DEKOMPANZE SİROTİK HASTALARDA HCV YÖNETİMİ

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Haziran 2019

OLGU

- D.E., 48 yaşında, erkek hasta, çiftçi, Niğde
- Başvuru tarihi: Aralık 2014
- Yakınmalar: Halsizlik, çabuk yorulma, bacaklarında şişme

Öykü:

- 2005 yılında sırt ağrısı, yorgunluk ve halsizlik nedeniyle Niğde'de başvurduğu hastanede tetkikleri yapılmış
- Anti-HCV ve HCV RNA'sı pozitif olan hastaya karaciğer biyopsisi yapılmış ve siroz tanısı konulmuş

Kronik Hepatit C'de Tedavi Öncesi Yapılması Gerekenler

- Komorbiditeleri dışlamak için otoantikorlar (ANA, ASMA,anti-LKM), açlık kan şekeri düzeyi, demir düzeyi, demir bağlama kapasitesi ve ferritin düzeyiyle birlikte, HBV, HAV ve
- HIV infeksiyonunun serolojik göstergeleri araştırılmalıdır

Aygen B et al. Kronik Hepatit C Virusu İnfeksiyonunun Yönetimi. *Klimik Dergisi 2017; 30(Ozel Sayı 1): 2-36*

Kronik Hepatit C'de Tedavi Öncesi Yapılması Gerekenler

- HBV ve HAV için seronegatif olan hastalar aşılanmalıdır

Aygen B et al. Kronik Hepatit C Virusu İnfeksiyonunun Yönetimi.
Klimik Dergisi 2017; 30(Ozel Sayı 1): 2-36

Kronik Hepatit C'de Tedavi Öncesi Yapılması Gerekenler

- Karaciğer hastalığının şiddeti ve fibroz duzeyi, karaciğer biyopsisi yapılarak ya da invazif olmayan yöntemlerle araştırılmalıdır
- Sirotik hastalar dekompansasyon acısından klinik ve laboratuvar olarak değerlendirilmelidir

Aygen B et al. Kronik Hepatit C Virusu İnfeksiyonunun Yönetimi.
Klimik Dergisi 2017; 30(Ozel Sayı 1): 2-36

Kronik Hepatit C'de Tedavi Öncesi Yapılması Gerekenler

- Duyarlı bir yöntemle HCV RNA kantitasyonu yapılmalıdır

Aygen B et al. Kronik Hepatit C Virusu İnfeksiyonunun Yönetimi.
Klimik Dergisi 2017; 30(Ozel Sayı 1): 2-36

Kronik Hepatit C'de Tedavi Öncesi Yapılması Gerekenler

- Tedavi rejimi ve süresini belirlemek icin HCV genotip tayini ve genotip 1 ile infekte hastalarda subtip tayini yapılmalıdır

Aygen B et al. Kronik Hepatit C Virusu İnfeksiyonunun Yönetimi.
Klimik Dergisi 2017; 30(Ozel Sayı 1): 2-36

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Recommendations

- All patients with HCV infection must be considered for therapy, including treatment-naïve patients and individuals who failed to achieve SVR after prior treatment (**A1**).
- Treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including compensated (Child-Pugh A) and decompensated (Child-Pugh B or C) cirrhosis, in patients with clinically significant extra-hepatic manifestations (*e.g.* symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B-cell lymphoma), in patients with HCV recurrence after liver transplantation, in patients at risk of a rapid evolution of liver disease because of concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, HBV coinfection, diabetes) and in individuals at risk of transmitting HCV (PWID, men who have sex with men with high-risk sexual practices, women of childbearing

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- Patients with decompensated (Child-Pugh B or C) cirrhosis and an indication for liver transplantation with a MELD score ≥18–20 should be transplanted first and treated after transplantation (**B1**).
- If the waiting time on a liver transplant list is more than 6 months, patients with decompensated (Child-Pugh B or C) cirrhosis with a MELD score ≥18–20 can be treated before transplantation, although the clinical benefit for these patients is not well established (**B2**).
- Treatment is generally not recommended in patients with limited life expectancy due to non-liver-related comorbidities (**B2**).

OLGU

Öykü:

- PEG-İFN + RBV - 48 hafta → Relaps (2012 yılı)
- PEG-İFN + RBV - 24 hafta → Yanıtsız (2013 yılı)
- PEG-İFN + RBV + BOC- 32 hafta → Yanıtsız (2013 yılı)

- Halsizlik dışında başka şikayeti olmayan hasta hepatit tedavisinde yeni ilaçların çıktığını duyduğu için başvurmuş

Özgeçmiş ve soygeçmiş:

- Özellik yok
- Propranolol (dideral) ve spironolakton (aldakton) kullanıyor

OLGU

Sistemik muayene:

- Obez görünümde, boy: 171 cm, vücut ağırlığı: 100 kg, yüzde ve gövdede “spider” anjiomalar, ellerde palmar eritem var, konjuktivalar hiperemik, traube kapalı ve alt ekstremitelerde gode bırakan (1+) ödem
- Laboratuvar bulguları:
- Hb: 13.7 g/dl, BK: 5.540/mm^3, trombosit: 86.000/mm^3
- Sedimentasyon hızı: 46 mm/saat, kantitatif CRP: 12.5 mg/dl (sınırlar 0-10 mg/dl)

OLGU 2

Laboratuvar bulguları:

- ALT: **51.7** İÜ/l, AST: **207.3** İÜ/l, GGT: **110.5** İÜ/l, total bilirubin: **3.42** mg/dl, direkt bilirubin: **1.72** mg/dl, albumin: **3.07** mg/dl, globulin: **4.1** mg/dl, PTZ: 16.5 sn, INR: **1.57**, BUN: 16 mg/dl, kreatinin: 0.83 mg/dl, eGFR: 133.1 ml/dk, alfa feto-protein: 8.26 ng/ml, diğer parametreler normal
- Otoantikorlar negatif, tiroid fonksiyon testleri normal
- Anti-HAV, anti-HBs ve anti-HCV pozitif
- HCV RNA: 539.000 İÜ/ml, genotip: 1b, İL28B: CT

- Sirotik hastalar dekompansasyon açısından klinik ve laboratuvar olarak değerlendirilmelidir

Aygen B et al. Kronik Hepatit C Virusu İnfeksiyonunun Yönetimi.
Klimik Dergisi 2017; 30(Ozel Sayı 1): 2-36

OLGU

Laboratuvar bulguları:

- Batın USG: Karaciğer boyutu 15 cm, konturları hafif düzensiz, parankimi granüler görünümde, dalak boyutu 13 cm
- Üst endoskopi: Portal hipertansif gastropati, II-III. derece özafagus varisleri
- Child-Pugh kategorisi: 8
- MELD skoru: 16

Child-Pugh Skoru

Kimyasal/Biyokimyasal	*Skor*	*Skor*	*Skor*
	1	2	3
Ensefalopati	yok	1-2	3-4
Assit	yok	az	orta
Albumin (g/dl)	> 3.5	2.8-3.5	< 2.8
PT (sn artış)	1-4	4-6	> 6
Bilirubin (mg/dl)	1-2	2-3	3

A: 5-6
B: 7-9
C:10-15

MELD Skoru = 10 [0.957 Log(Serum kreatinin) + 0.378 Log(Total biluribin) + 1.12 Log (INR) + 0.643]

MELD skoru	Mortalite
< 9	%2
10 - 19	%5
20 - 29	%20
30 - 39	%50
≥ 40	%70

Her parametre için minimum kabul edilebilir değer 1, serum kreatinin için maksimum kabıul edilebilir değer 4 dür. Maksimum MELD skoru 40 olabilir.

Sequence Information

Identifier:	Kayseri,……
predicted Genotype:	1
Included *NS3* region codons:	33 - 181 (amino acid similarity to reference = 88.51%)
Mutations *NS3* region:	I35V, A39[n.d.], A40T, T42S, I48V, T61S, R62K, I64L, S66G, V71I, I72T, P86Q, Q89A, S91A, I132V, A147S, N174L, L175M
Used reference sequence :	Consensus sequence from Strain HPCPLYPRE, HPCCGAA, HPCJCG, HPCHUMR, HPCCGS and AY051292

Drug Resistance

Drugs	Scored mutations	Resistance analysis
Boceprevir	none	susceptible
Telaprevir	none	susceptible

Patients With Decompensated Cirrhosis

Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis	
RECOMMENDED	RATING
Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center.	I, C

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, A[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[c]	12 weeks	I, A[d]
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg)[e] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.
[c] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
[d] Only available data for genotype 6 are in patients with compensated cirrhosis.
[e] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A[c]
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg)[d] plus sofosbuvir (400 mg)	24 weeks	II, C

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.
[c] Only available data for genotype 6 are in patients with compensated cirrhosis.
[d] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.

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Recommendations

- IFN-free regimens are the only options in HCV-monoinfected and in HIV-coinfected patients with decompensated (Child-Pugh B or C) cirrhosis, with or without an indication for liver transplantation, and in patients after liver transplantation because of their virological efficacy, ease of use, safety and tolerability (**A1**).
- Protease inhibitor-containing regimens are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis (**A1**).

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- Patients with decompensated (Child-Pugh B or C) cirrhosis, without HCC, awaiting liver transplantation with a MELD score <18–20 can be treated with sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6), or with sofosbuvir and velpatasvir (all genotypes), with daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) for 12 weeks (**A1**).

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- In patients with decompensated (Child-Pugh B or C) cirrhosis without HCC awaiting liver transplantation with a MELD score <18–20 treated with sofosbuvir and ledipasvir with ribavirin, or with sofosbuvir and velpatasvir with ribavirin, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**B1**).

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Patients with decompensated (Child-Pugh B or C) cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir

(genotypes 1, 4, 5 or 6), or the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), for 24 weeks without ribavirin (**A1**).

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- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18–20 can be treated before transplantation if the waiting time on the transplant list exceeds 6 months, depending on the local situation (**B2**).

OLGU

- Hastanın “insani amaçlı erken erişim programı” ile Ledipasvir (LDV) / SOF tedavisine ulaşma şansı oldu!

OLGU

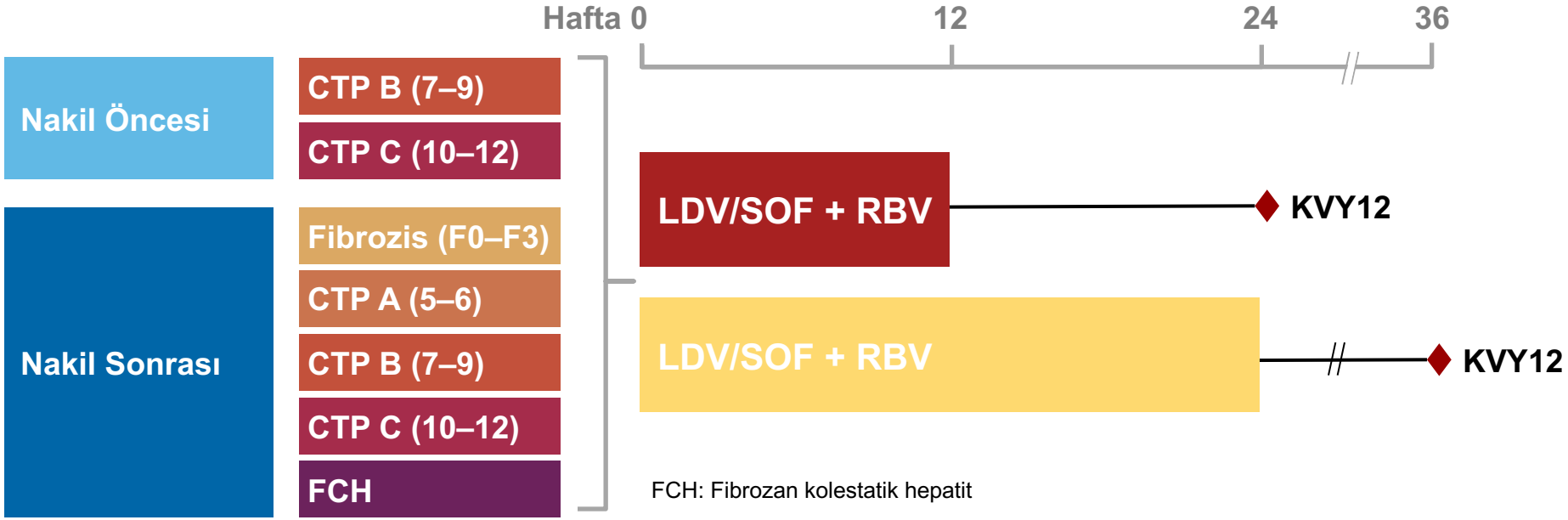
Klinik seyir:

- Hastaya LDV-SOF + RBV 600 mg/gün kombinasyon tedavisi başlandı
- Tedavi sonrası takibi ve KVY devam etmektedir

Klinik ve lab. takip	Baş.	2. hafta	4.hafta	6.hafta	8. hafta	10. hafta	12. hafta	16. hafta	20. hafta
Hb (g/dl)	13.7	13.5	13.3	13.7	14.8	14.6	14.8	13.4	15.1
Nötrofil (/mm^3)	2300	2150	1950	2440	2470	2380	2400	2390	2430
Trombosit (/mm^3)	86.000	98.000	110.000	141.000	119.000	110.000	112.000	117.000	116.000
ALT (Ü/l)	51.7	29	17.2	15.8	14.8	17.7	16.1	16.5	17.6
AST (Ü/l)	207.3	85	53.6	49.7	55	52	55.7	48.8	52
GGT (Ü/l)	110.5	93.7	87.1	72.4	66.5	59.1	60.2	50.4	46.8
T.bilirubin (mg/dl)	3.42	2.96	2.17	2.40	1.65	1.70	1.68	2	1.91
Direkt bil. (mg/dl)	1.72	1.60	1.31	1.23	1	1.04	1.03	0.88	0.91
PTZ (sn)	16.5	17.5	18.1	21.9	19	18.6	19	18	15
INR	1.57	1.71	1.66	1.78	1.69	1.70	1.69	1.69	1.18
HCV-RNA (İÜ/ml)	539.000	Bakılmadı	208	Bakılmadı	**Negatif**	Bakılmadı	Negatif	Bakılmadı	Negatif
Yan etkiler	Yok	Yok	Yok	Yok	Yok	Yok	Yok	Yok	Yok

Dekompanse siroz ve karaciğer nakli sonrası nüks olan hastalarda LDV/SOF + RBV tedavisi

SOLAR-1 ve SOLAR-2: ABD ve Avrupa'da naiv ve tedavi deneyimli HCV GT 1 ve 4 hastalarda LDV/SOF±RBV tedavisi uygulanan prospektif, çok merkezli çalışma(n=659)



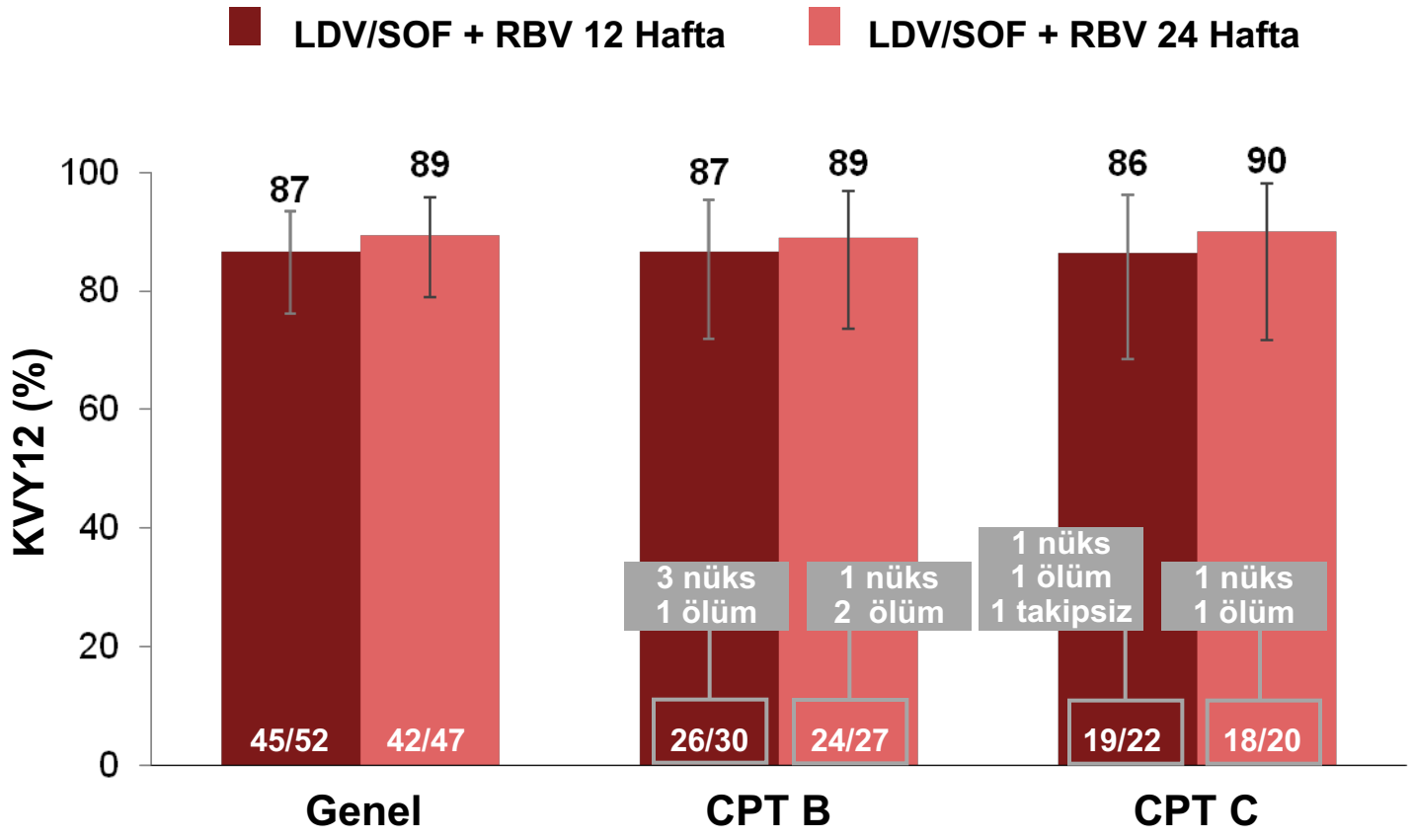
- Hastaların çalışmaya alınma kriterleri
  - Hepatoselüler karsinom olmaması
  - Total bilirubin ≤10 mg/dl, hemoglobin ≥ 10 g/dl
  - Kr. kl ≥ 40 ml/dk, trombosit > 30.000/ml
- RBV dozu
  - METAVIR F0–F3 ve CPT A siroz: Kiloya ayarlı (< 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
  - CPT B ve C siroz: 600 mg/gün, sonra doz artırımı (600-1200 mg/gün)

Samuel D, et al. EASL 2015. Abstract 0774.

SOLAR-1/2: Demografik özellikler

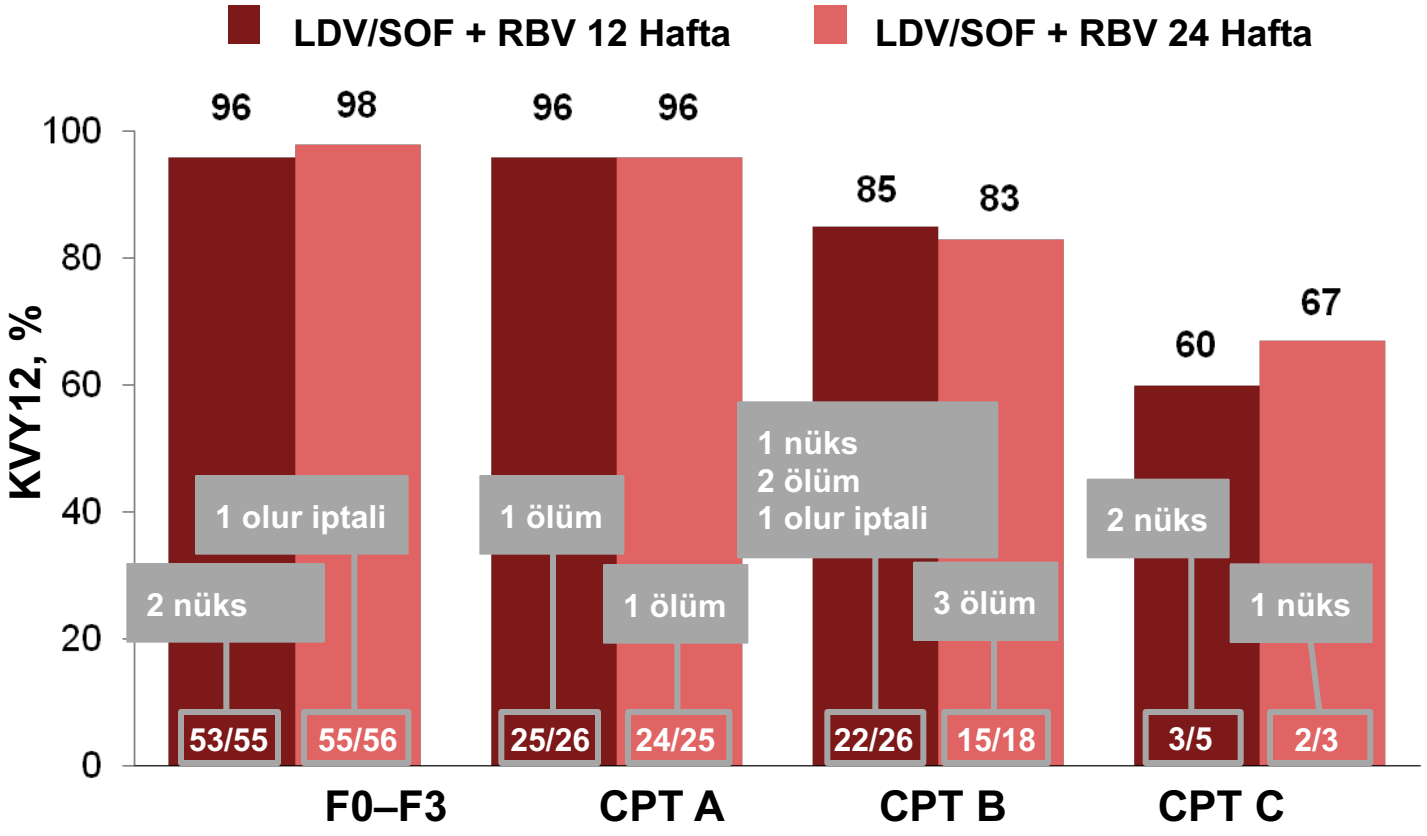
Hastalar, n (%)	Nakil Öncesi	Nakil Sonrası		Toplam
	CTP B + C n=215	F0–3 + CTP A n=330	CTP B + C n=114	n=659
HCV GT, n (%)				
1a	124 (58)	197 (60)	71 (62)	392 (59)
1b	78 (36)	111 (34)	36 (32)	225 (34)
4	13 (6)	22 (7)	7 (6)	42 (6)
IL28B CC yok, n (%)	167 (77)	272 (83)	92 (81)	431 (81)
Ön HCV tedavisi, n (%)	150 (70)	270 (82)	96 (84)	516 (78)
Siroz, n (%)	215 (100)	118 (36)	114 (100)	447 (68)
Ortalama eGFR, mL/dak/1,73 m^2 (aralık)	84 (34–224)	63 (20–132)	64 (29–124)	69 (20–224)
MELD, n (%)				
<10	24 (11)	64 (54)	26 (23)	114 (26)
10-15	132 (61)	51 (43)	69 (61)	252 (56)
16–20	54 (25)	3 (3)	16 (14)	73 (16)
21–25	5 (2)	0	3 (3)	8 (2)
Ortalama albumin, g/dL (aralık)	2,8 (1,6–4,0)	3,9 (2,4–4,8)	3,0 (1,6–4,2)	?
Ortalama platelet, x 10^3/µL (aralık)	76 (27–212)	136 (35–434)	90 (32–237)	?
Asit, n (%)	163 (76)	9 (3)	83 (73)	?
Ensefalopati, n (%)	140 (65)	4 (1)	53 (46)	?

SOLAR-1: Dekompanse siroz hastalarında sonuçlar



6 hasta (2 CPT B/24 Hf, 1 CPT C/12 Hf ve 3 CPT C/24 Hf) dışlanmıştır, 3 CPT C/24 Hf hastasında KVY 12 sağlanamamıştır
(%90 güven aralığı)

SOLAR-1: Nakil sonrası hastalarda sonuçlar



8 CPT B 24 hafta ve 1 CPT C 24 hafta hastası tedavi sonrası 12. hafta ziyaretini gerçekleştirmemiştir (%90 güven aralığı)

SOLAR-2: Sonuçlar

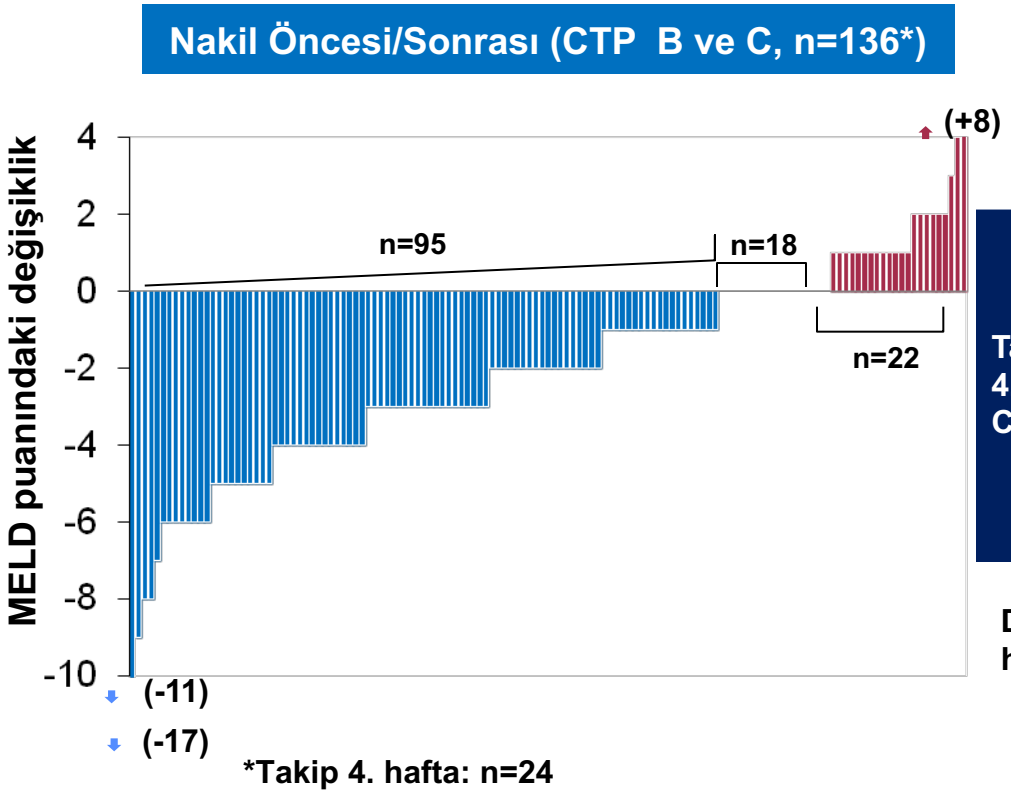
Sonuçlar	Posttransplantasyon F0-F3 veya CTP A		Pre- ve posttransplantasyon CTP B veya C	
	LDV/SOF + RBV 12 hafta (n = 86)	LDV/SOF + RBV 24 hafta (n = 82)	LDV/SOF + RBV 12 hafta (n = 78)	LDV/SOF + RBV 24 hafta (n = 82)
KVY12, % (n/N)				
Genotip 1	96 (72/75)	98 (57/58)	88 (57/65)	89 (54/61)
Genotip 4	91 (10/11)	100 (7/7)	57 (4/7)	86 (6/7)

KVY oranları 12 veya 24 haftalık LDV/SOF + RBV tedavilerinde benzerdir!

KVY12 oranları % (n/N)	CTP B		CTP C	
	LDV/SOF + RBV 12 hafta	LDV/SOF + RBV 24 hafta	LDV/SOF + RBV 12 hafta	LDV/SOF + RBV 24 hafta
Pretransplant	87 (20/23)	96 (22/23)	85 (17/20)	72 (13/18)
Posttransplant	95 (19/20)	100 (16/16)	50 (1/2)	75 (3/4)

SOLAR-2: Başlangıçtan 4. hafta takibe kadar karaciğer fonksiyonlarındaki değişim

MELD puan değişimi



*Takip 4. hafta: n=24

CTP sınıfındaki değişim

		Başlangıç CTP		
		A (5–6) n=73	B (7–9) n=100	C (10–12) n=54
Takip 4. hafta CTP	A (5–6)	67 (96)	31 (35)	2 (5)
	B (7–9)	3 (4)	57 (65)	20 (48)
	C (10–12)	0	0	20 (48)

Değerlendirme olamayan: CTP A 3 hasta, CTP B 12 hasta, CTP C 12 hasta

Hastaların büyük çoğunluğu MELD ve CTP skorlarında iyileşme ortaya koymuştur!

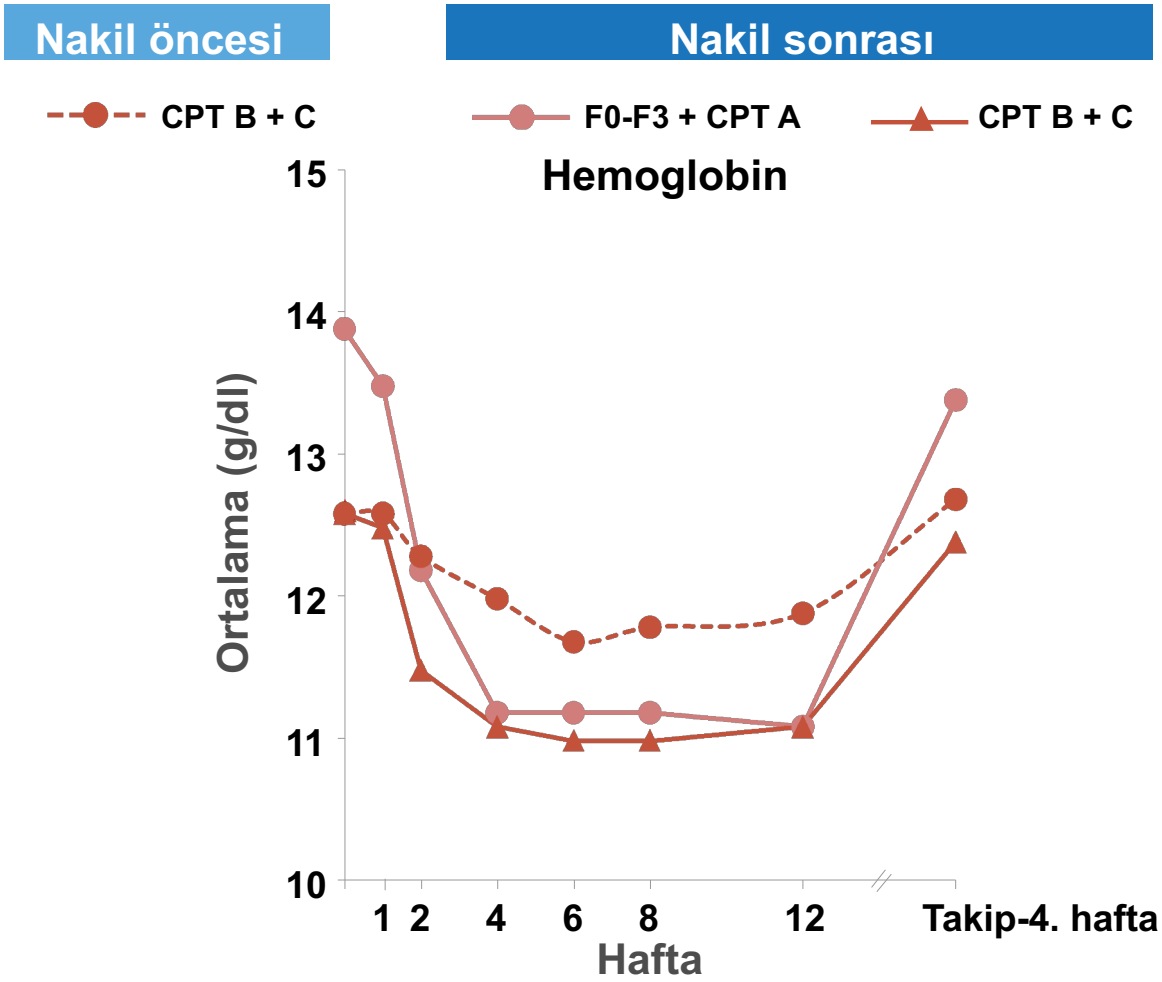
SOLAR-1/2: Güvenlilik ve yan etkiler

Hastalar, n (%)	Nakil Öncesi	Nakil Sonrası		Toplam n=659
	CTP B + C n=215	F0–3 + CTP A n=330	CTP B + C n=114	
Tüm YE'ler	208 (97)	316 (96)	109 (96)	633 (96)
Derece 3-4 YE	51 (24)	76 (23)	33 (29)	160 (24)
Ciddi YE	61 (28)	49 (15)	34 (30)	144 (22)
Tedaviye bağlı ciddi YE	5 (2)	10 (3)	4 (4)	19 (3)
LDV/SOF tedavisinin kesilmesine neden olan YE	9 (4)	5 (2)	5 (4)	19 (3)
Ölüm	10 (5)	4 (1)	6 (5)	20 (3)
Reddetme	0	1	0	1
Greft kaybı	1	1	0	2
Karaciğer transplantasyonu	11	0	0	11

- **Tedaviyle ilişkili YE'ler RBV tedavisiyle yakından ilişkilidir**
- **Ölüm ve LDV/SOF tedavisinin kesilmesine neden olan YE'ler çalışma tedavisine bağlanmamıştır**

LDV/SOF+RBV dekompanse sirozda ve nakil sonrasında iyi tolere edilmiştir!

SOLAR-1/2: Zaman içinde hemoglobin değerleri



Patient-reported outcomes with sofosbuvir and velpatasvir with or without ribavirin for hepatitis C virus-related decompensated cirrhosis: an exploratory analysis from the randomised, open-label ASTRAL-4 phase 3 trial

Zobair M Younossi, Maria Stepanova, Michael Charlton, Michael P Curry, Jacqueline G O'Leary, Robert S Brown, Sharon Hunt

	Sofosbuvir and velpatasvir plus ribavirin (12 weeks) (n=87)	Sofosbuvir and velpatasvir (12 weeks) (n=90)	Sofosbuvir and velpatasvir (24 weeks) (n=90)
Treatment-naive	40 (46%)	32 (36%)	48 (53%)
HCV genotype			
Genotype 1	68 (78%)	68 (76%)	71 (79%)
Genotype 2	4 (5%)	4 (4%)	4 (4%)
Genotype 3	13 (15%)	14 (16%)	12 (13%)
Genotype 4–6	2 (2%)	4 (4·4%)	3 (3%)
Alanine aminotransferase >1·5× ULN	41 (47%)	45 (50%)	43 (48%)
HCV RNA >6 $\log_{10}$ copies/mL	38 (44%)	50 (56%)	37 (41%)
Child-Pugh class			
A	6 (7%)	3 (3%)	7 (8%)
B	77 (89%)	86 (96%)	77 (86%)
C	4 (5%)	1 (1%)	6 (7%)
Ascites	65 (75%)	74 (82%)	75 (83%)
Encephalopathy	54 (62%)	52 (58%)	59 (66%)
Platelet count <75 × 10^3/μL	33 (38%)	45 (50%)	42 (47%)
MELD score ≥15	10 (12%)	6 (7%)	11 (12%)

Patient-reported outcomes with sofosbuvir and velpatasvir with or without ribavirin for hepatitis C virus-related decompensated cirrhosis: an exploratory analysis from the randomised, open-label ASTRAL-4 phase 3 trial

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	Sofosbuvir and velpatasvir plus ribavirin (12 weeks) (n=87)	Sofosbuvir and velpatasvir (12 weeks) (n=90)	Sofosbuvir and velpatasvir (24 weeks) (n=90)	p value
Anaemia or blood disorders	23 (26%)	0	0	<0·0001
Fatigue or asthenia	29 (33%)	16 (18%)	14 (16%)	0·0083
Gastrointestinal	23 (26%)	22 (24%)	11 (12%)	0·041
Musculoskeletal	4 (5%)	4 (4%)	1 (1%)	0·34
Nervous	14 (16%)	21 (23%)	9 (10%)	0·05
Psychiatric	12 (14%)	9 (10%)	8 (9%)	0·55
Skin and subcutaneous tissue	8 (9%)	9 (10%)	5 (6%)	0·51
Other adverse events	17 (20%)	5 (6%)	8 (9%)	0·0090
No adverse events	27 (31%)	45 (50%)	56 (62%)	0·0002

Data are number of patients with at least one reported treatment-related adverse event (%).

Table 2: **Treatment-related adverse events**

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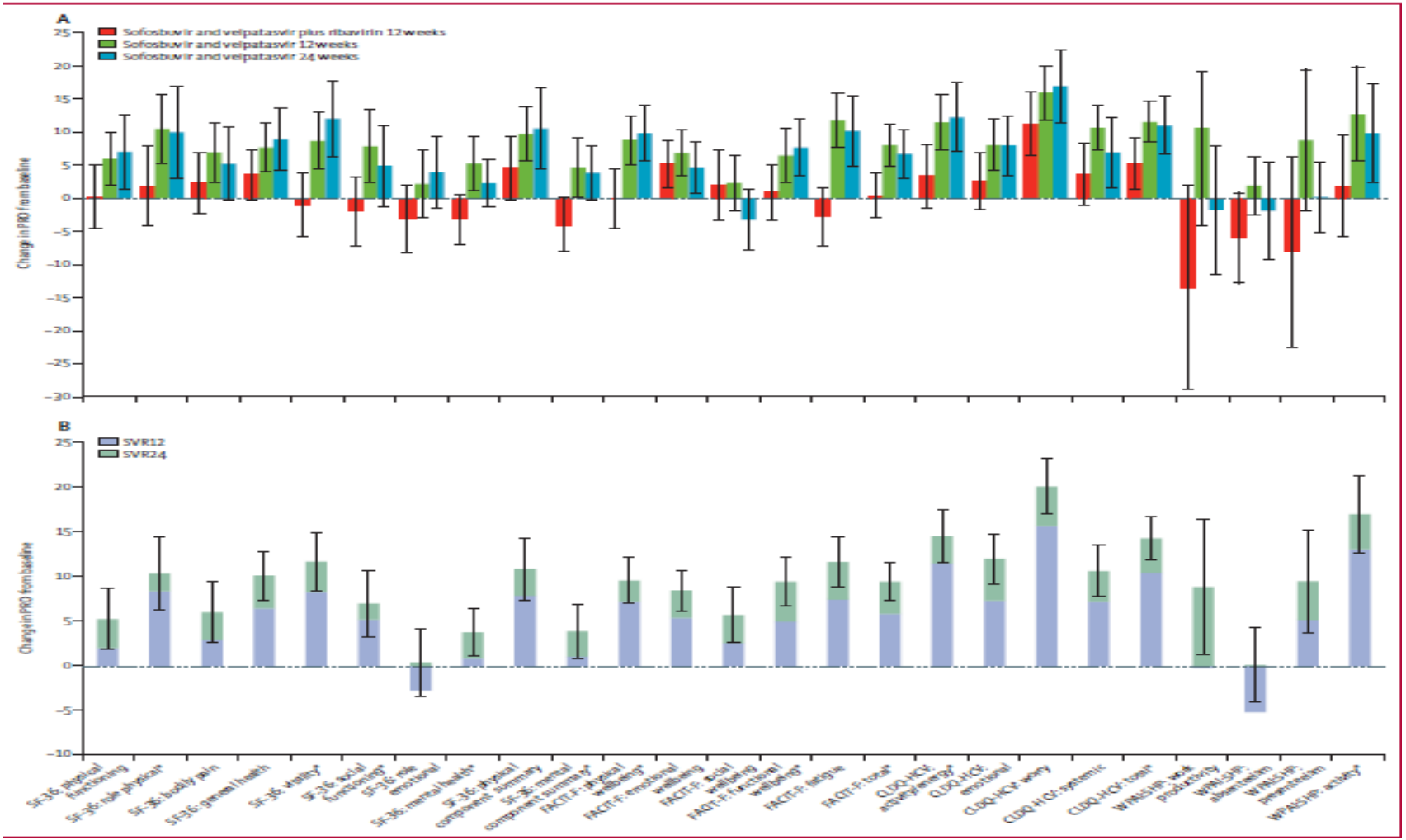

Patient-reported outcomes with sofosbuvir and velpatasvir with or without ribavirin for hepatitis C virus-related decompensated cirrhosis: an exploratory analysis from the randomised, open-label ASTRAL-4 phase 3 trial

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Bütün tedavi gruplarında ve bütün genotiplerde %90 üzerinde KVY
Ribavirin eklenen gruplarda yan etki daha fazla

TEŞEKKÜR EDERİM