Case: Patient with Liver Cirrhosis – CPT A

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MEDIZINISCHE KLINIK 1

Case 2: Liver Cirrhosis, CPT A

- Mr. AB is a 52-year-old overweight male
- Works alternatively in day and night shifts
- Diagnosed for HCV genotype 1a infection more than 15 years ago
- Comorbidities:
  - Diabetes mellitus (not well controlled)
  - Gastroesophageal reflux disease
- Refused IFN-based therapies due to work and concerns about job
- Treated with sofosbuvir/ledipasvir for 12 weeks
  - HCV RNA was 28 IU/mL after 4 weeks therapy
  - Undetectable at week 8 and 12

Case 2: History (cont'd)

- Virologic relapse diagnosed 12 weeks after EoT
  - 4 weeks after EoT, HCV RNA was still undetectable
- Due to his shift work, he admitted to have switched the intake of medications from morning to evening and forgot the medication on individual days approximately 4-5 times
- Due to worsening heart burn, his GP increased the omeprazole dose from 20 mg to 2 x 40 mg for 8 weeks

Case 2: Past History, Medications, Physical Examination

Past History

- Diabetes
- Obesity
- GERD

Meds

- Metformin 2 x 1,000 mg
- Omeprazole 20 mg (intermittently increased to 2 x 40 mg due to worsening of reflux)

Physical Examination

- Blood pressure 150/90
- Heart rate 76/min
- BMI 32 kg/m^2

Case 2: Laboratory Tests

- Hemoglobin 14.5 g/dL
- WBC 5.4/mm^3
- Platelets 115,000/µL
- Albumin 4.0 mg/dL
- INR 1.0
- Creatinine 1.0 mg/dL
- Sodium 140 mEq/L
- Bilirubin 0.8 mg/dL
- ALT 86 U/L, AST 49 U/L, GGT 135 U/L
- HCV RNA 2,256,000 IU/ml, genotype 1a

Case 2: Ultrasound Results

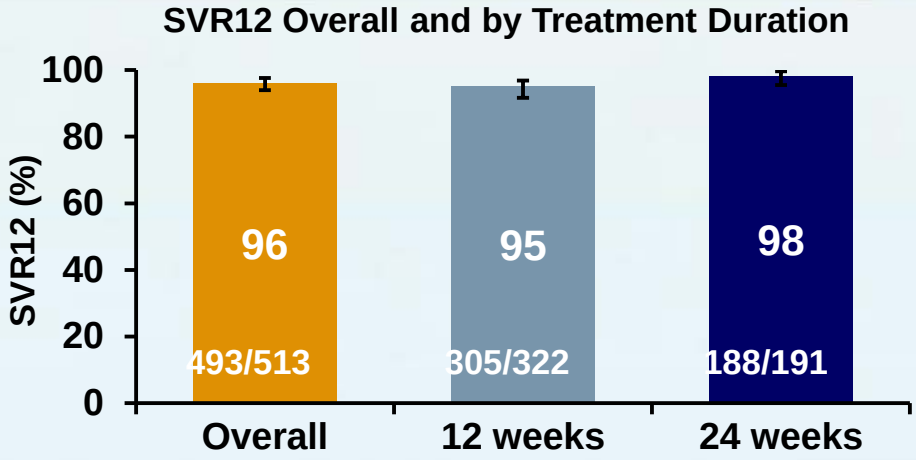
- Steatosis III
- No focal lesions
- Spleen 14.5 cm
- Stiffness 15.8 kPa (Fibroscan with XL probe)

Case 2: Question 1

Which of the following statements is most unlikely?

1. Non-compliance may have contributed to the virologic
   relapse after 12 weeks sofosbuvir/ledipasvir due to major
2. No virologic relapse, but rather HCV re-infection
3. Virologic relapse because treatment duration was too short and should have been 24 weeks, alternatively ribavirin should have been added to a 12 weeks treatment regimen
4. Virologic relapse due to omeprazole co-medication and insufficient bioavailability of ledipasvir

Compensated Cirrhosis Treated with LDV/SOF ± RBV



SVR12 by Treatment regimen		Total	Treatment-Naive	Treatment-Experienced
Overall SVR12		96%	98%	95%
Duration	12 wk	95%	97%	94%
	24 wk	98%	99%	98%
Regimen	LDV/SOF	95%	96%	95%
	LDV/SOF + RBV	97%	99%	96%
Duration/ ± RBV	LDV/SOF 12 wk	92%	96%	90%
	LDV/SOF + RBV 12 wk	96%	98%	96%
	LDV/SOF 24 wk	98%	97%	98%
	LDV/SOF + RBV 24 wk	100%	100%	100%

80 90 100 80 90 100 80 90 100

Bourlière M, et al. 65th AASLD; Boston, MA; November 7-11, 2014. Abst. 82.

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Guidelines: HCV Genotype 1

Population		EASL Recommendations 2015	AASLD/IDSA HCV Guidance 2015
TN	**No cirrhosis**	• LDV/SOF 12 weeks (8 weeks with caution, <6 MIU BL HCV)	• LDV/SOF 12 weeks (8 weeks at discretion of practitioner)
	Cirrhosis	• LDV/SOF + RBV 12 weeks or LDV/SOF 24 weeks (CI for RBV)	• LDV/SOF 12 weeks
TE (Peg-IFN + RBV)	**No cirrhosis**	• LDV/SOF 12 weeks	• LDV/SOF 12 weeks
	Cirrhosis	• LDV/SOF + RBV 12 weeks or LDV/SOF 24 weeks (CI for RBV) • LDV/SOF + RBV 24 weeks (negative predictors)	• LDV/SOF 24 weeks or LDV/SOF + RBV 12 weeks

EASL: IFN-containing options still acceptable for HCV-1 (PEG-IFN + RBV + SOF or SIM)

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Sofosbuvir and Ledipasvir: Effect of Acid Reducing Agents

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Acid Reducing Agents:	↓ Ledipasvir	Ledipasvir solubility decreases as pH increases, Drugs that increase gastric pH are expected to decrease concentration of ledipasvir
Antacids (e.g., aluminum and magnesium hydroxide)		It is recommended to separate antacid and [sofosbuvir/ledipasvir] administration by 4 hours
H_2-receptor antagonists (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from [sofosbuvir/ledipasvir] at a dose that does not exceed doses comparable to famotidine 40 mg twice daily
Proton-pump inhibitors (e.g., omeprazole)		Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with [sofosbuvir/ledipasvir] under fasted conditions

German P, et al. Effect of food and acid reducing agents on the relative bioavailability and pharmacokinetics of ledipasvir/sofosbuvir fixed dose combination tablet [abstract 15]; 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy; Washington, D.C. 2014; Harvoni [package insert]. Foster City, CA: Gilead Sciences, Inc. 2015.

Case 2: Follow-Up

- RAV testing (population sequencing) was performed and revealed a Y93H mutation in the NS5A gene
- Patient was carefully counseled with respect to optimal compliance
- He was advised against the concurrent use of (higher dose) PPIs with an NS5A inhibitor

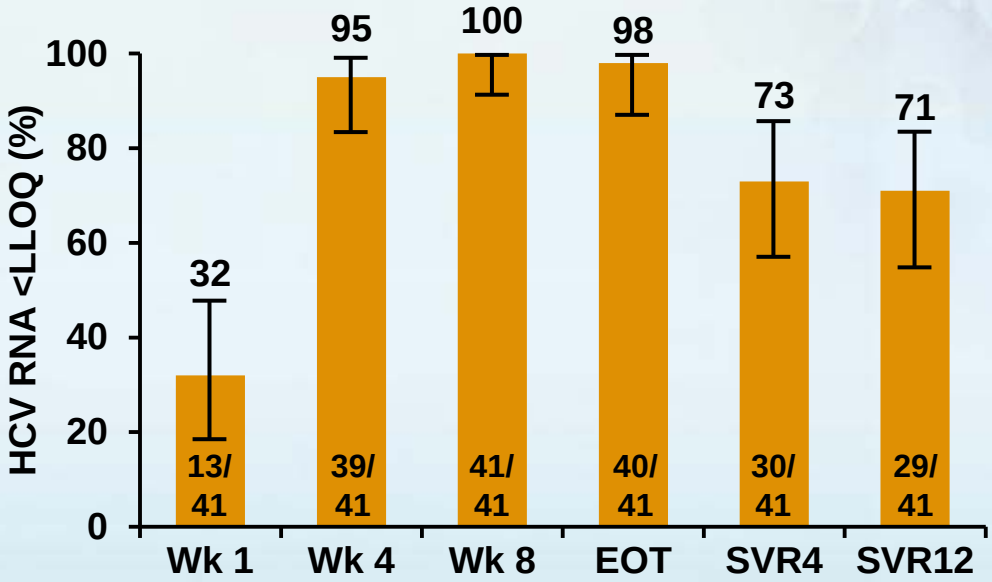
Case 2: Question 2

Which of the following statements is true?

1. No re-treatment options are available for patients who fail sofosbuvir/ledipasvir and have a confirmed Y93H RAV
2. Only IFN-based treatment options are reasonable for this patient
3. Recommended retreatment schedule is sofosbuvir/ledipasvir or sofosbuvir/daclatasvir for 24 weeks plus ribavirin
4. Sofosbuvir/simeprevir with or without RBV would be the alternative treatment option of choice

LDV/SOF for 24 Weeks in Patients Who Failed 8 or 12 Weeks of LDV/SOF-based Regimens

- 41 patients who failed LDV/SOF retreated for 24 weeks LDV/SOF
  - Prior Tx
    - LDV/SOF ± RBV; n=33 (80%)
    - LDV/SOF + GS-9669; n=8 (20%)
  - Tx durations
    - 8-wk Tx; n=30
    - 12-wk Tx; n=11
  - Cirrhosis; n=19 (46%)



- Safety
  - No d/c due to AE
    - HA (15%); fatigue (10%)
    - Grade 3 AE (7%) and SAE (5%)
      - None related to Tx

- Baseline resistance
  - 8-wk Tx; n=30
    - NS5A resistance; n=19 (63%)
    - No NS5B resistance
  - 12-wk Tx; n=11
    - NS5A resistance; n=11 (100%)
    - No NS5B resistance

- Post-Tx resistance
  - NS5B; n/N = 4/12 (33%)
    - S282T (n=2)
    - L159F (n=1)
    - Double-mutant S282T + L159F (n=1)

*Breakthrough

Lawitz E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O005.

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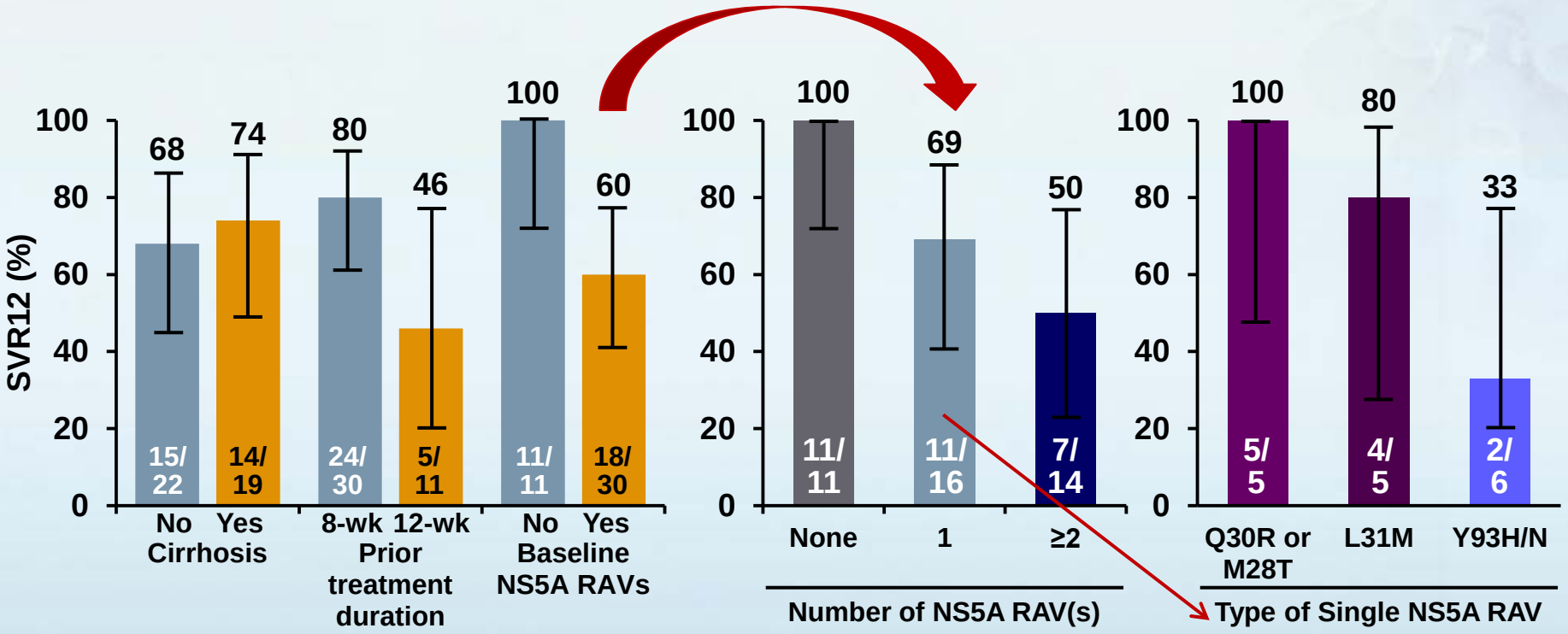
Lawitz: Treatment Duration and RAVs



- Shorter therapies produce less-frequent treatment-emergent RAVs
- More complex RAV pattern = less likely to achieve response
- Retreatment with longer duration more likely to be successful with fewer NS5A RAVs or RAVS with smaller shifts in EC_{50}

Lawitz E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O005.

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Case 2: Follow-Up (Cont.)

- Population sequencing of the NS3A region excluded the presence of a Q80K RAV
- Patient started on a regimen of sofosbuvir + simeprevir + ribavirin
- Planned treatment duration 12 weeks

Case 2: Summary

- Importance of compliance
- PK issues of NS5A inhibitors with PPIs
- Relevance of RAV selection
- What would have been the treatment option if Q80K RAV would have been present?
- Retreatment options