IX. ULUSAL VİRAL HEPATİT SİMPOZYUMU

12-14 MAYIS 2017

ANEMON MALATYA HOTEL

AKUT HEPATİTTEN TRANSPLANTASYONA

UVHS

ULUSAL VİRAL HEPATİT SİMPOZYUMU

KLİMİK

TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

Transplantasyon Sonrası Viral Hepatit C Yönetimi

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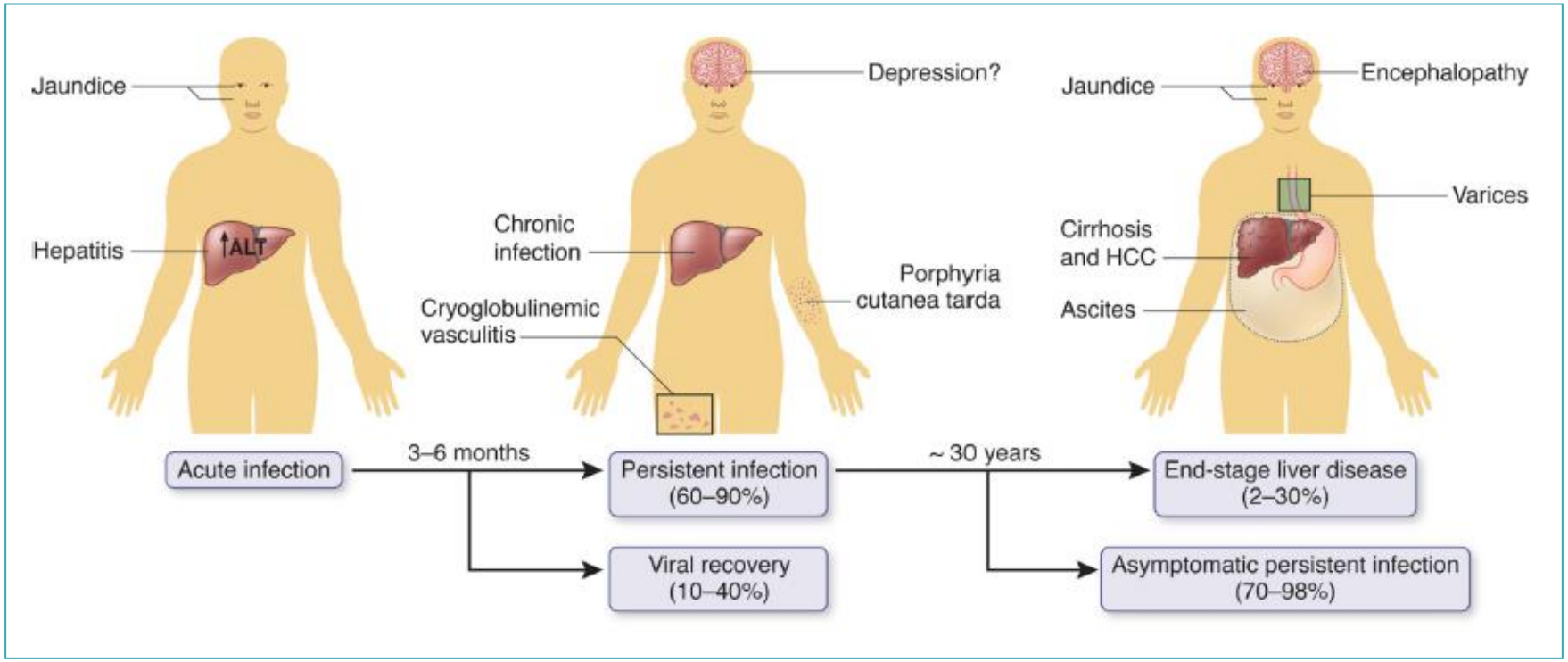
14.05.2017

UVHS, Malatya

Hepatit C: Doğal seyir



Thomas DL. Nat Med 2013;19(7):850–858

Nakil sonrası nüks

- Nakil sırasında saptanabilir HCV RNA'sı olan hastalarda nüks hızlı ve evrensel

- Nakil sonrası gelişen nüks HCV infeksiyonu daha agresif, siroza ve dekompanzasyona ilerlemesi nakil yapılmayan hastalara göre çok daha hızlı
  - Hastaların %25-30'unda 5 yılda siroz
  - Hastaların %50'sinde 10 yılda siroz

Nakil sonrası nüks

- Nakil karaciğerin nüks HCV infeksiyonu 2 farklı form halinde görülebilir
- Nüks kronik hepatit C infeksiyonu
  - Nakil yapılmamış hastalardakine benzer
  - Yıllık fibrozis oranı biraz hızlanmıştır (%0.2'ye karşın 0.5)
  - Hastaların %90'ında bu formdadır
- Hastaların %10'undan azında nüksün ciddi formu gelişir:
  - Fibrotizan kolestatik hepatit

Fibrotizan kolestatik hepatit

- Prognozu çok daha kötü
- Kolestazla birlikte serum total bilirubini 6 mg/dl'den fazla, ALP en az 5 kat yüksek, viral yük artmıştır
- Karaciğer histolojisinde kolestaz, sentrilobular balonlaşma ve spotty hepatosit nekrozu, Kupffer cell hipertrofisi ve portal kanal inflamasyonu bulunur
- Sıklıkla nakili takiben ilk 6 ayda görülür
- Tedavi edilmezse ilerleyici greft kaybı sonucu karaciğer yetmezliği ve 1-2 yıl içinde ölüme neden olur

Nakil sonrası nüks HCV'de tedavi

- IFN bazlı rejimler
  - Özellikle ciddi formda tolere edilemez, etkinlik düşük (%13-27) ve ilaç etkileşimi fazla
- Üçlü tedaviler
  - Etkinlik biraz daha iyi (%47-61) ancak yan etki ve ilaç etkileşimi daha fazla
- Retransplantasyon
  - Geriye kalan seçenek
  - Zorla yapılmış olduğu için uzun dönem sonuçları ilk nakile göre daha kötü

- Daha potent, daha iyi tolere edilebilen ve daha az ilaç etkileşiminin olduğu tedavilere ihtiyaç var

Nakil ne zaman yapılmalı?

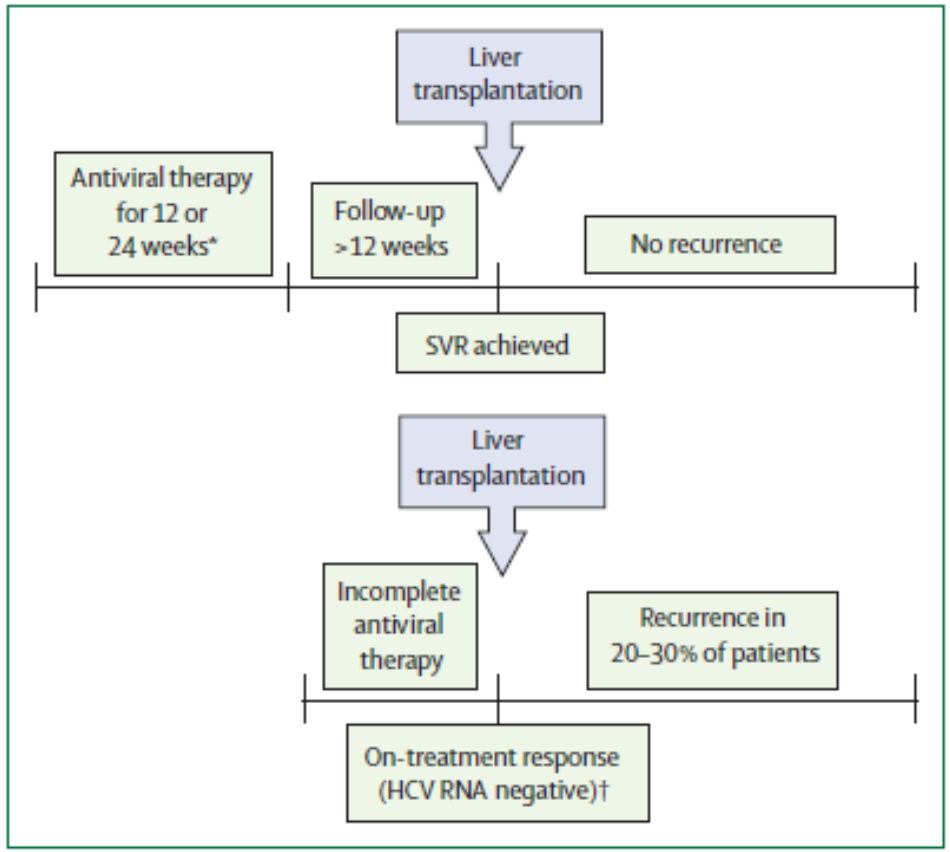


***Figure 1*: Strategies to prevent recurrence of HCV infection in liver transplant recipients**

Doğrudan Etkili Antiviraller

- Yeni DEA ilaçlar, farklı hasta gruplarında tedaviye izin vermekte
  - HCV'ye bağlı nakil adayları
  - İlerlemiş karaciğer hastalığı olan hastalar
  - Nüks hepatiti olan alıcılar
  - Hem HCV hem de nakille ilgili komorbiditesi olan hastalar

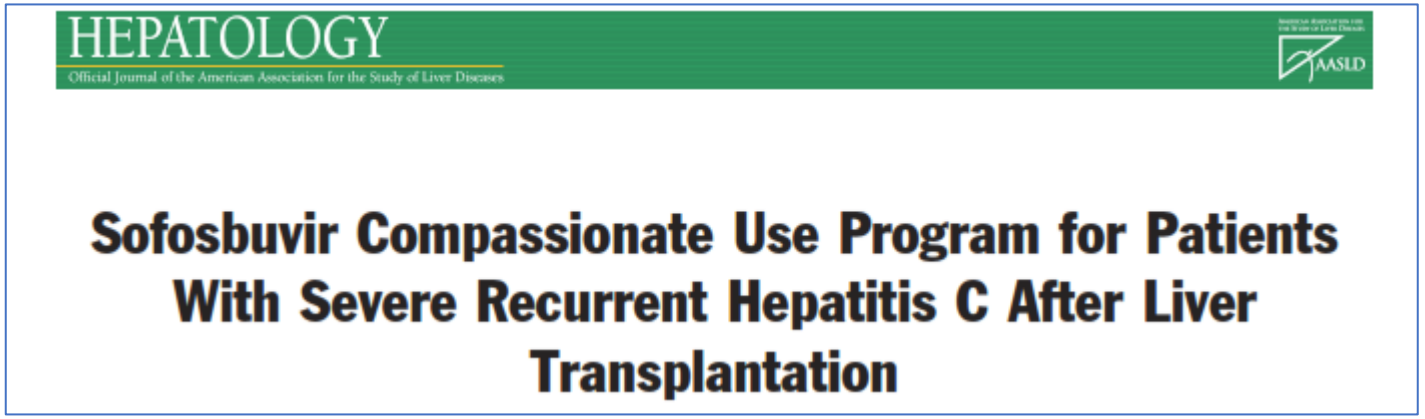
Sofosbuvir + ribavirin

Sofosbuvir + ribavirin

- 40 nakil sonrası hasta
- 24 hf SOF + RBV (400 mg/gün başlanıp tolere edilirse 1200 mg/gün)

Demografik özellikler	Hasta
Daha önce tedavi alan hasta	35
	11 nakil öncesi
	18 nakil sonrası
	6 hem nakil öncesi hem sonrası tedavi alan hasta
Daha önceki tedavi	9 hasta üçlü tedavi
Ortalama yaş	59
G1	%83
Siroz	%40
Nakil sonrası geçen süre	4,3 yıl
Tacrolimus alan hasta	%70

Charlton M. Gastroenterology 2015;148:108-17.



- Ciddi rekürren hepatit C
  - Fibrotizan kolestatik hepatitis (FCH) ve
  - Dekompanze siroz, 1 yıldan az yaşam beklentisi olan hastalar

- 52 hasta erken ciddi rekürrens (nakil sonrası <12 ayda tanı konan)
- 52 hasta siroz (nakil sonrası >12 ayda tanı konan)
- 12 hastaya yeniden transplantasyon
  - Etkinlik analizi 92 hastada yapılmış

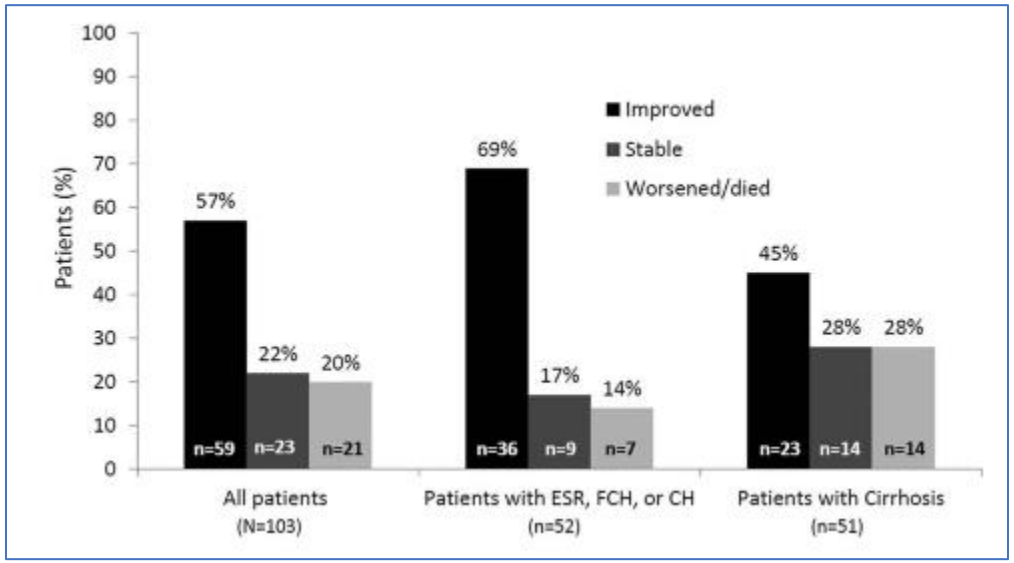
Forns X. Hepatology 2015;61:1485-149

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Sofosbuvir Compassionate Use Program for Patients With Severe Recurrent Hepatitis C After Liver Transplantation

Table 2. Response (HCV RNA <25 IU/mL) During and After Treatment

	Overall (N = 104)	Acute Hepatitis and Early Severe Recurrence (N = 52)	Compensated and Decompensated Cirrhosis (N = 52)
During treatment, % (n/n) %*			
At week 4	56/104 (54)	24/52 (46)	33/51 (65)
At week 12	82/104 (79)	42/50 (84)	40/49 (82)
At week 24	76/96 (73)	38/48 (79)	38/47 (81)
In post-treatment follow-up, n (%)			
At week 4 (SVR4)	62/93 (67)	38/48 (79)	24/46 (52)
At week 12 (SVR12)	54/92† (59)	35/48† (73)	19/44† (43)
Virological failure (%)			
On-treatment failure	0	0	0
Relapse	19/92 (21)	4/48 (8)	15/44 (34)
Lost to follow-up	2/92 (2)	2/48 (4)	0
Discontinuation because of SAE	3/92 (3)	1/48 (2)	2/44 (5)
Discontinuation because of nonadherence	1/92 (1)	0	1/44 (2)
Death	13/92 (14)	6/48 (13)	7/44 (16)



Forns X. Hepatology 2015;61:1485-149

Simeprevir/sofosbuvir

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Safety and Efficacy of Simeprevir/Sofosbuvir in Hepatitis C–Infected Patients With Compensated and Decompensated Cirrhosis

Table 1. Characteristics of Patients Treated With SIM+SOF by Baseline CP Class (B/C vs. A)

Characteristic at Start of Treatment	CP Class B/C (n = 55)	CP Class A (n = 101)	*P* Value
Age, years, median (IQR)	61 (58-64)	62 (58-67)	0.14
Male, no. (%)	27 (49)	68 (67)	0.03
Race/ethnicity, no. (%)			0.01
White, non-Hispanic	31 (56)	68 (67)	
Hispanic	12 (22)	5 (5)	
African American	9 (16)	17 (17)	
Asian	0 (0)	6 (6)	
Other	3 (5)	5 (5)	
Diabetes, no. (%)	15 (35)	40 (72)	0.84
Hemoglobin A1c, %, median (IQR)	6.9 (6.4-8.6)	6.5 (6.1-7.5)	0.13
Clinical diagnosis of HTN, no. (%)	18 (33)	51 (51)	0.03
Dyslipidemia requiring medication, no. (%)	2 (4)	13 (13)	0.07
Genotype 1a (vs. 1b), no. (%)	32 (58)	66 (65)	0.41
Q80K polymorphism, no. (%) [n = 24]	5 (45)	6 (46)	0.97
Previous treatment, no. (%)	34 (62)	52 (51)	0.22
Telaprevir or boceprevir triple therapy, no. (%)	7 (21)	6 (12)	0.26
Null/partial responders, no. (%)	26 (76)	37 (71)	0.81
Total bilirubin, mg/dL, median (IQR)	1.7 (1.2-2.4)	0.9 (0.7-1.2)	<0.01
INR, median (IQR)	1.3 (1.2-1.4)	1.1 (1.0-1.2)	<0.01
Albumin, g/dL, median (IQR)	3 (2.7-3.3)	3.9 (3.5-4.2)	<0.01
Platelet count, 1 K/mm^3, median (IQR)	78 (62-107)	111 (81-160)	<0.01
Creatinine, mg/dL, median (IQR)	0.85 (0.7-1.05)	0.83 (0.7-0.97)	0.40
Creatinine clearance*, mL/min/1.73 m^2, median (IQR)	77 (53-91)	81 (67-97)	0.09
Baseline HCV VL, log IU/mL, median (IQR)	5.9 (5.4-6.4)	6.4 (6.1-6.7)	<0.01
Any HE†, no. (%)	27 (49)	8 (8)	<0.01
Any ascites‡, no. (%)	35 (64)	3 (3)	<0.01
Nonbleeding or bleeding varices, no. (%)	19 (35)	5 (5)	<0.01
HCC, no. (%)	4 (7)	12 (12)	0.37
MELD, median (IQR)	12 (10-14)	8 (7-9)	<0.01

Saxena V. Hepatology 2015;62:715-725

HEPATOLOGY
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Safety and Efficacy of Simeprevir/Sofosbuvir in Hepatitis C–Infected Patients With Compensated and Decompensated Cirrhosis

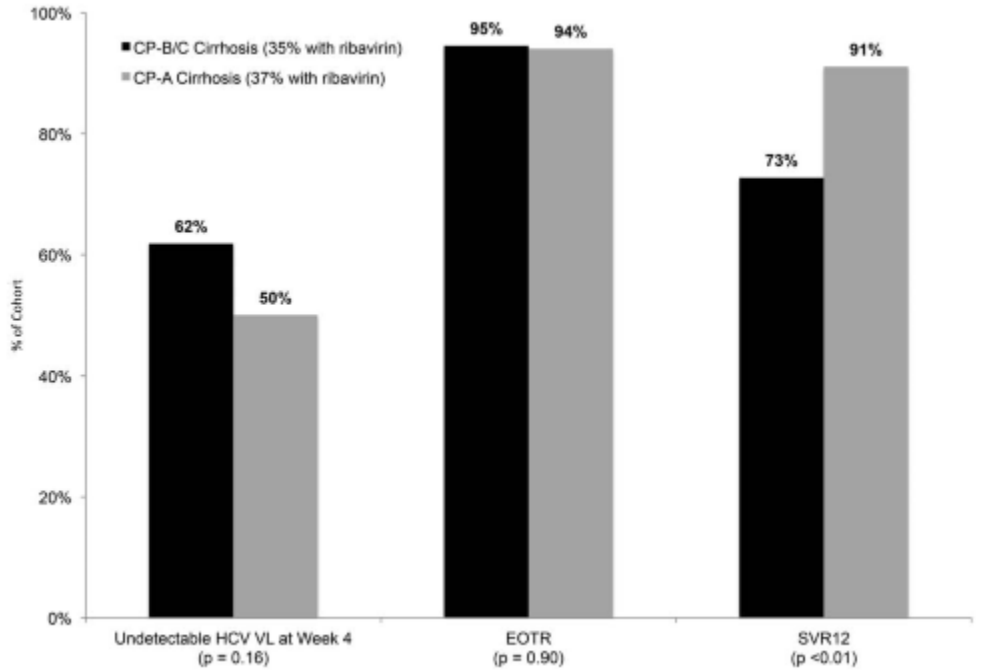

Table 3. Safety Outcomes In Patients Treated With SIM+SOF

Safety Outcome	CP Class B/C (n = 55)	CP Class A (n = 101)	*P* Value
CP score change from baseline to end of treatment, median (range)	0 (−2, 5)	0 (−1, 2)	0.46
MELD score change from baseline to end of treatment, median (range)	0 (−4, 7)	0 (−3, 8)	0.36
Early treatment discontinuation, no. (%)	6 (11)	1 (1)	<0.01
Early treatment discontinuation owing to AE, no. (%)	5 (9)	1 (1)	0.01
Hospitalization owing to AE, no. (%)	12 (22)	2 (2)	<0.01
Infection requiring antibiotics, no. (%)	11 (20)	1 (1)	<0.01
Hepatic decompensation, no. (%)	11 (20)	3 (3)	<0.01
Death, no. (%)	1 (2)*	1 (1)†	0.66

*Liver-related death.
†Not liver-related death.

Saxena V. Hepatology 2015;62:715-725

HEPATOLOGY
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Safety and Efficacy of Simeprevir/Sofosbuvir in Hepatitis C–Infected Patients With Compensated and Decompensated Cirrhosis

Table 2. Uni- and Multivariate Predictors of SVR12 in Patients Treated With SIM+SOF

	All Patients (n = 160)					
	Univariate*		Multivariate 1†‡		Multivariate 2†§	
Baseline Covariate	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CP-B/C cirrhosis	0.26 (0.11-0.65)	<0.01	0.27 (0.09-0.80)	0.02	–	–
Total bilirubin ≥1.3 mg/dL	0.45 (0.19-1.068	0.07	–	–	–	–
Albumin ≥3.5 g/dL	5.25 (1.95-14.1)	<0.01	–	–	4.17 (1.44-11.8)	0.01
Platelets ≥100 K/mm^3	2.73 (1.06-7.01)	0.04	2.19 (1.17-6.45)	0.02	2.42 (1.09-7.12)	0.04
Any HE	0.41 (0.16-1.04)	0.06	–	–	–	–
Any ascites	0.47 (0.19-1.18)	0.11	–	–	–	–
MELD, per 1 unit	0.90 (0.77-1.04)	0.15	–	–	–	–

Table 5. Uni- and Multivariate Predictors of Hepatic Decompensation in Patients Treated With SIM+SOF

	Univariate*		Multivariate 1†‡		Multivariate 2†§	
Baseline Covariate	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CP-B/C cirrhosis	8.12 (2.17-30.7)	<0.01	10.5 (2.03-54.1)	<0.01	–	–
Total bilirubin ≥1.3 mg/dL	9.81 (2.63-36.5)	<0.01	–	–	7.29 (1.72-31.0)	<0.01
INR ≥1.3	1.88 (0.74-3.01)	<0.01			–	–
Albumin ≥3.5 g/dL	0.17 (0.05-0.65)	<0.01	–	–	–	–
Platelets ≥100 K/mm^3	0.48 (0.16-1.47)	0.19	–	–	–	–
Any HE	6.56 (2.15-19.8)	<0.01	–	–	4.82 (1.27-18.4)	0.02
Any ascites	4.20 (1.41-12.5)	0.01	–	–	–	–
MELD, per 1 unit	1.34 (1.13-1.59)	<0.01	–	–	–	–

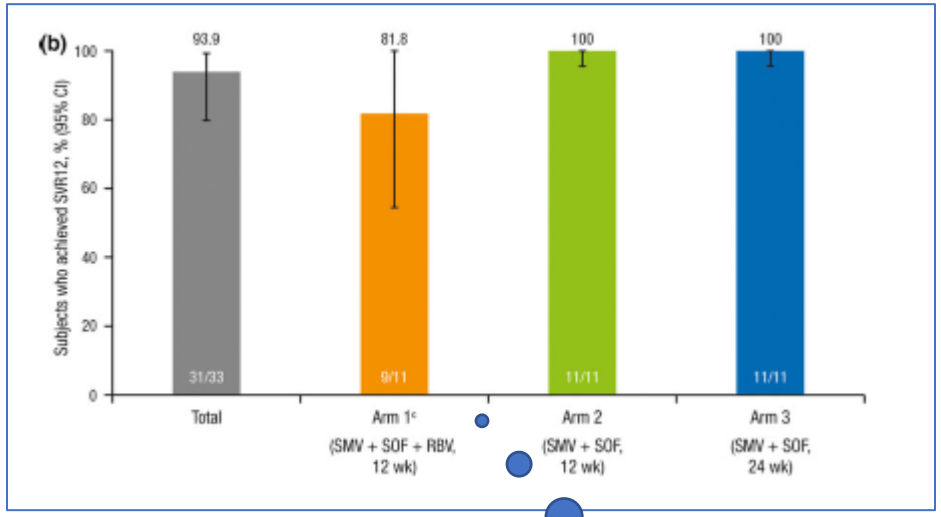
Saxena V. Hepatology 2015;62:715-725

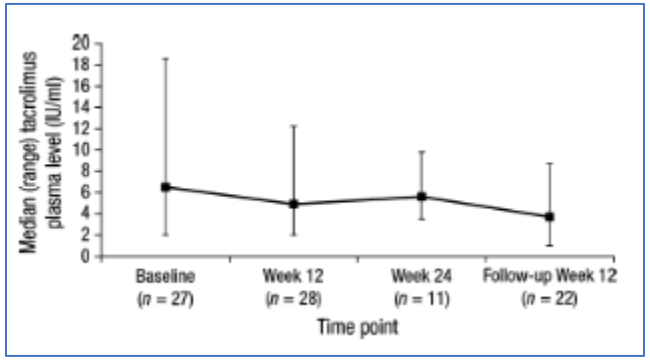
Transplant International

ORIGINAL ARTICLE

Efficacy and safety of simeprevir and sofosbuvir with and without ribavirin in subjects with recurrent genotype 1 hepatitis C postorthotopic liver transplant: the randomized GALAXY study

Arm 1	Arm 2	Arm 3	Arm 3 (nonrandomized)
SMV + SOF + RBV 12 wk (*n* = 11 analyzed)	SMV + SOF 12 wk (*n* = 11 analyzed)	SMV + SOF 24 wk (*n* = 11 analyzed)	SMV + SOF 24 wk (*n* = 13 analyzed)





Bu çalışmada sirozu olan hasta yok

O'Learly JG. Transplant International 2017; 30: 196–208

BMJ Open Gastroenterology

Tolerability and effectiveness of sofosbuvir and simeprevir in the post-transplant setting: systematic review and meta-analysis

Table 1 Study characteristics*

First author, year	Collaboration	Sample size with SVR12 data	Proportion of genotype 1a (%)	In combination with ribavirin†	Age (years)	Male, N (%)	Advanced fibrosis, N (%)	Median or mean time to post-LT treatment in months or years	Proportion with tacrolimus use (%)
Pungpapong, 2015[13]	Multicentre	105	60	Mix	61.6±6	77 (76)	37 (37)	32 (2–317) months	91
Gutierrez, 2015[16]	Single centre	61	57	Without	60.2±9.3	22 (59)	14 (38)	5.4 years (1.9–8.4)	80
Gordon, 2014[17]	Single centre	15	–	Without	–	–	1 (6)	–	82
Suliman, 2014[11]	Single centre	8	90	Without	62.5	6 (60)	–	–	–
Lutchman, 2014[15]	Single centre	31	64	Without	61.2±7.1	43 (81)	11 (33)	47.0 (1.4–1278.3) months	96
Nair, 2014[14]	Single centre	27	70	With	56±5	28 (61)	19 (41)	0.9±1.6 years	78
Ripper, 2014[12]	Single centre	23	60	Mix	60.9	21 (84)	7 (28)	32.3 (2–215.2) months	76
Crittenden, 2014[19]	Single centre	18	74	Mix	–	–	–	–	–
Ford, 2014[18]	Single centre	37	68	Mix	57	27 (73)	8 (22)	–	62

*Proportions and mean±SD were provided/abstracted from the total number of patients available from each study.
†Classification of studies that included patients: with ribavirin, without ribavirin, or a mix of patients with and without ribavirin.
LT, liver transplantation; SVR, sustained virological response.

Nguyen NH. BMJ Open Gastro 2016;3:e000066.

BMJ Open Gastroenterology

Tolerability and effectiveness of sofosbuvir and simeprevir in the post-transplant setting: systematic review and meta-analysis

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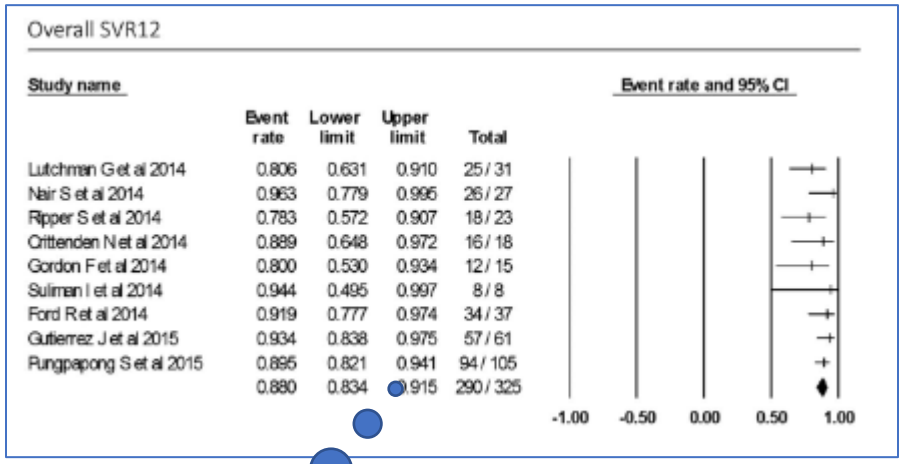
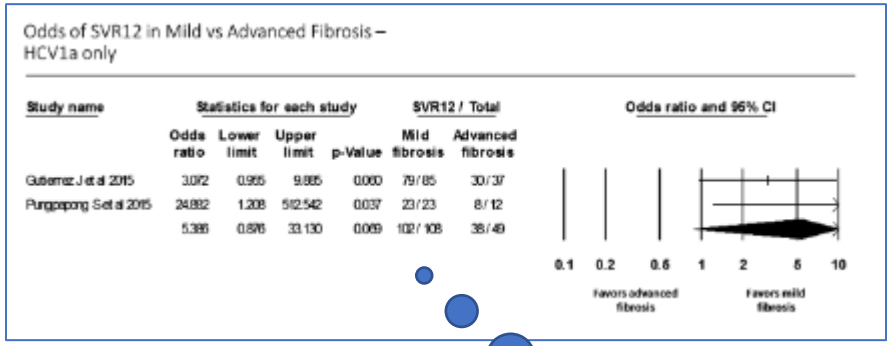


KVY %88



Hafif fibrozis %93,6
İleri fibrozis %76,9

Nguyen NH. BMJ Open Gastro 2016;3:e000066.

Simeprevir/sofosbuvir

- Simeprevir içeren rejimler dekompanze sirozu olan nakil sonrası nüks HCV infeksiyonunda önerilmemekte

Paritaprevir/ritonavir/ombitasvir ± dasabuvir

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Interferon-free Antiviral Regimen for HCV after Liver Transplantation

34 nakil sonrası hastada PROD+RBV, 24 hafta

Table 2. **Response during and after Treatment.**

Outcome	Patients with Outcome	
	no.	*% (95% CI)*
HCV RNA <25 IU/ml		
During treatment period		
At wk 4	34	100 (90–100)
At wk 24	34	100 (90–100)
After end of treatment		
At wk 4	33	97 (85–100)
At wk 12	33	97 (85–100)
At wk 24	33	97 (85–100)
Virologic failure during treatment	0	0 (0–10)
Relapse*	1	3 (0–15)

Neither tacrolimus nor cyclosporine substantially altered the trough concentrations of ombitasvir, ABT-450, dasabuvir, or ribavirin. The trough concentrations of the study drugs were within the range observed in phase 2 and 3 studies of this regimen.[27-31,34]

Metavir fibrosis score — no. (%)¶	
F0	6 (18)
F1	13 (38)
F2	15 (44)

Kwo PY. N Engl J Med 2014;371:2375-82.

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie

Safety Announcement

[10-22-2015] The U.S. Food and Drug Administration (FDA) is warning that hepatitis C treatments Viekira Pak and Technivie can cause serious liver injury mostly in patients with underlying advanced liver disease. As a result, we are requiring the manufacturer to add new information about this safety risk to the drug labels.

FDA emphasizes that Viekira Pak and Technivie are contraindicated in moderate and severe hepatic impairment (Child-Pugh Class B & C). Technivie is not indicated for use in patients with cirrhosis. Some of the postmarketing cases of hepatic failure occurred in patients for whom Viekira Pak and Technivie are contraindicated or not recommended. Some cases provided insufficient data to definitively assess baseline liver status.

Nakil sonrası ileri düzey karaciğer hastalığı olan alıcılarda PROD kontrendike

Ayrıca ilaç-ilaç etkileşimleri yönünden de sorun var

Daclatasvir/sofosbuvir

HEPATOLOGY, VOL. 63, NO. 5, 2016

Daclatasvir With Sofosbuvir and Ribavirin for Hepatitis C Virus Infection With Advanced Cirrhosis or Post-Liver Transplantation Recurrence

ALLY-1

TABLE 1. Demographics and Baseline Disease Characteristics

	Advanced Cirrhosis Cohort (n = 60)	Posttransplantation Cohort (n = 53)
Age, years, median (range)	58 (19-75)	59 (22-82)
Sex, n (%)		
Female	22 (37)	15 (28)
Male	38 (63)	38 (72)
Race, n (%)		
White	57 (95)	51 (96)
Black/African American	3 (5)	1 (2)
Asian	0 (0)	1 (2)
Ethnicity, n (%)		
Hispanic/Latino	25 (42)	13 (25)
Non-Hispanic/Latino	35 (58)	40 (75)
Body mass index, n (%)		
<25 kg/m^2	13 (22)	10 (19)
25 to <30 kg/m^2	27 (45)	27 (51)
≥30 kg/m^2	20 (33)	16 (30)
Hemoglobin, g/dL, median (range)	12.80 (8.7-16.3)	13.40 (7.9-16.6)
Creatinine, mg/dL, median (range)	0.84 (0.51-1.81)	1.18 (0.63-2.23)
HCV genotype, n (%)		
1	45 (75)	41 (77)
1a	34 (57)	31 (58)
1b	11 (18)	10 (19)
2	5 (8)	0
3	6 (10)	11 (21)
Estimated METAVIR fibrosis score, n (%)*		
F0	NA	6 (11)
F1	NA	10 (19)
F2	NA	7 (13)
F3	NA	13 (25)
F4	NA	16 (30)
Not reported	NA	1 (2)
MELD score, median (range)	13 (8-27)	NA
Immunosuppressive agents, n (%)		
Tacrolimus	NA	44 (83)
Cyclosporine	NA	6 (11)
Sirolimus	NA	3 (6)
Mycophenolic acid	NA	10 (19)

Poordad F. Hepatology 2016;63:1493-150

HEPATOLOGY, VOL. 63, NO. 5, 2016

Daclatasvir With Sofosbuvir and Ribavirin for Hepatitis C Virus Infection With Advanced Cirrhosis or Post-Liver Transplantation Recurrence

TABLE 3. SVR12 by Baseline Disease Characteristics

	Advanced Cirrhosis Cohort		Posttransplantation Cohort	
	% (n/N)	95% CI	% (n/N)	95% CI
All patients	83 (50/60)*,†	71.5%-91.7%	94 (50/53)	84.3%-98.8%
Child-Pugh class				
A	92 (11/12)	—	—	—
B	94 (30/32)	—	—	—
C	56 (9/16)	—	—	—
Genotype 1	82 (37/45)‡	68%-92%	95 (39/41)‡	84%-99%
Genotype 1a	76 (26/34)	—	97 (30/31)	—
Genotype 1b	100 (11/11)	—	90 (9/10)	—
Child-Pugh class				
A	91 (10/11)	—	—	—
B	92 (22/24)	—	—	—
C	50 (5/10)	—	—	—
Genotype 2	80 (4/5)	—	—	—
Genotype 3	83 (5/6)*	—	91 (10/11)	—
Genotype 4	100 (4/4)†	—	—	—
Genotype 6	—	—	100 (1/1)	—

Poordad F. Hepatology 2016;63:1493-150

Daclatasvir Combined With Sofosbuvir or Simeprevir in Liver Transplant Recipients With Severe Recurrent Hepatitis C Infection

TABLE 1. BL Characteristics of Evaluable Patients

Patient Characteristics	All Patients (n = 97)*	DCV + SOF ± RBV (n = 77)	DCV + SMV ± RBV (n = 18)
Age, mean (SD), years	59.3 (8.2)	59.6 (8.4)	58.5 (7.7)
Sex, male, n (%)	65 (67)	53 (69)	10 (56)
Race, n (%)			
White	79 (81)	60 (78)	18 (100)
African American	6 (6)	6 (8)	0
Asian	1 (1)	0	0
Other	11 (11)	11 (14)	0
Time from most recent LT to start of DCV therapy, mean (SD), months	44.5 (55.0)	42.7 (52.8)	55.1 (66.1)
HCV genotype, n (%)			
1a	38 (39)	36 (47)	2 (11)
1b	46 (47)	29 (38)	16 (89)
1 (subtype unknown)	6 (6)	6 (8)	0 (0)
2	1 (1)	1 (1)	0 (0)
3	2 (2)	2 (3)	0 (0)
4	4 (4)	3 (4)	0 (0)
HCV RNA, mean (SD), × 6 $\log_{10}$ IU/mL	14.3 (68.8)	16.3 (76.9)	7.0 (13.0)
ALT, mean (SD), IU/L	142 (357)	157 (398)	85 (76)
Alkaline phosphatase, mean (SD), IU/L†	189 (114)	187 (118)	200 (104)
Total bilirubin, mean (SD), mg/dL‡	3.8 (7.0)	4.3 (7.7)	1.7 (1.2)
Hemoglobin, mean (SD), g/dL	11.5 (2.1)	11.5 (2.3)	11.7 (1.5)
INR, mean (SD)§	1.2 (0.3)	1.2 (0.3)	1.1 (0.2)
Creatinine, mean (SD), mg/dL	1.1 (0.4)	1.1 (0.4)	1.1 (0.3)
CTP score, mean (SD)	7.0 (2.0)	7.2 (2.1)	6.6 (1.7)
CTP class, n (%)			
A (5-6)	49 (51)	36 (47)	12 (67)
B (7-9)	30 (31)	24 (31)	5 (28)
C (10-15)	12 (12)	11 (14)	1 (6)
Missing	6 (6)	6 (8)	0 (0)
MELD score, mean (SD)	13.0 (6.0)	13.5 (6.3)	11.0 (4.3)
Biopsy-proven cirrhosis, n (%)‖	30 (31)	19 (25)	11 (61)
HIV coinfection, n (%)	9 (9)	6 (8)	2 (11)
Severe cholestatic HCV, n (%)	36 (37)	31 (40)	4 (22)
Time from LT to start of DCV therapy, mean (SD), months	16.9 (19.5)	17.4 (20.3)	14.1 (15.6)

Yaklaşık %40'ı CP B/C

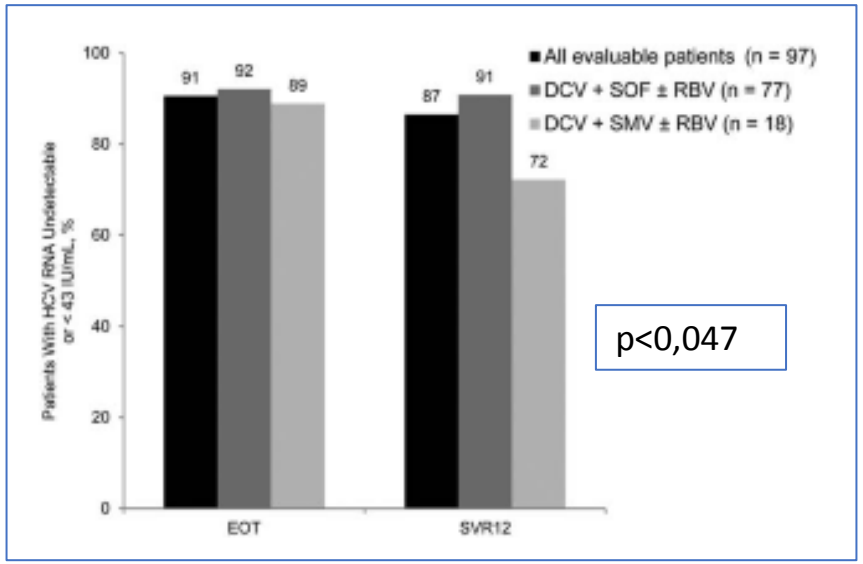
%40 FCH

Fontana RJ. Liver Transplantation 2016;22:446-458

Daclatasvir Combined With Sofosbuvir or Simeprevir in Liver Transplant Recipients With Severe Recurrent Hepatitis C Infection

TABLE 2. BL Characteristics and Virological Outcome in Patients With and Without Severe Cholestatic HCV

	Patients With Severe Cholestatic HCV (n = 36)		Patients Without Severe Cholestatic HCV* (n = 61)	
DCV-based regimen, n (%)				
DCV + SOF	23 (64)		34 (56)	
DCV + SOF + RBV	8 (22)		12 (20)	
DCV + SMV	1 (3)		5 (8)	
DCV + SMV + RBV	3 (8)		9 (15)	
DCV + SMV + SOF + RBV	1 (3)		1 (2)	
RBV users	12 (33)		22 (36)	
Treatment duration, mean (SD), weeks¶	22.5 (5.6)		24.3 (7.4)	
SVR12, n (%)				
Undetectable	21 (58)	%86	44 (72)	%87
Detected, but < 43 IU/mL	10 (28)		9 (15)	
Not available (any reason)**	5 (14)		6 (10)	

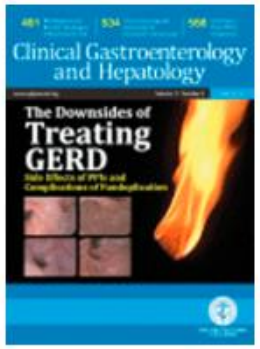


HIV koinfekte hastalarda KVY %78
HIV koinf olmayan hastalarda KVY %88

Fontana RJ. Liver Transplantation 2016;22:446-458

Efficacy of Sofosbuvir and Daclatasvir in Patients with Fibrosing Cholestatic Hepatitis C After Liver Transplantation

Vincent Leroy, Jérôme Dumortier, Audrey Coilly, Mylène Sebagh, Claire Fougerou-Leurent, Sylvie Radenne, Danielle Botta, François Durand, Christine Silvain, Pascal Lebray, Pauline Houssel-Debry, Nassim Kamar, Louis d'Alteroche, Ventzislava Petrov-Sanchez, Alpha Diallo, Georges-Philippe Pageaux, Jean-Charles Duclos-Vallee



	SOF + RBV ± Peg-IFNα (n=8)	SOF + DCV ± RBV (n=15)
Hepatic encephalopathy	0	1 (7%)
Hemoglobin (g/dL)	12.2 (10.9-13.3)	9.2 (9.0-12.5)
Neutrophil count (G/L)	2.8 (2.1-4.7) [1]	1.7 (1.3-4.1)
Platelet count (G/L)	130 (82-218)	100 (79-158)
Total bilirubin (µmol/L)	86.7 (26.5-166.2)	128.0 (62.4-202.0)
INR	1.2 (1.1-1.3) [1]	1.0 (1.0-1.1) [2]
Albumin (g/L)	24.4 (17.0-31.8) [1]	36.0 (29.1-38.0) [2]

	SOF + RBV ± Peg-IFNα(n=8)	SOF + DCV ± RBV (n=15)	Total (n=23)
After treatment (n, %)			
Week 4 HCV-RNA ND	7 (88)	15(100)	22 (96)
Week 12 HCV-RNA ND	7 (88)	15 (100)	22 (96)

36 ay süren takip boyunca aynı oran korunmuş

Leroy V. Clin Gastroenterol Hepatol 2015;13(11):1993-2001

Annals of Hepatology
The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

ORIGINAL ARTICLE

January-February, Vol. 16 No. 1, 2017: 86-93

Sofosbuvir and Daclatasvir in Mono- and HIV-coinfected Patients with Recurrent Hepatitis C After Liver Transplant

Lluís Castells,[*,†] Jordi Llaneras,[*] Isabel Campos-Varela,[‡] Itxarone Bilbao,[§] Manel Crespo,[||] Oscar Len,[||] Francisco Rodríguez-Frías,[†,¶] Ramon Charco,[§] Teresa Salcedo,[**] Juan Ignacio Esteban,[*,†] Rafael Esteban-Mur[*,†]

Table 2. Response (HCV RNA < 15 IU/mL) during and after antiviral therapy by HIV serostatus.

	Overall (n = 22)	HCV-monoinfected (n = 16)	HCV/HIC-coinfected (n = 6)
Histology, n (%)			
Ishak F3-F4	6 (33)	4 (33)	2 (33)
Ishak F5-F6	10 (56)	7 (59)	3 (50)
Cholestatic hepatitis	2 (11)	1 (8)	1 (17)
At week 4 (SVR4)	22 (100)	16 (100)	6 (100)
At week 12 (SVR12)	22 (100)	16 (100)	6 (100)

Ledipasvir/sofosbuvir

SOLAR-1

Gastroenterology 2015;149:649–659

Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease

Michael Charlton,[1,§] Gregory T. Everson,[2] Steven L. Flamm,[3] Princy Kumar,[4]

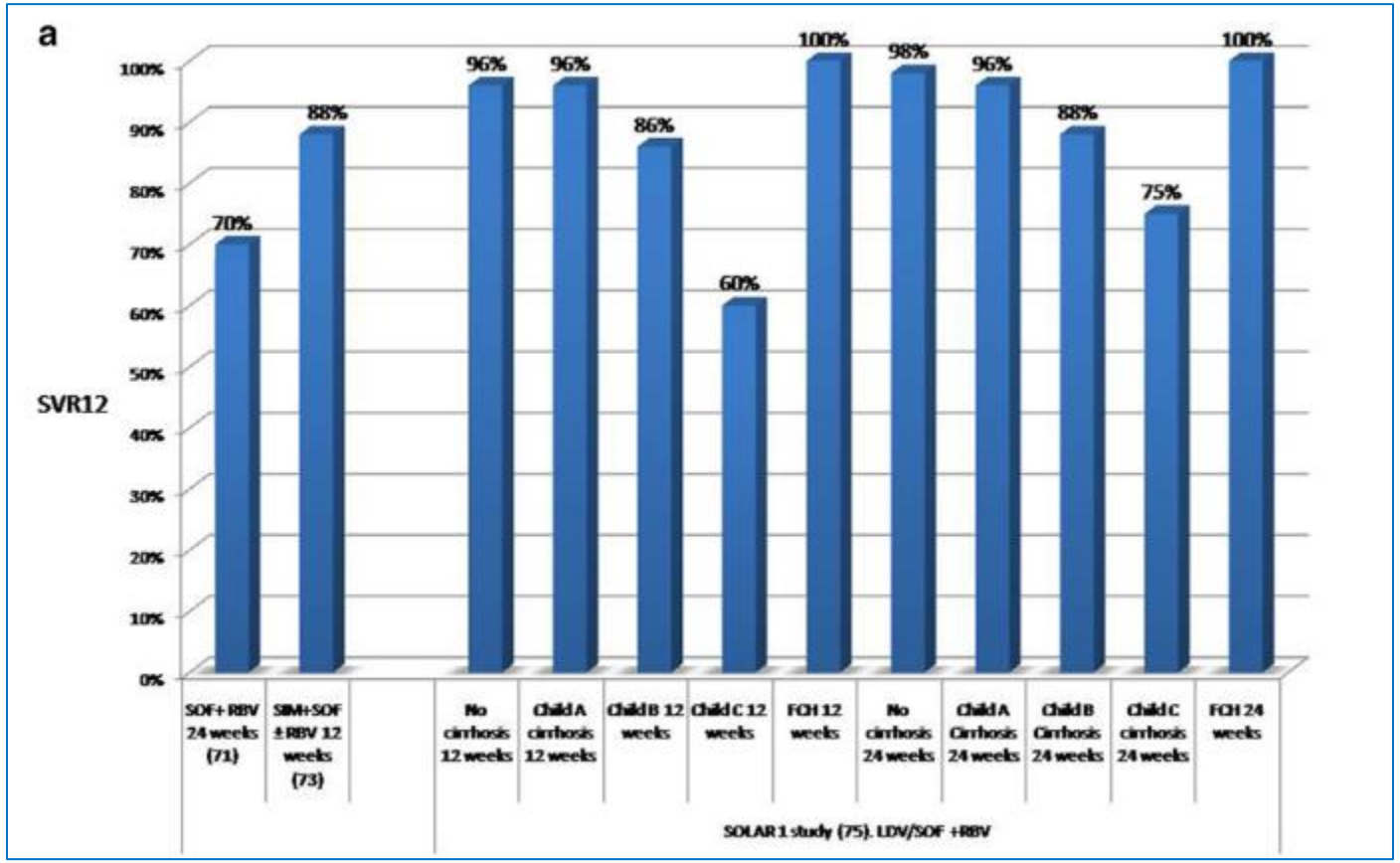
SOLAR-2

Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial

Michael Manns, Didier Samuel, Edward J Gane, David Mutimer, Geoff McCaughan, Maria Buti, Martín Prieto, José Luis Calleja,

Lancet Infect Dis 2016

SOLAR-1

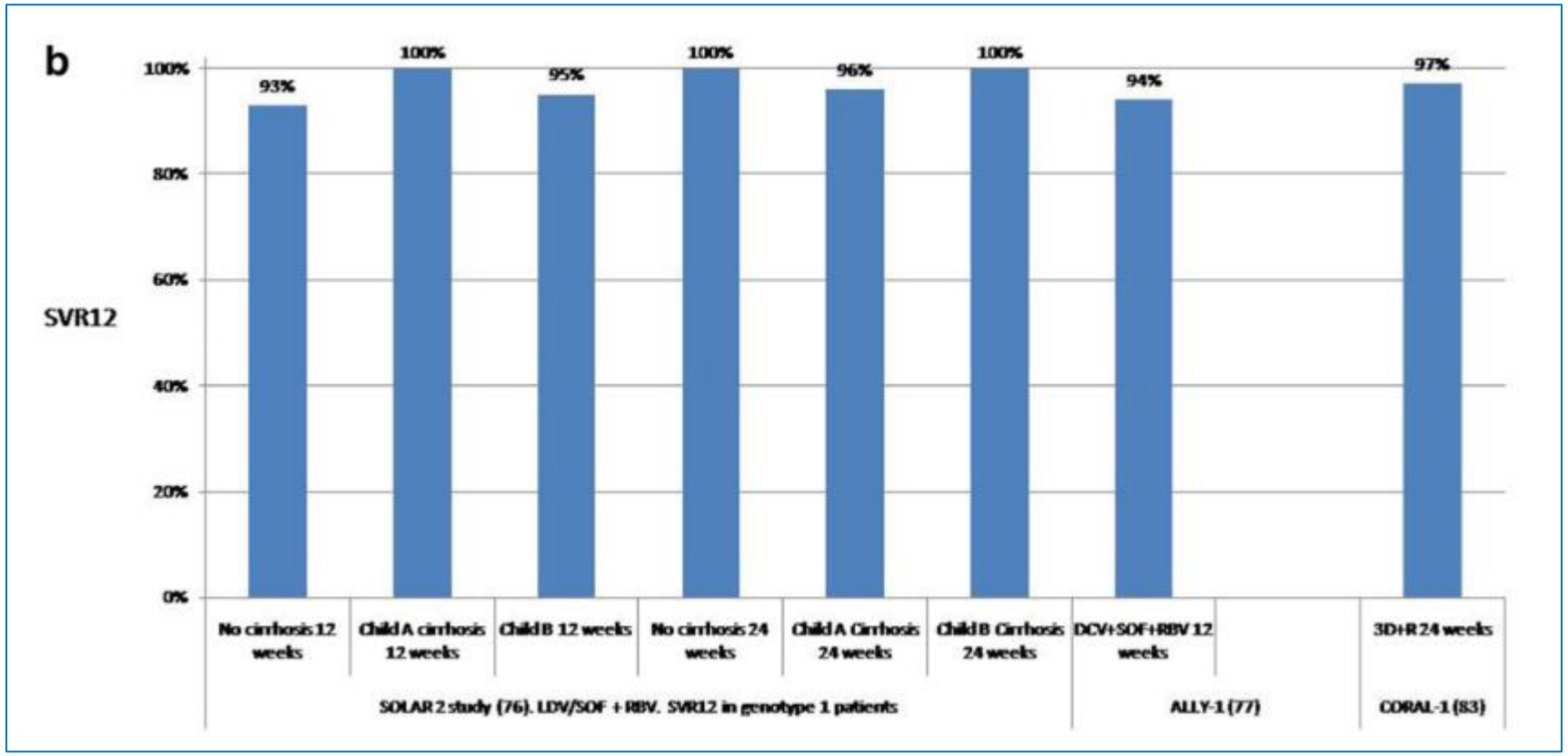


Hepatol Int (2016) 10:749–761

SOLAR-2

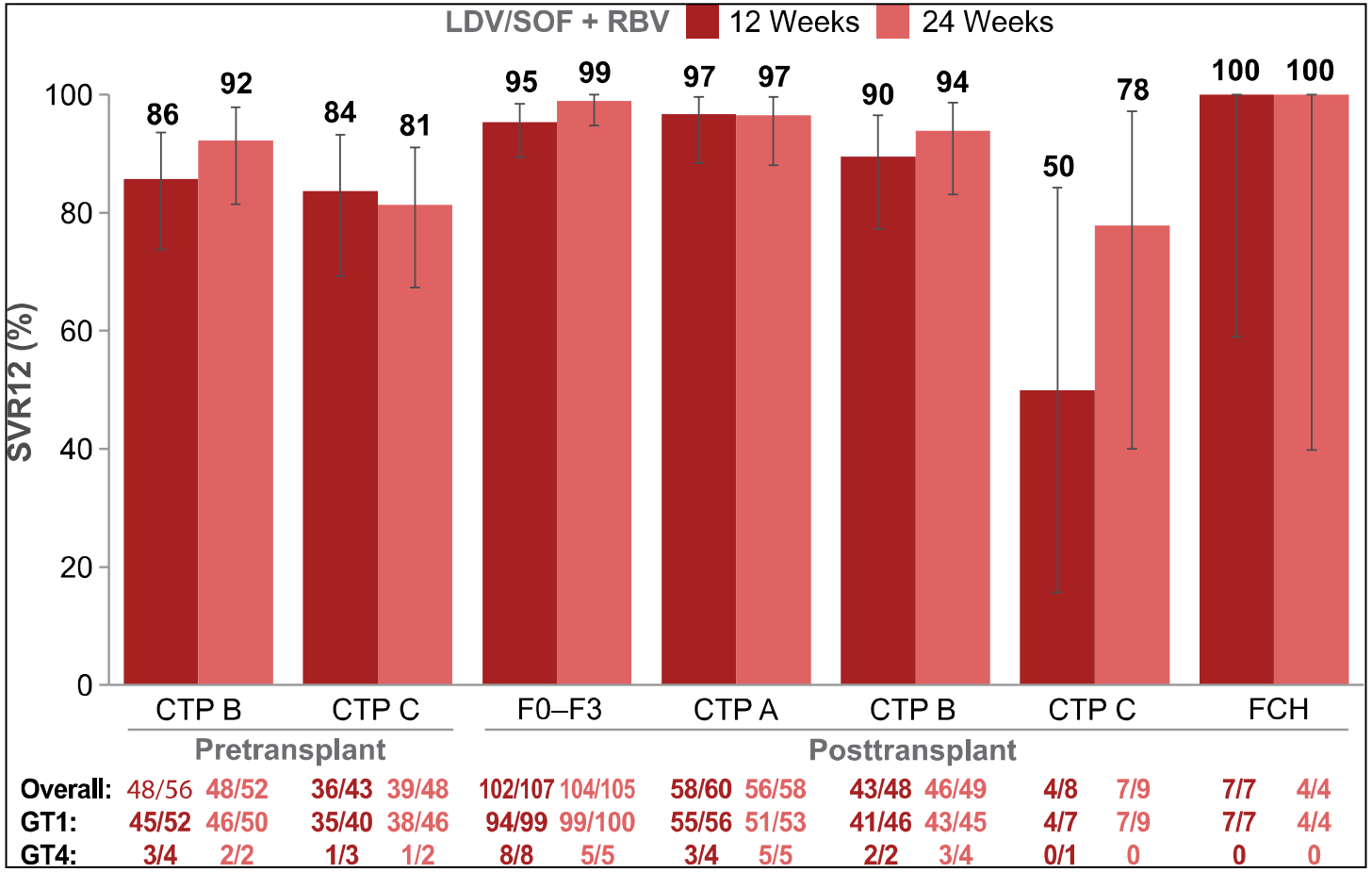
Child C:
12 hf: %50
24 hf: %80

FCH
12 ve 24 hf:
%100



Hepatol Int (2016) 10:749–761

SOLAR-1 ve 2


LDV/SOF + RBV
12 Weeks
24 Weeks
SVR12 (%)
100
80
60
40
20
0
86
92
84
81
95
99
97
97
90
94
50
78
100
100
CTP B
CTP C
F0–F3
CTP A
CTP B
CTP C
FCH
Pretransplant
Posttransplant
Overall: 48/56 48/52 36/43 39/48 102/107 104/105 58/60 56/58 43/48 46/49 4/8 7/9 7/7 4/4
GT1: 45/52 46/50 35/40 38/46 94/99 99/100 55/56 51/53 41/46 43/45 4/7 7/9 7/7 4/4
GT4: 3/4 2/2 1/3 1/2 8/8 5/5 3/4 5/5 2/2 3/4 0/1 0 0 0

SOLAR-2

Among the 226 post-transplantation patients in cohort B included in the efficacy analysis, the most commonly used immunosuppressants were tacrolimus or tacrolimus monohydrate in 144 patients (64%), mycophenolate mofetil, mycophenolate sodium, or mycophenolic acid in 100 patients (44%), and cyclosporine in 63 patients (28%). Less commonly used immunosuppressants were sirolimus (11 patients [5%]) and everolimus (nine patients [4%]). No patients had changes in immunosuppressant medications that were attributed to drug interaction with study treatment. Ten patients required an increase in immunosuppressant dosing (tacrolimus for all ten), possibly because of altered hepatic function after viral clearance.

Elbasvir/grazoprevir

Elbasvir/grazoprevir

- Nakil sonrası hastalarda veri yok

- Elbasvir/grazoprevirin farmakokinetiğinin immunsupresan ilaçlarla nasıl etkilendiği bilinmiyor
- Bu nedenle nakil alıcılarında tedavide kullanılması bugün için önerilmiyor

Sofosbuvir/velpatasvir

Sofosbuvir/velpatasvir

- Nakil sonrası hastalarda çalışma yok
- Velpatasvir, ledipasvir ile benzer farmakokinetiğe sahip
  - İlaç-ilaç etkileşimi az
- Nakil alıcılarında pangenotipik etkinliği olabilecek bir seçenek olması nedeniyle etkinlik ve etkileşim çalışmalarının yapılması gerekli

İlaç Etkileşimleri

Table 1 Drug interactions of second generation DAAs with tacrolimus, cyclosporine and in patients with renal impairment

Drug	Cyclosporine	Tacrolimus	Renal impairment
Simeprevir	3.74 fold increase in Cmax and 4.8 fold increase in AUC of cyclosporine. This co-administration is not recommended [89]	79 % increase in Cmax and 85 % increase in AUC of simeprevir. This combination can be considered [90]	In severe renal impairment, increase in Cmax by 34 % and AUC by 62 %. No dose adjustments required [91]
Sofosbuvir	No clinically relevant interaction. High cyclosporine levels can increase sofosbuvir by four-fold but are rarely a clinical problem	No clinically relevant interaction	No dose recommendation in severe renal impairment (eGFR <30). Trials ongoing with 200 mg per day
Ledipasvir	No clinically relevant interaction	No clinically relevant interaction	No recommended dose in severe renal impairment
Dacltasvir	No drug interaction with cyclosporine [92]	No drug interaction with tacrolimus	No adjustment required but limited data
Ombitasvir/paritaprevir-ritonavir/dasabuvir	Increases cyclosporine levels significantly. Reduction of cyclosporine to 1/5th of its dose	Increases tacrolimus levels significantly. Consider weekly tacrolimus dosing (eg. 0.5 mg weekly)	No dose adjustments required but insufficient data
Ribavirin	No significant drug interaction	No significant drug interaction	200 mg daily in patients with severe renal impairment

Most information obtained from the product monographs

AASLD-2016
Nakil sonrası nüks hastalar

Hasta	Öneri
G1-4 Kompanze siroz	Ledipasvir + SOF + RBV 12 hf Daclatasvir + SOF + RBV 12 hf
G1-4 Kompanze siroz RBV kullanılamıyor	Ledipasvir + SOF 24 hf Daclatasvir + SOF 24 hf
G1-4 Dekompanze siroz	Ledipasvir + SOF + RBV 12 hf
G1 Kompanze siroz, alternatif	Simeprevir + SOF ± RBV 12 hf
G1 F0-F2	PROD + RBV 24 hf

AASLD-2016
Nakil sonrası nüks hastalar

Hasta	Öneri
G2 Kompanze siroz	Daclatasvir + SOF + RBV 12 hf SOF + RBV 24 hf
G2 Kompanze siroz RBV kullanılamıyorsa	Daclatasvir + SOF 24 hf
G2 Dekompanze siroz	SOF + RBV 24 hf

AASLD-2016
Nakil sonrası nüks hastalar

Hasta	Öneri
G3 Kompanze siroz	Daclatasvir + SOF + RBV 12 hf
G3 Kompanze siroz RBV kullanılamıyorsa	Daclatasvir + SOF 24 hf

HCV'ye Bağlı Dekompanse Sirotik Hastalar

Dekompanze siroz, HCC olmayan, MELD skoru<18-20	• Nakilden önce tedavi edilebilir • Tedaviye bir an önce başlanmalıdır	
Dekompanze siroz, HCC olmayan, MELD<18-20, G1, 4, 5, 6	• Sofosbuvir ve ledipasvir+RBV, 12 hf • Sofosbuvir ve velpatasvir+RBV, 12 hf • Sofosbuvir ve daclatasvir+RBV, 12 hf	RBV kullanılamıyorsa 24 hf
Dekompanze siroz, HCC olmayan, MELD<18-20, G2	• Sofosbuvir ve velpatasvir+RBV, 12 hf • Sofosbuvir ve daclatasvir+RBV, 12 hf	
Dekompanze siroz, HCC olmayan, MELD<18-20, G3	• Sofosbuvir ve velpatasvir+RBV, 24 hf • Sofosbuvir ve daclatasvir+RBV, 24 hf	

EASL Recommendations on Treatment of Hepatitis C 2016

HCV'ye Bağlı Dekompanse Sirotik Hastalar

Dekompanze siroz, HCC olmayan, MELD skoru≥18-20	• Önce nakil yapılmalı • Nakil sonrası antiviral tedavi
Dekompanze siroz, HCC olmayan, MELD skoru≥18-20	• Ancak bekleme süresi 6 ayı aşacaksa nakil öncesi antiviral tedavi verilebilir

EASL Recommendations on Treatment of Hepatitis C 2016

EASL-2016
Nakil sonrası nüks hastalar

Hasta	Öneri
G1-4-5-6 Kompanze veya dekompanze siroz	Ledipasvir + SOF + RBV 12 hf Daclatasvir + SOF + RBV 12 hf
G2 Kompanze veya dekompanze siroz	Daclatasvir + SOF + RBV 12 hf
G3	Daclatasvir + SOF + RBV 12 hf
Tüm genotipler Non-sirotik, kompanze veya dekompanze siroz	Velpatasvir + SOF + RBV 12 hf (G3 ve dekompanze ise 24 hf)

EASL Recommendations on Treatment of Hepatitis C 2016

Table 5. Summary of regimens not currently recommended for treatment of hepatitis C virus (HCV) recurrence in post-liver transplant recipients.

Regimens not recommended regardless of degree of liver disease	**Evidence rating**
Sofosbuvir + ribavirin	Class IIb, level A
Peg-IFN monotherapy	Class III, level A
Peg-IFN + ribavirin	Class IIb, level A
Peg-IFN/sofosbuvir	Class IIb, level A
Peg-IFN/simeprevir	Class IIb, level A
Peg-IFN/telaprevir	Class IIb, level A
Peg-IFN/boceprevir	Class IIb, level A
Ribavirin monotherapy	Class III, level A
Any DAA as monotherapy	Class III, level A
Regimens not recommended in patients with compensated cirrhosis	
Elbasvir/grazoprevir-containing regimens	Class III, level C
Regimens not recommended in patients with decompensated cirrhosis	
Simeprevir-containing regimens	Class III, level B
Paritaprevir-containing regimens	Class III, level B
Elbasvir/grazoprevir-containing regimens	Class III, level C

SUT ne diyor?

4.2.13.3.2.C- Karaciğer nakli olan hastalarda tedavi

(1) Karaciğer nakli olan HCV RNA pozitif olan hastalarda;

a) Sofosbuvir+Ledipasvir ile tedavi; genotip 1 ve 4 non-sirotik hastalar için tedavi süresi ribavirin ile birlikte veya ribavirinsiz toplam 12 haftadır. Kompanse sirotik ve dekompanse sirotik hastalarda tedavi süresi ribavirin ile birlikte toplam 12 hafta veya ribavirinsiz toplam 24 haftadır.

b)(Ombitasvir+Paritaprevir+Ritonavir)+Dasabuvir +Ribavirin ile tedavi; genotip 1 hastalarda tedavi süresi toplam 24 haftadır.

c) (Ombitasvir+Paritaprevir+Ritonavir)+Ribavirin ile tedavi; genotip 4 hastalarda tedavi süresi toplam 24 haftadır.”

Nakil sonrası nüks HCV

- Nüks hastaların tedavisinde iki rejim öne çıkıyor
  - Ledipasvir/sofosbuvir
  - Daclatasvir/sofosbuvir

- Ancak nakilin ne zaman yapılması gerektiği ile ilgili net bir öneri bulunmamakta

IX. ULUSAL VİRAL HEPATİT SİMPOZYUMU

12-14 MAYIS 2017

ANEMON MALATYA HOTEL

AKUT HEPATİTTEN TRANSPLANTASYONA

UVHS
ULUSAL VİRAL HEPATİT SİMPOZYUMU

KLİMİK
TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ