Chronic Hepatitis C: Challenges in Special Populations

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Disclosures

Honoraria for consulting or speaking (last 5 years):
Abbott, AbbVie, Biolex, BMS, Boehringer Ingelheim, Eiger, Gilead, ITS, JJ/Janssen-Cilag, Medgenics, Merck/Schering-Plough, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, ViiV

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Lasker Award 2016

Ralf Bartenschlager  
Charles M. Rice  
Michael J. Sofia
The hepatitis C-associated disease burden is increasing!

Mortality due to HCV 2013 ~ 700,000

HCV-Cirrhosis Mortality Increase 68%

HCV-HCC Mortality Increase 292%

Stanaway et al., Lancet. 2016 Sep 10;388:1081-8
Hepatitis C is not only a liver disease!

- Cryoglobulinemia
- Autoimmune Diseases
- Fatigue, depression
- Vasculitis
- Diabetes
- Social and legal consequences
- ....
HCV cure is associated with reduced mortality

ALL CAUSE MORTALITY

SVR patients have a survival similar to the general population

Van der Meer AJ, et al. JAMA 2012


Similar Data: France: Nahon et al., Gastroenterology 2017; 152: 142-156
Italy: Bruno et al., J Hepatol 2016; 64: 1217-23; Scotland: Innes et al., J Hepatol 2017; 66: 19-27
HCV Therapy: EMA-Approved Direct Acting Antivirals

16. Mai 2014: approval Simeprevir
18. Nov. 2014: approval Ledipasvir/Sofosbuvir
16. Jan 2015: approval Paritaprevir/Ombitasvir/r
16. Jan 2015: approval Dasabuvir
8.7.2016: Velpatasvir/Sofosbuvir
18.7.2016: Grazoprevir/Elbasvir
Q3/4 2017: Glecaprevir/Pibrentasvir
Q3/4 2017: Velpatasvir/Sofosbuvir/Voxilaprevir
HCV Therapy: Direct Acting Antivirals

**Non-Nucs**
- Sofosbuvir
- Ledipasvir
- Velpatasvir

**NS5A-Inhibitors „...asvirs“**
- Paritaprevir/r
- Elbasvir
- Daclatasvir

**Protease-Inhibitors „...previrs“**
- Grazoprevir
- Asunaprevir
- Simeprevir

**Polymerase-Inhibitors „...buvirs“**
- Glecaprevir
- Pibrentasvir
- Simeprevir
- Daclatasvir

**Sofosbuvir + RBV**

- Wedemeyer, Der Internist 2014 & Lancet 2015

H. Wedemeyer: 03-2017
HCV-Special Populations
Phase 2/3 studies of DAAs against HCV

SVR (%)

95-100 %

With almost no side effects

>50 x NEJM, Lancet, JAMA, Ann Intern Med, Lancet ID
When to start? Which treatment when? How long?
Ribavirin yes/no? Resistance testing?
Child B/C-cirrhosis? Impaired renal function?
Optimal treatment for HCV Genotype 3?
How to manage DAA failures?
Selecting the optimal HCV treatment

- HCV Genotype
- Stage of liver disease ($F0$-$F4$-decompensation)
- HCV Viral Load
- Kidney Function

Selection of DAAs

- Ribavirin: yes / no
- Duration: 8, 12, 16, 24 weeks

Costs
- DDI
- Adherance
- Comorbidities
- Age
EASL Recommendations 2016

- The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death (A1).

- The endpoint of therapy is undetectable HCV RNA in blood by a sensitive assay (lower limit of detection ≤15 IU/ml) 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment (A1).

- Undetectable HCV core antigen 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment is an alternative endpoint of therapy in patients with detectable HCV core antigen prior to therapy if HCV RNA assays are not available or not affordable (A1).

- In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients surveillance for HCC should be continued (A1).
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EASL Recommendations 2016

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- In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients surveillance for HCC should be continued (A1).
HCV-core-Antigen testing: Good correlation with HCV RNA

... but low HCV viremia may be missed with HCVcoreAg testing
Manfred

♂
52 years
Child B Cirrhosis
HCV GT3
PEG-IFNa/RBV relapser

Helga

♀
59 years
HCV GT1a
Relapse after 8 weeks LDV/SOF

Stefan

♂
41 years
Surgeon, needle stick
Acute Hepatitis C
GT 1b
How does HCV therapy influence immune responses?
HCV alters the systemic inflammatory milieu

Healthy

NASH

Hepatitis C

... which is not completely restored by HCV clearance!
Manfred
- 52 years
- Child B Cirrhosis
- HCV GT3
- PEG-IFNa/RBV relapser

Helga
- 59 years
- HCV GT1a
- Relapse after 8 weeks LDV/SOF

Stefan
- 41 years
- Surgeon, needle stick
- Acute Hepatitis C
- GT 1b
Manfred

52 years
Child B Cirrhosis (ascites)
HCV GT3
PEG-IFNa/RBV relapser

Albumin: 29 mg/dl
Platelets: 72,000/µl
eGFR: 43 ml/min
MELD 17

Chance for SVR in GT3 decompensated cirrhosis?
Does liver function improve with HCV clearance?

Decomp. Cirrhosis

DAAs
Lower SVR rates in HCV-GT3 decompensated cirrhosis
Sofosbuvir-Velpatasvir (Astral-4)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sofosbuvir-Velpatasvir for 12 Wk (N = 90)</th>
<th>95% CI</th>
<th>Sofosbuvir-Velpatasvir plus Ribavirin for 12 Wk (N = 87)</th>
<th>95% CI</th>
<th>Sofosbuvir-Velpatasvir for 24 Wk (N = 90)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained virologic response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All genotypes</td>
<td>75/90 (83)</td>
<td>74–90</td>
<td>82/87 (94)</td>
<td>87–98</td>
<td>77/90 (86)</td>
<td>77–92</td>
</tr>
<tr>
<td>Genotype 1a</td>
<td>44/50 (88)</td>
<td>76–96</td>
<td>51/54 (94)</td>
<td>85–99</td>
<td>51/55 (93)</td>
<td>82–98</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>16/18 (89)</td>
<td>65–99</td>
<td>14/14 (100)</td>
<td>77–100</td>
<td>14/16 (88)</td>
<td>62–98</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>4/4 (100)</td>
<td>40–100</td>
<td>4/4 (100)</td>
<td>40–100</td>
<td>3/4 (75)</td>
<td>19–99</td>
</tr>
<tr>
<td><strong>Genotype 3</strong></td>
<td>7/14 (50)</td>
<td>23–77</td>
<td>11/13 (85)</td>
<td>55–98</td>
<td>6/12 (50)</td>
<td>21–79</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>4/4 (100)</td>
<td>40–100</td>
<td>2/2 (100)</td>
<td>16–100</td>
<td>2/2 (100)</td>
<td>16–100</td>
</tr>
<tr>
<td>Genotype 6</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>1/1 (100)</td>
<td>3–100</td>
</tr>
</tbody>
</table>

Curry et al., N Engl J Med. 2015
Glecaprevir/Pibrentasvir may become a rescue option for GT3
Surveyor-II: GT3 12-16 weeks

98% of patients had HCV RNA <LLOQ by treatment week 4
Improvement of liver stiffness during and after IFN-free therapy of hepatitis C

FibroScan

Deterding, ... Wedemeyer, AP&T 2016

ARFI

Attia, ... Potthoff, EASL-ILC 2016

Improvement of MELD-Scores in patients with Child B/C cirrhosis by IFN-free therapy

* including relapse patients documented at the timepoint of relapse

Point of no return?

Deterding et al., Aliment Pharmacol Ther. 2015
Manfred

♂

52 years
Child B Cirrhosis
HCV GT3
SVR
Albumin: 34 mg/dl
Platelets: 85,000/µl
eGFR: 52 ml/min
MELD 13

- HCC despite HCV clearance?

Decomp. Cirrhosis

DAAs
HCCs still occur after HCV clearance

*Journal of Hepatology October 2016*

<table>
<thead>
<tr>
<th>Erstautor Studien</th>
<th>Reig(^8) (Spanien)</th>
<th>Pol(^9) (Frankreich)</th>
<th>Conti(^5) (Italien)</th>
<th>Cheung(^4) (UK)</th>
<th>Kozbial(^7) (Österreich)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohorten</td>
<td>HCC-Rezidine</td>
<td>HCC-Rezidine vs. unbehandelte Kontrollkohorte (HEPATHER-Kohorte)</td>
<td>HCC-Rezidine vs. Denovo-HCC</td>
<td>HCC-Rezidine und Denovo-HCC kombiniert (SVR) vs. Therapieversager</td>
<td>Denovo-HCC</td>
</tr>
<tr>
<td>Patientenzahl</td>
<td>58</td>
<td>189 vs. 78</td>
<td>285 vs. 59</td>
<td>317 vs. 89</td>
<td>192</td>
</tr>
<tr>
<td>Beobachtungszeitraum [Monate]</td>
<td>5,7</td>
<td>20,2 vs. 26,1</td>
<td>6</td>
<td>15</td>
<td>48</td>
</tr>
<tr>
<td>HCC-Häufigkeit</td>
<td>27,6%</td>
<td>0,73/100 Patientenmonate vs. 0,66/100 Patientenmonate (p=0,8756)</td>
<td>Denovo-HCC: 3,16% HCC-Rezidiv: 28,81%</td>
<td>SVR: 5,4% Therapieversager: 11,2% (p=0,049)</td>
<td>5,2%</td>
</tr>
</tbody>
</table>
HCCs still occur after HCV clearance

*The Hannover Cohort*

DAAs → SVR

historical control
HCV-RNA+ untreated
Manfred

52 years
Child B Cirrhosis (ascites)
HCV GT3
PEG-IFNa/RBV relapser
Albumin: 24 mg/dl
Platelets: 49,000/µl
eGFR: 37 ml/min
MELD 21

—they—
Better to treat after liver transplantation?

Decomp. Cirrhosis

DAAs

Post-Liver Tx
High SVR rates for IFN-free therapy after liver transplantation

- Daclatasvir + Sofosbuvir
  Herzer, Zeuzem et al., Transplant International; epub Dec 24 2016

- Ledipasvir + Sofosbuvir
  Ciesek, Sterneck et al., Transpl Infect Dis 2016; 18: 326-32

- Simeprevir + Sofosbuvir
  Crittenden, Cave et al., Liver Transpl 2016; 22: 635-43

- Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir
  Flisiak et al. AP&T 2016; 44: 946-56

- SVR-Rates 95%-100%
- No major safety signals, no increase in rejection episodes, improvement of liver function, regression of fibrosis
Manfred

52 years
Child B Cirrhosis (ascites)
HCV GT3
PEG-IFNa/RBV relapser
Albumin: 29 mg/dl
Platelets: 72,000/µl
eGFR: 43 ml/min
MELD 17

- Treatment: Velpatasvir/Sofosbuvir + Ribavirin (if NS5A RAS excluded w/o RBV possible)
- If SVR: Continue HCC screening!
- If MELD >18-20: List for Liver Transplantation and consider treatment after LTx
**Helga**

- **Age**: 59 years
- **HCV**: GT1b
- **Relapse after**: 8 weeks LDV/SOF
- **Baseline fibrosis stage**: F1
- **Fatigue**

### Sustained Virological Response 8 vs. 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>LDV/SOF 8 weeks</th>
<th>LDV/SOF 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>98.3 (827/841)</td>
<td>98.1 (1,289/1,314)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤70 yrs</td>
<td>98.3 (762/775)</td>
<td>98.3 (1,151/1,171)</td>
</tr>
<tr>
<td>&gt; 70 yrs</td>
<td>98.5 (65/66)</td>
<td>96.5 (138/143)</td>
</tr>
<tr>
<td><strong>Treatment history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naïve</td>
<td>98.6 (757/768)</td>
<td>97.7 (516/528)</td>
</tr>
<tr>
<td>Experienced</td>
<td>95.9 (70/73)</td>
<td>98.3 (773/786)</td>
</tr>
<tr>
<td>Prior IFN</td>
<td>95.8 (69/72)</td>
<td>98.3 (759/772)</td>
</tr>
<tr>
<td>Prior DAA</td>
<td>100 (4/4)</td>
<td>98.6 (142/144)</td>
</tr>
<tr>
<td>Other</td>
<td>100 (1/1)</td>
<td>100 (24/24)</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>90.5 (19/21)</td>
<td>94.1 (176/187)</td>
</tr>
<tr>
<td>No</td>
<td>98.5 (808/820)</td>
<td>98.8 (1,113/1,127)</td>
</tr>
<tr>
<td><strong>Baseline fibrosis stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0 – F1</td>
<td>98.8 (240/243)</td>
<td>99.6 (266/267)</td>
</tr>
<tr>
<td>F2</td>
<td>97.5 (79/81)</td>
<td>98.7 (151/153)</td>
</tr>
<tr>
<td>F3</td>
<td>94.7 (18/19)</td>
<td>97.7 (85/87)</td>
</tr>
<tr>
<td>F4</td>
<td>90.5 (19/21)</td>
<td>94.1 (176/187)</td>
</tr>
<tr>
<td><strong>Baseline viral load, IU/mL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2,000,000</td>
<td>98.3 (620/631)</td>
<td>98.4 (762/774)</td>
</tr>
<tr>
<td>&gt; 2,000,000 – ≤ 6,000,000</td>
<td>98.3 (171/174)</td>
<td>97.4 (337/346)</td>
</tr>
<tr>
<td>&gt; 6,000,000</td>
<td>100 (21/21)</td>
<td>97.7 (173/177)</td>
</tr>
</tbody>
</table>

*Baseline fibrosis stage: F0 = No fibrosis, F1 = Mild, F2 = Moderate, F3 = Severe, F4 = Cirrhosis*
HCV-RNA Assays differ! Lower HCV RNA values with the Abbott ART compared to Roche Cobas TaqMan
Helga

59 years
HCV GT1b
Relapse after 8 weeks LDV/SOF
F1 fibrosis
Fatigue

Does HCV resistance matter?
Treatment options?

HCV Resistenztest

Patienten-Nr.: 4100610930
Fall-Nr.: 16029098 (ST)
Entnahme-Datum: 01.02.2016

Auftragsnr.: 04656362 / 1097.16
Proben-Nr.: 2803/01.02.16
Datum / Seite: 04.03.16 08:18 / 1

Analyse | Resultat
--- | ---
P-Res.Mut-NS3 | 1

B-ResTest: Mutat.NS5A | L28M, L31V

B-ResTest: Mutat.NS5B | C316N, V499A

3 Wert: In der Populationsssequenzierung keine Resistenz-assoziierte Mutation nachgewiesen.
Resistance after NS5A-DAA failure

- PI + NUC?
- RBV?
- Longer therapy?
- Combine 3-5 classes? New DAAs?

NS5A- Inhibitors „...asvirs“

Protease- Inhibitors „...previrs“

Polymerase- Inhibitors „...buvirs“

Non-Nucs

Nucleos(t)ide

Sofosbuvir + RBV
Re-Treatment of NS5A failure patients

Sofosbuvir/Velpatasvir/Voxilaprevir (Polaris-1)

![Graph showing SVR12 percentages for different groups of patients with and without RASs and with NS3 or NS5A targeting.]
Re-Treatment of NS5A failure patients with MK3682, Grazoprevir, Ruzasvir (C-SURGE)
Helga

59 years
HCV GT1b

Relapse after 8 weeks LDV/SOF
F1 fibrosis
Fatigue

Why did she fail therapy?

• 7 different comediations
Comedication is very frequent in HCV infection. DDIs can occur with all DAA regimens.
Helga

59 years
HCV GT1b
Relapse after 8 weeks LDV/SOF
F1 fibrosis
Fatigue

Why did she fail therapy?

- 7 different comedications
- Partial Gastrectomy 1986

- Currently no re-treatment (F1-Fibrosis!)
- Wait for approval of new regimens with high efficacy against NS5A RASs
Stefan

41 years
Surgeon, needle stick

Acute Hepatitis C
GT 1a

ALT 1860 U/L
Bilirubin 14 mg/dl

➢ Treatment to prevent HCV transmission?
➢ How to treat?
➢ Safety of DAA therapy in severe hepatitis?
➢ Risk for HCV reinfection?
IFNa monotherapy is highly effective in acute hepatitis C

- Conventional interferon alpha-2b – Monotherapy 6 month
- SVR 98% (n = 44)

**German Acute HCV II – Study (2001 – 2004)**
- Peg-interferon alpha-2b – Monotherapy 6 months
- SVR 89% (n = 89)

**German Acute HCV III – Study (2004 – 2010)**
- Delayed versus immediate PEG-IFN-treatment – Treatment 6 months
- SVR delayed therapy 93%, SVR immediate therapy 90% (n = 132)
IFN-free treatment of acute hepatitis C

Infection → Symptoms → Presentation

**Acute hepatitis C**

- host Immune response
- potency of required therapy

**Chronic hepatitis C**

SOF/RBV alone possible?
- no! 6 weeks SVR 32%
  (Martinello, Hepatology 2016; 64: 1911-21)

How short is possible?
- (4-) 6 weeks! SVR 100%
  (Deterding, Lancet Infect Dis epub Oct28 2016)
Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study

Katja Deterding, Christoph D Spinner, Eckart Schott, Tania M Welzel, Guido Gerken, Hartwig Klinker, Ulrich Spengler, Johannes Wiegand, Julian Schulze zur Wiesch, Anita Pathil, Markus Cornberg, Andreas Umgelter, Caroline Zöllner, Stefan Zeuzem, Armin Papkalla, Kristina Weber, Svenja Hardtke, Heiko von der Leyen, Armin Koch, Dorothee von Witzendorff, Michael P Manns, Heiner Wedemeyer, the HepNet Acute HCV IV Study Group

**Graph:**
- **HCV RNA < 15 IU/ml, detectable**
- **HCV RNA undetectable**

**Weeks:**
- Week 2
- Week 4
- Week 6
- FU 12

**Number of Patients (n):**
- Week 2: 15
- Week 4: 15
- Week 6: 20
- FU 12: 20
Early treatment of symptomatic acute hepatitis C is safe and leads to rapid improvement of symptoms.

**Individual ALT levels over time**
However: Relapses with LDV/SOF for 6 weeks in acute HCV infection in **HIV+ patients** with high baseline viral load.
Cure of HCV infection does not lead to protective immunity! High rates of HCV re-infection in HIV+ MSM
Stefan

41 years
Surgeon, needle stick

Acute Hepatitis C
GT 1a

HCV-RNA $5.6 \times 10^6$ IU/ml

- HCV RNA kinetic, wait for 4 weeks
- If no significant decline:
  treat with LDV/SOF (6-) 8 weeks
  (only 4 week packages available)
- Alternative: wait for chronic hepatitis C
- No recommendation to treat all patients with acute hepatitis C!
Manfred

52 years
Child B Cirrhosis
HCV GT3
PEG-IFNa/RBV relapser

SOF-VEL +RBV
(to avoid liver Tx)
HCC monitoring

Helga

59 years
HCV GT1a
Relapse after 8 weeks LDV/SOF

Re-Treatment Q3/4 2017

Stefan

41 years
Surgeon, needle stick
Acute Hepatitis C GT 1b

LDV/SOF 8 weeks no immunity!
Acknowledgements

AG Cornberg + AG Wedemeyer

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Twincore:
T. Pietschmann, E. Steinmann


Dr. Y. Serfert, Bianka Wiebner, D. Hüppe
Was kann der Patient noch tun?

Kaffee ist gut für die Leber