ACKNOWLEDGEMENTS

- Heiko Mix
- Katja Detereding
- Markus Cornberg
- Elmar Jaeckel
- Sandra Ciesek
- Thomas von Hahn
- Heiner Wedemeyer
Most liver transplants (LT) in Europe due to cirrhosis are caused by hepatitis viruses

- European analysis of 55,714 transplants in Europe\(^1\)

- HCV-related cirrhosis is the main indication for LT in EU and the US\(^2\)

Study period January 1998-December 2012

1. ELTR
Increase in patients with decompensated cirrhosis driving up prevalence and costs of sequelae

TREATMENT UPTAKE

All HCV PATIENTS

OLD PEG-IFN/RBV

100%

90% SVR

90% SVR

Higher Treatment Uptake

CURE

5%

9%

81%
Outcome of liver transplantation: HCV

Cumulative survival after liver transplantation
(MHH 1998-2005)**

Cumulative survival after LTx
(Mainz 1998-2008)****

* Berenguer M et al., J Hepatol 2000, ** Forman LM et al., Gastroenterology 2002,
HCV recurrence post-LT

OLT → 1 MTH

1 MTH →

ACUTE HEPATITIS 70%

NO HEPATITIS 20%

CHRONIC HEPATITIS

6 MTH →

CHOLESTATIC HEPATITIS < 10%

DEATH 50%

VIRAL RECURRENT

6 MTH →

CHRONIC HEPATITIS

CIRRHOSIS →

These patterns result in increased Allograft loss
- Cholestatic HCV
- More rapid progression of chronic hepatitis to cirrhosis

Donor and recipient age are increasing

Donor age

Recipient age

ET report 2013
In the US, many patients waiting for HCV referral have HCC or ESLD at the time of registration.
Germany with transplantation of sicker patients since MELD

One year survival
84%
52%

Weissmüller et al. Transpl. Int. 2011

Recipient-survival according to MELD-score categories (n = 450)

<table>
<thead>
<tr>
<th>Days post OLT</th>
<th>90</th>
<th>365</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD &lt; 10</td>
<td>91.5% (65/71)</td>
<td>84.5% (60/71)</td>
</tr>
<tr>
<td>MELD 10–20</td>
<td>90.6% (164/181)</td>
<td>83.4% (151/181)</td>
</tr>
<tr>
<td>MELD 20–30</td>
<td>86.4% (89/103)</td>
<td>78.6% (81/103)</td>
</tr>
<tr>
<td>MELD &gt; 30</td>
<td>65.3% (62/95)</td>
<td>52.6% (50/95)</td>
</tr>
</tbody>
</table>

$p < 0.001$
Decreasing number of transplantations in Germany
De novo HCC develops while patients are on the LT waiting list – mainly patients with HCV

- HCV: 66%
- Alcohol: 13%
- NASH / Cryptogenic: 11%
- HBV: 4%
- HBV / Chronic: 4%
- PBC: 2%
- PSC: 2%
- AIH: 1%
- HH/A1AT: 1%
BUT....HCV is curable

Listed

Prevent graft infection

Pre-transplant anti-viral therapy

Transplant

Prevent infection or ↓ risk of disease progression

Prophylactic or pre-emptive therapies

Chronic hepatitis

Prevent cirrhosis and graft failure

Antiviral therapy for recurrent disease

Graft loss

Re-transplant
Use of PEG-IFN + RBV-based therapy in LT recipients has been limited

- Poor tolerance and side effects of PEG-IFN\(^1\)
  Contraindicated in 26–75% of screened patients: severe cytopenia

- Patients with advanced disease may be intolerant to standard PEG-IFN + RBV doses

- Triple therapy with protease inhibitors is only effective in patients with HCV GT 1 and significant side effects\(^2\)

- Potential DDIs with ciclosporin and tacrolimus with triple therapy\(^2\)

1. Roche B & Samuel D. Liver Int 2012;32 Suppl 1:120–8;
2. Coilly A et al. J Hepatol 2014;60:78–86
Time for change…

- New treatment options
  - Simple, effective regimens
  - IFN-free options
  - (Lack of DDIs)

- Cure of HCV becomes an opportunity for more patients

- Transformation in LT management towards cure of HCV
  - Halting the disease before transplant may remove the subsequent need for transplant – reduce the waiting list; making livers available for other ESLD patients
  - Treating before or after transplant should improve graft survival and long-term outcomes
IFN-free treatment options since 2014

...previr
- Simeprevir
- Paritaprevir (1/15)
- Grazoprevir (2016)

...buvir
- Sofosbuvir
- Dasabuvir (1/2015)
- More from >2016

...asvir
- Daclatasvir
- Ledipasvir (12/14)
- Ombitasvir (1/15)
- Elbasvir (2016)

Manns & Cornberg, Lancet Infectious Diseases 2013
Open issues in HCV therapy

• Decompenated cirrhosis

• Genotype non-1

• Liver transplantation (treatment before or after Tx)?

• Renal insufficiency / dialysis

• Access to therapy
Harvoni (SOF + LDV): GERMANY (EMA) 18.11.2014 Genotypes 1 & 4

Compensated Cirrhosis:

Harvoni (SOF/LDV) 24 weeks
12 weeks in low risk patients with alternatives

Decompensated Cirrhosis; before and after LTX:

Harvoni (SOF/LDV) 24 weeks plus RBV
Compensated Cirrhosis:

SOF BASED THERAPIES: GFR > 30 !!!

Decompensated Cirrhosis; before and after LTX:

Harvoni (SOF/LDV) 24 weeks plus RBV
**GERMANY since January 2015: 3DAA Labelling Compensated Cirrhosis**

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Therapy</th>
<th>Duration</th>
<th>SVR&lt;sub&gt;12&lt;/sub&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1b</td>
<td>viekirax + exviera + RBV</td>
<td>12 Weeks</td>
<td>99% (67/68)</td>
</tr>
<tr>
<td>GT1a</td>
<td>viekirax + exviera + RBV</td>
<td>24 Weeks*</td>
<td>95% (115/121)</td>
</tr>
<tr>
<td>GT4</td>
<td>viekirax + RBV</td>
<td>24 Weeks</td>
<td>No data (PhIII ongoing)</td>
</tr>
</tbody>
</table>

* Lagen zu Therapiebeginn bei Studienteilnehmern alle drei günstigen Laborwerte vor (AFP < 20 ng/ml, Thrombozytenzahl ≥ 90 x 10^9/l und Albumin ≥ 35 g/l), waren die Relapseraten für Studienteilnehmer, die 12 Wochen lang behandelt wurden, vergleichbar mit denen der 24 Wochen lang behandelten.

Fachinformation viekirax (Stand: Januar 2015)

**same regimen in HCV- / HIV - coinfection**
<table>
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<th>Patient population</th>
<th>Therapy</th>
<th>Duration</th>
<th>SVR_{12} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT4</td>
<td>viekirax + RBV</td>
<td>24 Weeks</td>
<td>No data (PhIII ongoing)</td>
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</tbody>
</table>

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Fachinformation viekirax (Stand: Januar 2015)
SOLAR 1: Improvement of liver function with SOF/LDV in patients with advanced liver cirrhosis

Sofosbuvir 400 mg 1/d
Ledipasvir 90 mg 1/d
± Ribavirin

12-24 Wochen

Week 4 Follow-Up (12 Weeks of Treatment)

- Improved (n=33)
- No change (n=10)
- Worsened (n=4)

Arrows represent individual patients.

Flamm et al., AASLD 2014
SOLAR 1: Improvement of liver function with SOF/LDV in patients with advanced liver cirrhosis

Flamm et al., AASLD 2014

Sofosbuvir 400 mg 1/d
Ledipasvir 90 mg 1/d
± Ribavirin

12-24 Wochen
SOLAR 1: Improvement of liver function with SOF/LDV in patients with advanced liver cirrhosis

SOF based therapies: GFR > 30
3DAA regimen not approved for decomp cirrhosis

± Ribavirin

12-24 Wochen
SOLAR 1: Improvement of liver function with SOF/LDV in patients with advanced liver cirrhosis

SOLAR 2 to be presented at: EASL, Vienna, 23 April 2015!
Prevention of Recurrence: Proof of Concept
Prevention of Recurrence: Proof of Concept

AND THE WINNER IS……….
Prevention of Recurrence: Proof of Concept

AND THE WINNER IS……..

CURRY ….. AFDHAL !

AASLD 2013

GASTROENTEROLOGY 2015
**Phase 2 Pre-Liver Transplant Pilot Study**

**SOF + RBV to Prevent HCV Recurrence Post-Transplant**

- **Objective:** prevention of HCV recurrence after orthotopic liver transplant (LT)
  - pTVR at Week 12
- **Inclusion criteria:**
  - Meeting MILAN criteria undergoing LT for HCC 2° to HCV
    - Model for End-Stage Liver Disease (MELD) < 22 and HCC-exception MELD ≥ 22
  - Compensated cirrhosis: Child-Pugh-Turcotte score ≤ 7

---

Objective: prevention of HCV recurrence after orthotopic liver transplant (LT)
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Inclusion criteria:
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  - Model for End-Stage Liver Disease (MELD) < 22 and HCC-exception MELD ≥ 22
- Compensated cirrhosis: Child-Pugh-Turcotte score ≤ 7

SOF 400 mg + RBV 1000–1200 mg
Liver transplant
(up to 48 weeks)

Undergoing LT for HCC ²° to HCV, N=61

12 weeks Post-transplant virological response (pTVR)
PATIENT DISPOSITION

92 screened

63 enrolled

2 were never dosed

61 dosed

15 discontinued study prior to transplantation
  5 due to viral relapse
  3 due to progressive disease
  2 due to non-response
  2 due to viral breakthrough
  2 died (15 and 38 days post last dose)
  1 removed from the transplant list

46 underwent liver transplantation

3 had HCV RNA >LLOQ at transplantation
  2 relapsed after treatment
  1 had on-treatment viral breakthrough

43 with HCV RNA <LLOQ at transplantation were analyzed for post-transplant virologic response
## Pre-Transplant Patient Demographics

**SOF + RBV to Prevent HCV Recurrence Post-Transplant**

<table>
<thead>
<tr>
<th></th>
<th>SOF + RBV (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>49 (80)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>59 (46–73)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>55 (90)</td>
</tr>
<tr>
<td>BMI &lt; 30 kg/m², n (%)</td>
<td>43 (70)</td>
</tr>
<tr>
<td>HCV RNA &gt; 6 log₁₀ IU/mL, n (%)</td>
<td>41 (67)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>24 (39)</td>
</tr>
<tr>
<td>1b</td>
<td>21 (34)</td>
</tr>
<tr>
<td>2</td>
<td>8 (13)</td>
</tr>
<tr>
<td>3a</td>
<td>7 (12)</td>
</tr>
<tr>
<td>4</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Non-CC allele, n (%)</td>
<td>47/60 (78)</td>
</tr>
<tr>
<td>CTP score, n (%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>26 (43)</td>
</tr>
<tr>
<td>6</td>
<td>18 (30)</td>
</tr>
<tr>
<td>7</td>
<td>14 (23)</td>
</tr>
<tr>
<td>8</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Median MELD score, (range)</td>
<td>8 (6–14)</td>
</tr>
<tr>
<td>Prior HCV treatment, n (%)</td>
<td>46 (75)</td>
</tr>
</tbody>
</table>
Pre-Transplant Patient Disposition

SOF + RBV to Prevent HCV Recurrence Post-Transplant

- 61 patients enrolled and dosed
  - 12 D/C prior to LT
    - 2 due to AE*; 2 deaths
  - 5 completed 48 weeks of treatment and are in follow-up

- 46 patients received LT
  - HCV RNA < 25 IU/mL prior to LT
    - 43 patients
  - HCV RNA ≥ 25 IU/mL prior to LT
    - 3 patients

*AEs unrelated to study drug: acute renal failure, pneumonitis
Pre-Transplant On-Treatment Virological Response
SOF + RBV to Prevent HCV Recurrence Post-Transplant

Post-Transplant Virological Response
SOF + RBV to Prevent HCV Recurrence Post-Transplant

Post-Transplant Virological Response

Viral Response Rate (%)

<table>
<thead>
<tr>
<th></th>
<th>Transplant</th>
<th>pTVR 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41/44*</td>
<td>25/39*†</td>
</tr>
<tr>
<td>*3 subjects were &gt;LLOQ at transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>†1 subject has not reached PTVR12, 1 subject LTFU at Week 8 post transplant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post-Transplant Virological Response
SOF + RBV to Prevent HCV Recurrence Post-Transplant

HCV RNA < 25 IU/mL at time of transplantation 43/46

pTVR: 30/43 (70%)

Recurrent infection: 10/43 (23 %)

Death posttransplantation 03/43 (07 %)
Analysis of Post-Transplant Recurrence in GT 1–4
Days HCV RNA Continuously TND Prior to Transplant

No recurrence in 24/25 (96%) of patients who maintained HCV RNA TND > 4 weeks

- No recurrence: 95
- Recurrence: 5.5
  Median days TND
  - No recurrence: 95
  - Recurrence: 5.5
  \( p < 0.001 \)

*3 patients with recurrent HCV had 0 consecutive days TND before transplant.

Conclusions
Pre-Transplant SOF + RBV to Prevent HCV Recurrence Post-Transplant

♦ SOF + RBV treatment prior to transplantation prevented HCV recurrence in the majority (64%) of patients

♦ Achieving > 4 weeks of HCV RNA TND prior to transplant appears to be the strongest predictor of pTVR

♦ On treatment HCV RNA suppression was rapid and similar to other patient populations on SOF regimens

♦ Treatment with SOF + RBV was well tolerated
PREVENTION OF HCV RECURRENCE
PREVENTION OF HCV AND HCC RECURRENCE
PREVENTION OF HCV AND HCC RECURRENCE
PREVENTION OF HCV AND HCC RECURRENCE: OPEN ISSUES

1) Up to date regimen: Harvoni, 3DAA, others

2) Decompensated cirrhosis with HCV and HCC

3) Cadaveric versus Live donors (LRLD)

4) All genotypes

5) HCV without HCC: decompensated only
Ledipasvir/Sofosbuvir With Ribavirin for the Treatment of HCV in Patients With Post-Transplant Recurrence: Preliminary Results of a Prospective, Multicenter Study

K. Rajender Reddy1, Gregory T. Everson2, Steven L. Flamm3, Jill M. Denning4, Sarah Arterburn4, Theo Brandt-Sarif4, Phillip S. Pang4, Hadas Dvory-Sobol4, John G. McHutchison4, Michael P. Curry5, Michael Charlton6

1University of Pennsylvania School of Medicine, Philadelphia, PA; 2University of Colorado Denver, Aurora, CO; 3Northwestern Feinberg School of Medicine, Chicago, IL; 4Gilead Sciences, Inc., Foster City, CA; 5Beth Israel Deaconess Medical Center, Boston, MA; 6Intermountain Medical Center, Murray, UT
Study Design
GT 1 or 4: Post-Transplant F0–F3, CPT A, B, C

- 223 patients randomized 1:1 to 12 or 24 weeks of treatment
- GT 1 or 4 treatment-naïve or -experienced post-transplant patients
- Broad inclusion criteria:
  - Total bilirubin ≤10 mg/dL
  - Hemoglobin ≥10 g/dL
  - Platelets >30 x 10^3/µL
  - CLcr ≥40 mL/min
  - ≥3 months from liver transplant
  - No hepatocellular carcinoma
- Stratified at screening: F0–F3, CPT A, B, C
- RBV dosing:
  - F0–F3 and CPT A cirrhosis: weight-based
  - CPT B and C cirrhosis: dose escalation, 600–1200 mg/d

Reddy et al. AASLD 2014
Results: SVR12
GT 1 or 4: Post-Transplant F0–F3, CPT A, B, C

LDV/SOF + RBV 12 Weeks  |  LDV/SOF + RBV 24 Weeks

F0–F3
- 96/98
- 53/55
- 25/26

CPT A
- 96/96
- 55/56
- 24/25

CPT B
- 85/83
- 22/26
- 15/18

CPT C
- 60/67
- 3/5
- 2/3

8 CPT B 24 Week and 1 CPT C 24 Week subjects have not reached the Week 12 post-treatment visit.
Error bars represent 2-sided 90% exact confidence intervals.

Reddy et al. AASLD 2014
Laboratory Results: Change in MELD Score
Change From Baseline to Follow-Up Week 4

CPT A Patients (n=48)
- 12 Wk (n=23)
- 24 Wk (n=25)

CPT B Patients (n=41)
- 12 Wk (n=21)
- 24 Wk (n=20)

Missing FU-4: n=3 CPT A 12 wk; n=5 CPT B 12 wk; n=5 CPT B 24 wk
Reddy et al. AASLD2014
SOLAR 2 to be presented at: EASL, Vienna, 23 April 2015 !
In the US, many patients waiting for HCV referral have HCC or ESLD at the time of registration.
De novo HCC develops while patients are on the LT waiting list – mainly patients with HCV

UNOS data (2002–2011)
Standard exception (SE): Hepatocellular carcinoma (HCC)

Request criteria

A Biopsy

B AFP > 400 ng/ml and one positive result with/without hypervascularisation with imaging technique (Spiral-CT, MRI)

C Two positive results with/without hypervascularisation with imaging technique (Spiral-CT, MRI, Angiography). Two different techniques must be applied
Hepatocellular carcinoma (HCC): Milan criteria and treatment options

**Curative Options**

<table>
<thead>
<tr>
<th>Very early stage</th>
<th>Early stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 HCC &lt;2 cm Carcinoma in situ</td>
<td>1 HCC or 3 nodules &lt;3 cm, CP A or B, PS 0</td>
</tr>
</tbody>
</table>

- 1 HCC
- Portal pressure / bilirubin
- Normal
- High
- Associated diseases

**Bridging therapy (Germany)**

- Radiofrequency ablation (RFA)
- Transarterial chemoembolisation (TACE)
- Resection (Rx)

Recipient has one tumor ($\geq 2$ and) < 5 cm in diameter (Eurotransplant)

- Recipient has $\leq 3$ tumors each < 3 cm in diameter
- Recipient has no extrahepatic metastases
- Recipient has no macrovascular invasion

HCC: hepatocellular carcinoma  PV: portal  RFA: radiofrequency ablation

Greten TF et al, Z Gastroenterol. 2013
Treatment of pre-transplant HCC patients with compensated cirrhosis

Hepatocellular carcinoma

List patient for liver transplantation

Start bridging treatment

Single small nodule (<3cm)
- Child A

Portal hypertension
- Yes → RFA/MWA

Single large nodule (3-5 cm)
- Child A/B

Portal hypertension
- No → Resection

Up to 3 nodules (<3cm)
- Child A/B

Contraindications to TACE/RFA/resection
- Child A/B

Sequential TACE + RFA/MWA

Combined TACE + RFA/MWA

Sorafenib
Does liver function improve in patients with advanced HCV-associated liver cirrhosis by IFN-free antiviral therapies?
Study cohort - Hannover Medical School
patients with liver-cirrhosis

IFN-free treatment
n = 80

- sofosbuvir + ribavirin
  n = 56

- sofosbuvir + simeprevir +/- ribavirin
  n = 15

- sofosbuvir + daclatasvir +/- ribavirin
  n = 9

Deterding et al.; submitted
Conclusion

HCV treatment improves MELD Scores in patients with compensated and decompensated liver cirrhosis

consequences for liver transplantation!
IFN-free treatment options in the context of liver transplantation

- Who should be treated?
- When should be treated?
- How should be treated?
Algorithm for HCV in Liver Transplantation MHH 2015

HCV-infected patient on waiting list

- Child A/B, GFR>30
  - GT1
    - Sof/LDV+Riba 12 w
    - Sof/LDV  24 w
    - 3D+Riba 12-24 w
    - (Sof/Sim 12 w)
- GFR<30
  - comp. Cirrh.

HCV-recurrence after LTx

- GT1
  - 3D+Riba 24 w
- GT2
  - Sof+Riba 16 w
- GT3
  - Sof+Riba 24 w
  - Sof/LDV+RBV  24 w
  - Sof/DCV+RBV24 w

Decompensated cirrhosis: consider therapy after LTx

- GFR<30 comp. Cirrh.

HCV-re-cirrhosis after LTx

- Child A/B, GFR>30
  - GT1 or 4
    - Sof/LDV+RBV 12 w
    - 3D+RBV 24 w
  - GFR<30 comp. Cirrh.

- indiv. decision
  - also consider re-Tx