification would be needed for more accurate estimates
- Patients with a history of HCC should receive HCV DAA treatment due to multiple treatment-related benefits
Impact of HCV treatment on extrahepatic manifestations

• SVR significantly decreases the risk of extrahepatic manifestations
  – Mixed cryoglobulinemia
  – Porphyria cutanea tarda
  – Glomerulonephritis
  – Non Hodgkin lymphoma
  – Diabetes mellitus
  – Stroke
How do we use DAAs?

• Efficacy and safety of different DAA drug combinations has been shown in registration studies as well as in real-life studies.

• Still we have recommendations in order to achieve the optimal efficacy, treat special groups, and avoid DDIs.
### DAAs combinations in EU 2018

<table>
<thead>
<tr>
<th>Drugs</th>
<th>activity</th>
<th>Genotype efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir / Ledipasvir</td>
<td>NS5B/NS5A</td>
<td>G 1 i 4</td>
</tr>
<tr>
<td>Grazoprevir/ Elbasvir</td>
<td>NS3-4A/NS5A</td>
<td>G 1 i 4</td>
</tr>
<tr>
<td>Sofosbuvir/ Velpatasvir</td>
<td>NS5B/NS5A</td>
<td>PANGENOTYPIC</td>
</tr>
<tr>
<td>Glecaprevir/ Pibrentasvir</td>
<td>NS3-4A/NS5A</td>
<td>PANGENOTYPIC</td>
</tr>
<tr>
<td>Sofosbuvir/ Velpatasvir/ Voxsilaprevir</td>
<td>NS5B/NS5A/NS3-4A</td>
<td>PANGENOTYPIC</td>
</tr>
</tbody>
</table>

Slide courtesy of Vince A
The WHO guidelines recommend the use of pangenotypic regimens

EASL Recommendations

HCV
Recommendations panel

- **Chair**
  - Jean-Michel Pawlotsky

- **Panel members**
  - Alessio Aghemo, Marina Berenguer, Olav Dalgard, Geoffrey Dusheiko, Fiona Marra, Massimo Puoti, Heiner Wedemeyer, Francesco Negro (EASL governing board representative)

- **Reviewers**
  - Jordan Feld, Thomas Berg, Graham Foster

Literature: 307 references

Grading evidence and recommendations

- Grading is adapted from the GRADE system\(^1\)

<table>
<thead>
<tr>
<th>Evidence quality</th>
<th>Notes</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
<td>A</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
<td>B</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Notes</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost</td>
<td>1</td>
</tr>
<tr>
<td>Weak</td>
<td>Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption</td>
<td>2</td>
</tr>
</tbody>
</table>

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**Indications for treatment: who should be treated?**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with HCV infection must be considered for therapy, including treatment-naïve and treatment-experienced* patients</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patients who should be treated without delay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Significant fibrosis or cirrhosis (METAVIR score ≥F2): including compensated (Child–Pugh A) and decompensated (Child–Pugh B or C) cirrhosis</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>• Clinically significant extra-hepatic manifestations†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HCV recurrence after liver transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients at risk of rapid evolution of liver disease due to concurrent comorbidities‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Individuals at risk of transmitting HCV</td>
<td></td>
<td></td>
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<tr>
<td>— PWID</td>
<td></td>
<td></td>
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<tr>
<td>— MSM with high-risk sexual practices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Women of child-bearing age who wish to get pregnant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Haemodialysis patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Incarcerated individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• In patients with decompensated cirrhosis and an indication for liver transplantation (MELD score ≥18–20), transplant first and treat after transplantation</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>• For waiting time &gt;6 months, treat before transplant (clinical benefit not well established)</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>• Treatment is generally not recommended in patients with limited life expectancy due to non-liver-related comorbidities</td>
<td>B</td>
<td>2</td>
</tr>
</tbody>
</table>

*Individuals who failed to achieve SVR after prior treatment; †Symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B-cell lymphoma; ‡Non-liver solid organ or stem cell transplant recipients, HBV coinfection, diabetes
Pre-therapeutic assessment

- Evaluate:
  - Comorbidities
  - Liver disease severity (cirrhosis?)
  - Extrahepatic manifestations
  - Renal function
    - HIV, HBV coinfection
  - F3 and F4: follow-up for HCC
## Non-invasive assessment of liver disease severity

<table>
<thead>
<tr>
<th>Test</th>
<th>Stage of fibrosis</th>
<th>Number of patients</th>
<th>Cut-off(s)</th>
<th>AUROC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FibroScan®</td>
<td>F3</td>
<td>560 HCV+</td>
<td>10 kPa*</td>
<td>0.83</td>
<td>72%</td>
<td>80%</td>
<td>62%</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>1,855 HCV+</td>
<td>13 kPa*</td>
<td>0.90–0.93</td>
<td>72–77%</td>
<td>85–90%</td>
<td>42–56%</td>
<td>95–98%</td>
</tr>
<tr>
<td>ARFI (VTQ*)</td>
<td>F3</td>
<td>2,691 (1,428 HCV+)</td>
<td>1.60–2.17 m/sec</td>
<td>0.94 (0.91–0.95)†</td>
<td>84% (80–88%)‡</td>
<td>90% (86–92%)‡</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>2,691 (1,428 HCV+)</td>
<td>2.19–2.67 m/sec</td>
<td>0.91 (0.89–0.94)†</td>
<td>86% (80–91%)‡</td>
<td>84% (80–88%)‡</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Aixplorer®</td>
<td>F3</td>
<td>379 HCV+</td>
<td>9 kPa*</td>
<td>0.91</td>
<td>90% (72–100%)‡</td>
<td>77% (78–92%)‡</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>379 HCV+</td>
<td>13 kPa*</td>
<td>0.93</td>
<td>86% (74–95%)‡</td>
<td>88% (72–98%)‡</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>FibroTest®</td>
<td>F4</td>
<td>1,579 (1,295 HCV+)</td>
<td>0.74</td>
<td>0.82–0.87</td>
<td>63–71%</td>
<td>81–84%</td>
<td>39–40</td>
<td>93–94</td>
</tr>
<tr>
<td>FIB-4</td>
<td>F4</td>
<td>2,297 HCV+</td>
<td>1–45†</td>
<td>0.87§ (0.83–0.92)</td>
<td>90% 55%</td>
<td>58% 92%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>APRI</td>
<td>F4</td>
<td>16,694 HCV+</td>
<td>1.0† 2.0†</td>
<td>0.84§ (0.54–0.97)</td>
<td>77% 48%</td>
<td>75% 94%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Scales for liver stiffness cut-offs (in kPa) are different between FibroScan® and Aixplorer®;
†Two cut-offs are provided for FIB-4 and for APRI, respectively, with their own sensitivities and specificities;
‡95%CI; §Median (range)

Contraindications to therapy

• Sofosbuvir
  – Caution if renal clearance < 30 ml/min
  – Contraindicated if amiodarone treatment and no possibility to switch to another treatment

• NS3-4 protease inhibitor
  – Contraindicated in patients with decompensated cirrhosis (CPT B or C), risk of toxicity

• Certain CYP/P-gp-inducing agents (e.g. carbamazepine, phenytoin)
  – are contraindicated with all regimens; risk of significantly reduced DAA concentrations
Factors that may impact the outcome

• Patients with decompensated cirrhosis are more difficult to treat

• Genotype

• Previous treatment (DAAs-RAS)
  – Treatment naive
  – Treatment experienced
### Treatment recommendations for TN or TE patients with CHC without cirrhosis

**GT** | **SOF/VEL** | **GLE/PIB** | **SOF/VEL/VOX** | **SOF/LDV** | **GZR/EBR** | **OBV/PTV/r + DSV**  
--- | --- | --- | --- | --- | --- | ---  
**1a** | TN | 12 weeks | 8 weeks | No | 8–12 weeks | 12 weeks (HCV RNA ≤800,00 IU/mL) | No  
| TE | 12 weeks | 8 weeks | No | No | 12 weeks (HCV RNA ≤800,00 IU/mL) | No  
**1b** | TN | 12 weeks | 8 weeks | No | 8–12 weeks | 8 weeks (F0–F2) 12 weeks (F3) | 8 weeks (F0–F2) 12 weeks (F3)  
| TE | 12 weeks | 8 weeks | No | 12 weeks | 12 weeks | 12 weeks  
**2** | TN | 12 weeks | 8 weeks | No | No | No | No  
| TE | 12 weeks | 8 weeks | No | No | No | No  
**3** | TN | 12 weeks | 8 weeks | No | No | No | No  
| TE | 12 weeks | 12 weeks | No | No | No | No  
**4** | TN | 12 weeks | 8 weeks | No | 12 weeks | 12 weeks (HCV RNA ≤800,00 IU/mL) | No  
| TE | 12 weeks | 8 weeks | No | No | No | No  
**5** | TN | 12 weeks | 8 weeks | No | 12 weeks | No | No  
| TE | 12 weeks | 8 weeks | No | No | No | No  
**6** | TN | 12 weeks | 8 weeks | No | 12 weeks | No | No  
| TE | 12 weeks | 8 weeks | No | No | No | No
Treatment recommendations for TN or TE patients with CHC with compensated (Child–Pugh A) cirrhosis

<table>
<thead>
<tr>
<th>GT</th>
<th>SOF/VEL</th>
<th>GLE/PIB</th>
<th>SOF/VEL/VOX</th>
<th>SOF/LDV</th>
<th>GZR/EBR</th>
<th>OBV/PTV/r + DSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>TN</td>
<td>12 weeks</td>
<td>No</td>
<td>12 weeks</td>
<td>12 weeks (HCV RNA (\leq 800,00) IU/mL)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>TE</td>
<td>12 weeks</td>
<td>No</td>
<td>No</td>
<td>12 weeks (HCV RNA (\leq 800,00) IU/mL)</td>
<td>No</td>
</tr>
<tr>
<td>1b</td>
<td>TN</td>
<td>12 weeks</td>
<td>No</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>TE</td>
<td>12 weeks</td>
<td>No</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>2</td>
<td>TN</td>
<td>12 weeks</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>TE</td>
<td>12 weeks</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>TN</td>
<td>12 weeks</td>
<td>No</td>
<td>12 weeks</td>
<td>12 weeks (HCV RNA (\leq 800,00) IU/mL)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>TE</td>
<td>12 weeks</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>TN</td>
<td>12 weeks</td>
<td>No</td>
<td>12 weeks</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>TE</td>
<td>12 weeks</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>TN</td>
<td>12 weeks</td>
<td>No</td>
<td>12 weeks</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>TE</td>
<td>12 weeks</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Genotype 1a (F1-F4 including CTP A)

- Sofosbuvir/velpatasvir (12 weeks)
- Glecaprevir/pibrentasvir (8 weeks, no cirrhosis)
- Sofosbuvir/ledipasvir (12 weeks, only treatment naive)
- Grazoprevir/elbasvir (12 weeks, if < 800,000 IU/ml)
Genotype 1b (F1-F4 including CTP A)

- Sofosbuvir/velpatasvir (12 weeks)
- Glecaprevir/pibrentasvir (8 weeks-no cirrhosis, 12 weeks cirrhosis)
- Sofosbuvir/ledipasvir (12 weeks, consider 8 weeks TN-no cirrhosis)
- Grazoprevir/elbasvir (12 weeks, consider 8 weeks TN, F0-F2)
- Ombitasvir/paritaprevir(r)/dasabuvir (12 weeks, consider 8 weeks TN, F0-F2)
Genotype 3 without cirrhosis

- Sofosbuvir/velpatasvir 12 weeks
- Glecaprevir/pibrentasvir
  - Treatment naive, F0-F3 can be treated 8 weeks
  - Treatment experienced, F0-F3, should be treated 12 weeks
Genotype 3 with compensated cirrhosis

- **Sofosbuvir/velpatasvir 12 weeks+ribavirin** (*if Y93H present or unknown*),
- Glecaprevir/pibrentasvir
  - Treatment naive, 12 weeks
  - Treatment experienced should be treated 16 weeks
- **Sofosbuvir/velpatasvir/voxilaprevir 12 weeks** (*if Y93H present, or unknown*)

*The presence of the NS5A RAS Y93H at baseline is by population sequencing or >15% by deep sequencing;
†Data with 12 weeks of treatment with GLE/PIB in TE patients with cirrhosis are needed EASL. J Hepatol 2018; doi: 10.1016/j.jhep.2018.11.004;
Sofosbuvir/velpatasvir with and without ribavirin in GT 3 HCV-infected patients with cirrhosis

- 204 patients were randomised to receive SOF/VEL or SOF/VEL + RBV for 12 weeks in an open-label study in GT 3 patients with compensated cirrhosis (TN and TE)

This study was not powered to assess noninferiority of the two treatment arms, and the numeric difference in relapse rate between the two treatment arms does not suggest a clinically meaningful difference in outcome

- SVR12 in patients with Y93H
  - SOF/VEL: 50% (2/4)
  - SOF/VEL + RBV: 89% (8/9)
DAA effectiveness in England: high response rates in GT3 HCV infection regardless of degree of fibrosis, but RBV improves response in cirrhosis

14,603 subjects had a PP outcome

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>SVR12, % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison 1 (SVR12 in GT 3 patients with moderate fibrosis)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLE/PIB (8 weeks)</td>
<td>92</td>
<td>96.6 (90.0-98.9)</td>
<td>0.793</td>
</tr>
<tr>
<td>SOF/VEL (12 weeks)</td>
<td>214</td>
<td>97.1 (93.7-98.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Comparison 2 (SVR12 in GT 3 patients with compensated cirrhosis)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF/VEL + RBV (12 weeks)</td>
<td>196</td>
<td>98.0 (94.7-99.2)</td>
<td>Comparator regimen</td>
</tr>
<tr>
<td>SOF/VEL</td>
<td>218</td>
<td>91.6 (87.3-94.5)</td>
<td>0.005*</td>
</tr>
<tr>
<td>SOF + DCV + RBV</td>
<td>868</td>
<td>92.2 (90.2-93.8)</td>
<td>0.002*</td>
</tr>
<tr>
<td>GLE/PIB (12 weeks)</td>
<td>167</td>
<td>96.4 (92.2-98.4)</td>
<td>NS†</td>
</tr>
</tbody>
</table>

In the large, non-selective English HCV treatment registry SVR12 rates with SOF/VEL + RBV were higher vs SOF/VEL or SOF + DCV + RBV in subjects with GT3 HCV and compensated cirrhosis. No other statistically significant differences were found.

*vs SOF/VEL + RBV (12 weeks); †vs all other regimens.
Drysdale K, et al. ILC 2019; LB-08
Decompensated liver cirrhosis without HCC, awaiting liver transplant

- MELD score <18–20: treat prior to liver transplantation
- MELD score ≥18–20:
  - Transplant first without antiviral treatment and treat HCV infection after transplantation
  - Treat before transplant if waiting time exceeds 6 months (depending on the local situation)

Treatment options:
- SOF/LDV (GT 1, 4, 5 and 6) or SOF/VEL (all genotypes) + RBV* for 12 weeks / or if poor tolerance to RBV 24 weeks
Treatment of acute hepatitis C

- Rare event, chronicity 50-90%
- Optimal time point to start with therapy unknown, wait 12 weeks?
- Treatment with the same regimens as for CHC for 8 weeks, according to HCV genotype
  - Can treat with: SOF/LDV (GT 1, 4, 5 and 6) or OBV/PTV/r + DSV (GT 1b)
  - May treat with: SOF/VEL (all genotypes), GLE/PIB (all genotypes), GZR/EBR (GT 1b and 4) pending confirmation in clinical trials
Retreatment

- After failure of PEG-IFNα + RBV, SOF + PEG-IFNα/RBV or SOF + RBV
- Retreat according to recommendations for TE patients, by HCV genotype

- After failure of DAA (PI and/or NS5A inhibitor)-containing regimen
  - SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis)
  - SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis)
Special groups
HBV-HCV coinfection

- Patients with chronic hepatitis B should be treated according to EASL guidelines 2017
- HBsAg positive (HBV DNA low or undetectable) should receive prophylaxis at least 12 weeks after ending the HCV treatment
- “Anti-HBc” alone should be monitored for ALT monthly, if elevated test for HBsAg and HBV DNA-if positive treat

Patients with renal impairment, including haemodialysis

Severe renal impairment (eGFR <30 mL/min/1.73 m² or ESRD*)

- Treat in expert centres with close monitoring by a MDT
- GLE/PIB for 8 or 12 weeks (all GT)
- GZR/EBR for 12 weeks (GT 1a, 1b and 4)†
- OBV/PTV/r + DSV for 12 weeks (GT 1b)
- Use SOF with caution, only if an alternative treatment is not available

*ESRD on haemodialysis (CKD stage 4/5) without an indication for liver transplant; †With HCV RNA level ≤800,000 IU/mL (GT 1a/4)
Adolescents and children

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adolescents aged ≥12 years</strong></td>
<td></td>
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</tr>
<tr>
<td>• GT 1, 4, 5 or 6: fixed-dose SOF/LDV for 12 weeks</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>• GT 2 or 3: other regimens approved for adults, with caution pending more safety data in this population</td>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td><strong>Children &lt;12 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defer treatment until DAAs, including pangenotypic regimens, are approved for this age group</td>
<td>B</td>
<td>1</td>
</tr>
</tbody>
</table>

Monitoring of drug-drug interactions

• Review of all the drugs taken by the patient
  – Including over-the-counter and recreational drugs

• When possible, an interacting comedication should be stopped or switched for the duration of HCV treatment (statin)
  – Check:

  • www.hep-druginteractions.org
  • Interaction checker
# Safety

<table>
<thead>
<tr>
<th></th>
<th>Main reported AE</th>
<th>% stopping for AE</th>
</tr>
</thead>
</table>
| Sofosbuvir/ledipasvir | Fatigue, headache  
Few cases pulmonary arterial hypertension: link not established | < 1%              |
| Sofosbuvir/velpatasvir  | Fatigue, headache                                                          | <1%              |
| Paritaprevir/r/ombitasvir/dasabuvir | Pruritus, fatigue, nausea, insomnia  
Transient ALT increases ALT*, and indirect bilirubin** | 1-2%              |
| Grazoprevir/elbasvir   | Fatigue, headache, nausea, transient ALT increases ALT*                   | 0.1               |
| Glecaprevir/pibrentasvir | Fatigue, headache,                                                         | <0.5%             |
| Ribavirin             | Anemia, teratogenic effect                                                   |                   |

* Mainly if oestroegen comedication  **Inhibition of bilirubin transporter with paritaprevir
In each country

National recommendations according to available drugs repertoire
Case presentation

• 38 years, M, genotype 3a, F3 (FS 10.7 kPa), 1650 000 IU/ml
  – No comorbidities, TN

• How would you treat?

A. Sofosbuvir/ledipasvir 12 weeks
B. Sofosbuvir/velpatasvir 12 weeks
C. Glecaprevir/elbasvir 12 weeks
D. Glecaprevir/elbasvir 8 weeks
E. Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
Case presentation

• 38 years, M, genotype 3a, F3 (FS 10.7 kPa), 1650 000 IU/ml
  – No comorbidities, TN

• How would you treat?

A. Sofosbuvir/ledipasvir 12 weeks
B. **Sofosbuvir/velpatasvir 12 weeks**
C. Glecaprevir/elbasvir 12 weeks
D. **Glecaprevir/elbasvir 8 weeks**
E. Sofosbuvir/velpatasvir/voxilaprevir 12 weeks
Case presentation

• Female 64 years, Genotype 1a, 360.000 IU/ml, F4 (FS 16.5 kPa)
  Hypertension, DM Type 2, TE peg+riba

• How would you treat?

A. Sofosbuvir/ledipasvir 12 weeks
B. Sofosbuvir/velpatasvir 12 weeks
C. Glecaprevir/pibrentasvir 8 weeks
D. Grazoprevir/elbasvir 12 weeks
E. Glecaprevir/pibrentasvir 12 weeks
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B. Sofosbuvir/velpatasvir 12 weeks
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D. Grazoprevir/elbasvir 12 weeks
E. Glecaprevir/pibrentasvir 12 weeks
Case presentation

- 59 years, female, 1991 had postraumatic surgery
- Genotype 3a, HCV RNA 7 659 530 IU/ml,
- Treatment naive, FibroScan 7.4 kPa, ALT 279

- Glecaprevir/pibrentasvir for 8 weeks was started
- ETR+, HCV RNA< 12 IU/ml
- SVR 12—HCV RNA 957 289 IU/ml, relapse within 12 weeks

- Started on sof/vel/voxi....
- Resistance testing? (Y93H)
Useful links:

• https://easl.eu/publication/easl-recommendations-treatment-of-hepatitis-c/
• https://www.hcvguidelines.org/
• https://www.hepatitisc.uw.edu