What is needed for paving the way to HCV elimination?

Treatment

Prof. Dr. Markus Cornberg
Klinik für Gastroenterologie, Hepatologie und Endokrinologie
Conflict of Interest

I have financial relationships to disclose within the past 12 months relevant to my presentation:

Consultant and Speaker Bureau
Abbvie, Biogen, BMS, Gilead, Merck/MSD, Roche
What is needed for paving the way to HCV elimination?

• Finding the patients (screening)

• Treatment
  – Effective
  – Safe
  – Simple (oral, short, no complicated management)
  – Affordable and accessible
Treatment of chronic hepatitis C in 2019

- No Interferon alfa
- Ribavirin only in very special situations (usually not needed)
- RAS test not required for naive patients
- Almost all patients can be treated
- Treatment is short (8 - 12 weeks) and safe
- SVR „Cure“ in >95% of patients
- HCV elimination may be possible
Hepatitis C: „Step by step to the ideal HCV therapy“*

---


**...asvir**
- Daclatasvir
- Ledipasvir
- Ombitasvir
- Elbasvir
- Velpatasvir
- Ribasvir

**...previr**
- Paritaprevir/ritonavir
- Grazoprevir
- Glecaprevir
- Vosevaprevir

**...buvir**
- Sofosbuvir (NI)
- Dasabuvir (NNI)

---

Figure: Manns & Cornberg, Lancet Infectious Diseases 2013 May;13(5):378-9
Treatment recommendations for chronic hepatitis C (no cirrhosis)

Table 7. Treatment recommendations for HCV-monoinfected or HCV/HIV-coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naive patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with peginterferon-α and ribavirin, or peginterferon-λ and ribavirin).

<table>
<thead>
<tr>
<th>Patients</th>
<th>Prior treatment experience</th>
<th>SOF/VEL</th>
<th>GLE/PIB</th>
<th>SOF/VEL/VOX</th>
<th>SOF/LDV</th>
<th>GZR/EBR</th>
<th>CBV/PTV/r + DSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a</td>
<td>Treatment-naive</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>8-12 wk</td>
<td>12 wk (HCV RNA ≤800,000 IU/ml)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment-experienced</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>12 wk (HCV RNA ≤800,000 IU/ml)</td>
<td>No</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>Treatment-naive</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>8-12 wk</td>
<td>8 wk (F0-F2) 12 wk (F3)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment-experienced</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>12 wk (F0-F2) 12 wk (F3)</td>
<td>12 wk</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>Treatment-naive</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment-experienced</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Treatment-naive</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment-experienced</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>Treatment-naive</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>12 wk (HCV RNA ≤800,000 IU/ml)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment-experienced</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Genotype 5</td>
<td>Treatment-naive</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment-experienced</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Genotype 6</td>
<td>Treatment-naive</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment-experienced</td>
<td>12 wk</td>
<td>8 wk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTB, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, voxilaprevir.

Glecaprevir/Pibrentasvir

84% naive without cirrhosis: always 8 weeks

Cornberg M, et al. ILC 2019; GS-07
Glecaprevir/Pibrentasvir

Patients who discontinued G/P prematurely and achieved SVR12 were counted as virologic responders. mITT analysis excluded: patients who discontinued G/P prematurely and did not achieve SVR12; patients who were LTFU; patients with HCV reinfecion. G/P, glecaprevir/pibrentasvir; HIV, human immunodeficiency virus; ITT, intention-to-treat; LTFU, lost to follow-up; mITT, modified ITT; OST, opioid substitution therapy; SVR12, sustained virologic response at post-treatment Week 12.

84% naive without cirrhosis: always 8 weeks
Sofosbuvir/Velpatasvir

RESULTS

• SVR data available for 5,541 patients
  – Median age 54 years; 59.5% male
  – Genotype distribution:
    ‒ 0.8% (5,8) GT 1
    ‒ 30.0% (33,2) GT 2
    ‒ 5.8% (30,0) GT 3
    ‒ 30.2% (30,2) GT 4–6
    ‒ 0.8% (GT mixed/unknown)
  – 20.7% (1,107) patients had CC
  – 12.4% (660) patients were treatment-experienced
• 5,134 patients achieved SVR*

  PP: 98.5%; ITT: 92.7%

*LT FU (4%) was the most common reason for not reaching SVR;‡Confirmed no cirrhosis, but fibrosis score not recorded.

Mangia A, et al. ILC 2019; GS-03

FIGURE

PP SVR12/24 according to patient status

CONCLUSIONS

SOF/VEL for 12 weeks is a simple, highly effective regimen that cures HCV patients, irrespective of genotype, cirrhosis status or treatment history, with a manageable drug interaction profile and broad clinical utility, which will help simplify the care pathway and will contribute to the WHO 2030 targets for HCV elimination.

Mangia A, et al. ILC 2019; GS-03
To improve linkage to treatment we need „guidelines on the beermat“

**Screening risk groups**

HCV-RNA / HCV Core Ag (simplified test)
ALT, AST, platelets (APRI-Score)

- **No cirrhosis**
  - 8-12 weeks **pangenotypic** therapy

- **cirrhosis (APRI)**
  - 12 weeks **pangenotypic** therapy

**Referral to experts**
- Cirrhosis: HCC Surveillance
- DAA treatment failure
Cascade of Care Egypt

Expansion of the community-based “Educate, test and treat” project at scale across 73 villages

Summary of outcomes across testing and treatment cascade in the 73 villages

Abdel-Razek et al., LBP-08; ILC 2019;
Shiha et al., ILC 2019; PS-069
Cascade of Care USA

Frequency of Patients at Each Step in HCV Care Cascade

<table>
<thead>
<tr>
<th>Step in HCV Care Cascade</th>
<th>Frequency (N)</th>
<th>Proportion of Indicated Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening (first Ab test)</td>
<td>17,177,546</td>
<td></td>
</tr>
<tr>
<td>Detection (first positive Ab test)</td>
<td>974,277</td>
<td>5.7% of screened</td>
</tr>
<tr>
<td>Confirmatory test (first HCV RNA test [positive or negative] following positive Ab test)</td>
<td>527,340</td>
<td>54.1% of Ab+</td>
</tr>
<tr>
<td>HCV RNA+ (first positive HCV RNA test following positive Ab test)</td>
<td>337,846</td>
<td>64.1% of Ab+ RNA-tested</td>
</tr>
<tr>
<td>Awareness (first HCV RNA test irrespective of Ab test)</td>
<td>1,721,020</td>
<td></td>
</tr>
<tr>
<td>Diagnosis (first positive HCV RNA test irrespective of Ab test)</td>
<td>913,529</td>
<td>53.1% of RNA-tested</td>
</tr>
<tr>
<td>Genotype test (first genotype test following positive HCV RNA test)</td>
<td>487,263</td>
<td>53.3% of RNA+</td>
</tr>
<tr>
<td>Liver function test (first liver function test following positive HCV RNA test)</td>
<td>390,162</td>
<td>42.7% of RNA+</td>
</tr>
<tr>
<td>Diagnosis and linkage to care (positive HCV RNA test &amp; ≥2 HCV RNA lab tests)</td>
<td>172,835</td>
<td></td>
</tr>
<tr>
<td>Treatment (after diagnosis)</td>
<td>18,220</td>
<td>10.5% of diagnosed linked to care</td>
</tr>
</tbody>
</table>

Reau et al., ILC 2019; PS-066
<table>
<thead>
<tr>
<th>Year of elimination</th>
<th>Country or territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>United States</td>
</tr>
<tr>
<td>2022</td>
<td>United Arab Emirates</td>
</tr>
<tr>
<td>2024</td>
<td>Taiwan (Province of China)</td>
</tr>
<tr>
<td>2026</td>
<td>Sweden</td>
</tr>
<tr>
<td>2028</td>
<td>Slovenia</td>
</tr>
<tr>
<td>2030</td>
<td>Slovak Republic</td>
</tr>
<tr>
<td>2032</td>
<td>Singapore</td>
</tr>
<tr>
<td>2034</td>
<td>Qatar</td>
</tr>
<tr>
<td>2036</td>
<td>Portugal</td>
</tr>
<tr>
<td>2038</td>
<td>Oman</td>
</tr>
<tr>
<td>2040</td>
<td>Norway</td>
</tr>
<tr>
<td>2042</td>
<td>Lithuania</td>
</tr>
<tr>
<td>2044</td>
<td>Luxembourg</td>
</tr>
<tr>
<td>2046</td>
<td>New Zealand</td>
</tr>
<tr>
<td>2048</td>
<td>Iceland</td>
</tr>
<tr>
<td>2050+</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

Germany: Grazoprevir/Elbavir 5000€ cheaper than other therapies

Cornberg et al., ILC 2019

Hellard et al., ILC 2019; PS-065
Norway
Re-Infection can be a problem

HCV reinfection incidence per 100 py

- MSM
- IVDU
- Overall

14.3
1.8
2.8

Follow-up time was 1141 person-years overall (median: 26 weeks per patient; range 4-205 weeks), 390 py in IVDU, 175 py in MSM

Ingiliz et al., EACS 2017

Treatment of active IVDU’s in Scotland (mean age: 34.0 years)

18-month reinfection rate, per 100-pyrs:

18.3 (11.1-30.4)

Schulkind, Dillon et al., ILC 2018
“Treatment as prevention“ works and can reduce new infections in high risk groups

unrestricted access to DAA to treat early HCV infection in HIV+ MSM

→ Reduction of new acute HCV infections by 51% in HIV+ MSM

Treatment as prevention

1,000 treated → 1,045 infections cured / prevented (104.5%)
Do we need HCV elimination?

Incidence of liver-related and drug-related deaths by age among people diagnosed with HCV in NSW Australia (Amin et al, Lancet 2006)

“Our data highlight that young people with hepatitis C and with co-infection face a higher mortality risk from continued drug use than from their infection”

Overall survival in patients with chronic HCV and cirrhosis compared with an age and sex matched general population

Incidence of HCC after SVR is still high in cirrhotics

N= 21,948 HCV+ US Veterans, treated with DAA

Ioannou GN et al., J Hepatol. 2017 Sep 5. pii: S0168-8278(17)32273-0.
A typical case

- 62 year old man shows up in the emergency room with jaundice
- Since 2 years Diabetes mellitus type II, Otherwise he had no severe illness before. Fatigue.
- Elevated ALT 5 years ago. Primary care physician: „Drink less alcohol and come back in 6 months“
- ALT 54, AST 49, Bilirubin 56 µmol/l, INR 1.4
- Anti-HCV positiv, HCV-RNA positiv
A typical case

Hepatocellular carcinoma (HCC)

Source: Sonographie MHH, PD Dr. A. Potthoff
Late presentation of chronic viral hepatitis for medical care: a consensus definition

Stefan Mauss, Sianislas Pol, Maria Buti, Erika Duffell, Charles Gore, Jeffrey V. Lazarus, Hilje Logtenberg-van den Griet, Jens Lundgren, Antonis Mozalevski, Dorthe Raben, Eberhard Schatz, Stefan Wiktor, Jürgen K. Rockstroh, and on behalf of the European consensus working group on late presentation for Viral Hepatitis Care

Abstract

Introduction: We present two consensus definitions of advanced and late stage liver disease being used as epidemiological tools. These definitions can be applied to assess the morbidity caused by liver diseases in different health care systems. We focus on hepatitis B and C virus infections, because effective and well tolerated treatments for both of these infections have greatly improved our ability to successfully treat and prevent advanced and late stage disease, especially if diagnosed early. A consensus definition of late presentation with viral hepatitis is important to create a homogenous, easy-to-use reference for public health authorities in Europe and elsewhere to better assess the clinical situation on a population basis.

Methods: A working group including viral hepatitis experts from the European Association for the Study of the
Hepatitis C is not only a liver disease

Immunological and epigenetic imprints may not be reversible

Increasing incidence of acute HCV infection in the USA

https://wwwn.cdc.gov/nndss/
Yes, we do need a vaccine, especially in risk groups (also based on models)!

Scott et al., BMC Medicine 2015, 13:198
HCV vaccine pipeline

Ad/MVA vaccines (GSK/MRC)

Class-II invariant chain (PEACHI-EU consortium)

E1/E2 HCV protein vaccines

T cell vaccines

B cell vaccines

Phase I

Phase II

Phase III

Approved

Slide from E. Barnes:
https://easl.meta-dcr.com/ilc2019/crs/what-is-the-most-effective-approach-to-a-hcv-vaccine
Towards the Elimination of Hepatitis B and C by 2030
The draft WHO Global Hepatitis Strategy, 2016-2021
and global elimination targets

It is not over – The endgame has started