Hepatit C Kompanze sirotik

(*naiv yada tedavi deneyimli*)

hastanın tedavisi

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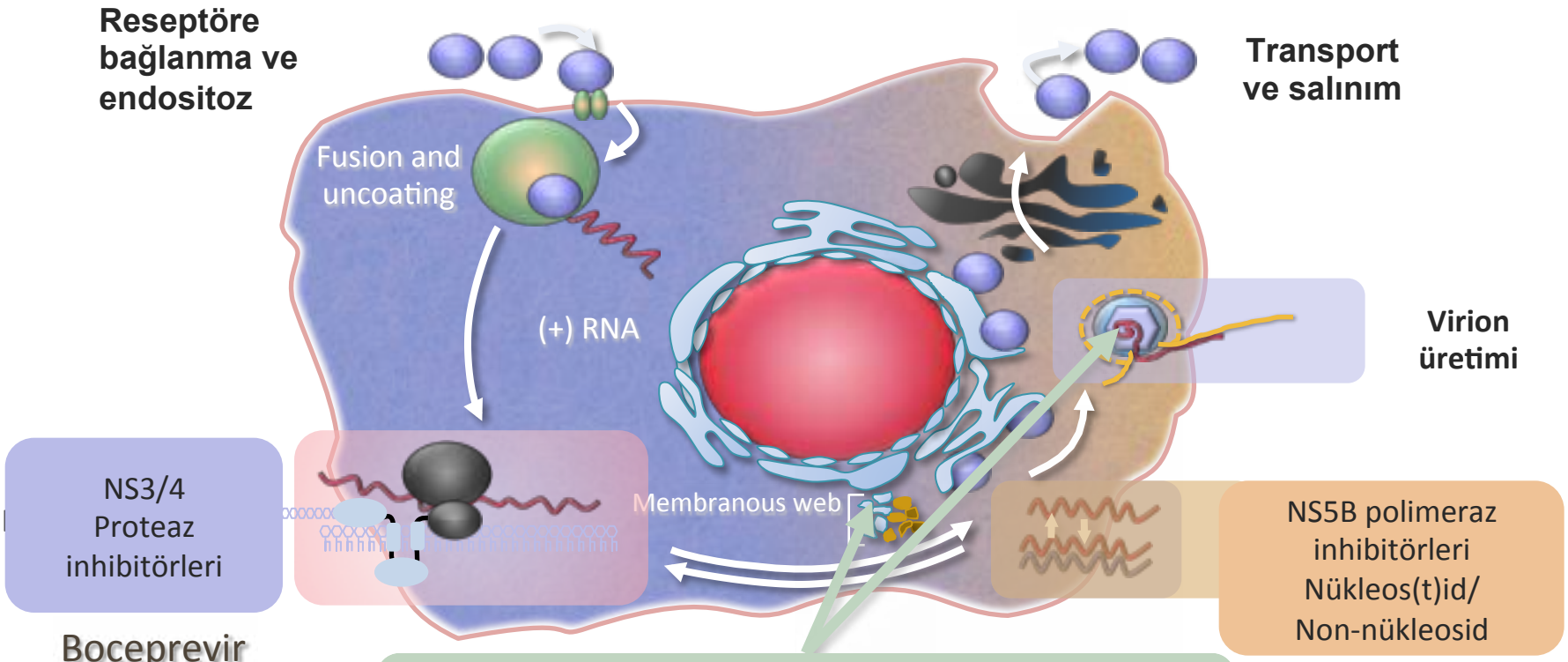
Tedavi üzerine etkili faktörler

- Genotip
- Viral yük (<6 milyon IU/mL, <800,000 IU/mL)
- ~~Yaş~~
- ~~Irk~~
- ~~Cinsiyet~~
- ~~IL28B~~
- Önceki tedaviye yanıt
- Uyum
- Hastalığın ağırlığı (fibroz)
- Metabolik sendrom !

DOĞRUDAN ETKİLİ ANTİVİRALLER İÇİN HEDEFLER



Manns MP, et al. Nat Rev Drug Discov. 2007

YENİ DOĞRUDAN ETKİLİ AJANLAR

NS3/4A Proteaz Inh.
(…previr)
Yüksek potens
Sınırlı genotipik etkililik
Dirence karşı düşük bariyer

NS5B-NI *(sofosbuvir)*
Orta potens
Pangenotipik etkililik
Dirence karşı yüksek bariyer

NS5A Inh. *(…asvir)*
Yüksek potens
Multi genotipik etkililik
Orta derecede direnç bariyeri

NS5B-NNI *(dasabuvir)*
Orta potens
Sınırlı genotipik etkililik
Dirence karşı düşük bariyer

Elbaz T. Et. Al. Journal of Advanced Research (2015) 6, 301–310

Farklı sınıf kombinasyon içeren HCV ilaçları

	DRUG	GENERIC NAME	PHARMACEUTICAL COMPANY
	Harvoni	ledipasvir/sofosbuvir	Gilead Sciences
	Technivie	ombitasvir/paritaprevir/ritonavir	AbbVie
	Viekira Pak	ombitasvir/paritaprevir/ritonavir and dasabuvir	AbbVie
	Zepatier	elbasvir/grazoprevir	Merck
E	ABT-493 + ABT-530	N/A	AbbVie
E	daclatasvir + asunaprevir + beclabuvir	daclatasvir/asunaprevir/beclabuvir	Bristol-Myers Squibb
E	sofosbuvir + velpatasvir	sofosbuvir/velpatasvir	Gilead Sciences

HCV yada HCV/HIV Kompanze sirotik naif yada pegIFN+RBV'ne yanıtsız olanlarda

(EASL 2015)

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

DAA tedavisi başarısız olan HCV yada HCV/HIV naif yada pegIFN+RBV'ne yanıtsızlarda

(EASL 2015)

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
PegIFN-α, RBV and either telaprevir or boceprevir	Genotype 1	12 wk with RBV	No	No	No	12 wk with RBV
Sofosbuvir alone, in combination with RBV or in combination with PegIFN-α and RBV	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 2 or 3	No	No	No	No	12 weeks with RBV or 24 weeks with RBV if F3 or cirrhosis
	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
PegIFN-α, RBV and simeprevir	Genotype 1 or 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
PegIFN-α, RBV and daclatasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Sofosbuvir and simeprevir	Genotype 1 or 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

DAA tedavisi başarısız olan HCV yada HCV/HIV naif yada pegIFN+RBV'ne yanıtsızlarda 2

(EASL 2015)

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Sofosbuvir and daclatasvir or Sofosbuvir and ledipasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir and ombitasvir	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

Recommendations for Testing, Managing, and Treating Hepatitis C

Updated: February 24, 2016. Changes made: April 25, 2016.

Elbasvir/grazoprevir

- ✓ Siroz varlığı etkinliğini değiştirmiyor
- ✓ Başlangıçtaki RAV, GT1a olgularında kalıcı yanıtı etkiliyor (%58 vs %99)
- ✓ GT1a olgularında başlangıçta direnç testi önerilmekte
- ✓ 28,30, 31, 93 aa pozisyonlarında polimorfizm varsa tedavi 16 haftaya uzatılmalı +RBV

Ledipasvir/sofosbuvir

- ✓ Siroz varlığı tedavi yanıtını etkilemiyor
- ✓ Sirotik olgularda 8 hafta önerilMemekte…

Paritaprevir/ritonavir/ombitasvir + dasabuvir

- ✓ PEG-IFN/RBV yanıtsızlarda 12 haftalık tedaviyle başarı oranı %95'ten %89'a düşmekte
- ✓ Siroz olgularında kalıcı yanıt %92
- ✓ Dekompanze sirozda kontrendike
- ✓ Sirotiklerde ilk ay haftalık KCFT izlenmeli

Simeprevir + sofosbuvir

- ✓ GT1a ve Q80K mutasyonunda 12 haftalık tedaviyle kalıcı yanıt %74
- ✓ Sirotiklerde 24 hafta±RBV olabilir yada kullanılmamalı

Daklatasvir + sofosbuvir

- ✓ Sirotik olgularda süre belirsiz
- ✓ ±RBV 24 hafta önerilmekte…

Daklatasvir + asunaprevir (*aasld kılavuzunda yok !*)

<u>24 haftalık tedavi sonrası;</u>

- ✓ İnterferon kullanmamışlarda %87.4
- ✓ İnterferon yanıtsızlarda %80.5
- ✓ Siroz varlığı yanıtı etkilemiyor (%90.9 *vs* %84)
- ✓ İstenmeyen etki: KCFT yüksekliği !..

Naiv Sirotik HCV GT1 Hastalar:

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	Genotip 1a	Genotip 1b
İlk seçenek	LDV/SOF, 12 h	PROD, 12 h
	GZA+ ELB, 12 h	LDV/SOF, 12 h
		GZA+ ELB, 12 h
Alternatif	PROD +RBV, 24 h	SMV+SOF±RBV, 24 h
	SMV+SOF±RBV, 24 h	DAC+SOF±RBV, 24 h
	DAC+SOF±RBV, 24 h	
	GZA+ ELB+RBV, 16 h	

Genotype 3 Treatment-naïve Patients with Compensated Cirrhosis‡ - Recommended

DAC+SOF±RBV, 24 h

SOF+RBV+PegIFN, 12 h

ALTERNATİF:
SOF+RBV, 24 h

Recommended regimens are listed in groups by level of evidence, then alphabetically.

Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis.
Rating: Class IIa, Level C

Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who havecompensated cirrhosis and who are eligible to receive PEG-IFN.
Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 3 Treatment-naïve Patients with or without Cirrhosis‡ - Alternative

Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 3 infection, regardless of cirrhosis status, who are daclatasvir and IFN ineligible.
Rating: Class I, Level A

Genotype 4 Treatment-naïve Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

PROD+RBV, 12 h

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ ombitasvir (25 mg) and weight-based RBV for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, with compensated cirrhosis.†
Rating: Class I, Level B

GZA+ELB, 12 h

Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection withcompensated cirrhosis.
Rating: Class IIa, Level B

LDV/SOF, 12 h

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, withcompensated cirrhosis.
Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.

† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

ALTERNATİF:
SOF+RBV+PegIFN, 12 h

Genotype 4 Treatment-naïve Patients with or without Cirrhosis‡ - Alternative

Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 4 infection who are IFN eligible, regardless of cirrhosis status.
Rating: Class II, Level B

Tedavi deneyimli sirotik HCV GT1 hastalar

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PegIFN/RBV GT1a	**PegIFN/RBV GT1b**	***SOF+RBV±PegIFN GT1a/b***	**NS3 PI + PegIFN/RBV *GT1a/b***	**SIM+SOF *NS5A inhibitor GT1a/b***
GZA/ELB, 12 h LDV/SOF, 24 h LDV/SOF+RBV, 12 h *ALTERNATİF:* PROD+RBV, 24 h GZA/ELB+RBV, 16 h DAC+SOF±RBV, 24 h SIM+SOF±RBV, 24 h	GZA/ELB, 12 h LDV/SOF, 24 h LDV/SOF+RBV, 12 h PROD, 12 h *ALTERNATİF*: DAC+SOF±RBV, 24 h SIM+SOF±RBV, 24 h	LDV/SOF + RBV, 24 h	LDV/SOF+RBV, 12 h LDV/SOF, 24 h DCV+SOF±RBV, 24 h GZA/ELB+RBV, 12 h	Direnç testi ve +RBV, 24 h

Tedavi deneyimli sirotiklerde önerilen rejimler
AASLD 2016

Genotip 3

PEG-IFN/RBV yada
SOF+RBV

SOF+RBV+PegIFN, 12 H

DAC+SOF+RBV, 24 h

Genotip 4

PEG-IFN/RBV

GRA/ELB, 12 h (ted. Sırasında kırılma ise;

+RBV, 16 h)

LED+SOF+RBV, 12 h

LED+SOF, 24 h

Tüm rejimler genel olarak;

- ✓ Tüm rejimlerin güvenlik profili iyi →

  Siroz olan ve olmayanlarda erken tedavi sonlandırma; %2 ve %1.

- ✓ İstenmeyen etkiler en sık RBV ile…
- ✓ NS3 proteaz inhibitor *(paritaprevir, simeprevir, grazoprevir)* rejimlerinde KCFT yüksekliği açısından daha dikkatli olunmalı
- ✓ Tedavi öncesi, simeprevir için Q80K, GRA/ELB için RAV bakılması…

Tüm rejimlerde izlem;

- ✓ Tedavinin 4. haftasında
  - ➢ Tam kan
  - ➢ Kreatinin, GFR
  - ➢ KCFT (öz.le GZR/EBR) → 10 kat artış yada klinik bulgular olursa sonlandırılmalı
- ✓ PROD alanlarda 2 ve 4. haftada KCFT
- ✓ HCV RNA: 4. ve 12. hafta, tedavi sonu ve 24 hafta sonrasında önerilmekte
- ✓ Direnç açısından izleme gerek yok

Table. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs

	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)	Paritaprevir, ritonavir, ombitasvir (PrO)	Grazoprevir/ Elbasvir
Ritonavir-boosted atazanavir	No data	No data	Ledipasvir ↑; atazanavir ↑* (okay with TAF not TDF)	Daclatasvir ↑ [b]	Paritaprevir ↑; atazanavir ↑	Paritaprevir ↑; atazanavir ↔	Grazoprevir ↑; elbasvir ↑; atazanavir ↑
Ritonavir- boosted darunavir	Simeprevir ↑; darunavir ↔	Sofosbuvir ↑; darunavir ↔	Ledipasvir ↑, darunavir ↔ * (okay with TAF not TDF)	Daclatasvir ↑ ; darunavir ↔	Paritaprevir ↓/↑; darunavir ↓	Paritaprevir ↑; darunavir ↔	Grazoprevir ↑; elbasvir ↑; darunavir ↔
Ritonavir-boosted lopinavir	No data	No data	No data*	Daclatasvir ↑ ; lopinavir ↔	Paritaprevir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔	Grazoprevir ↑; elbasvir ↑; lopinavir ↔
Ritonavir-boosted tipranavir	No data	No data	No data	No data	No data	No data	No data
Efavirenz	Simeprevir ↓; efavirenz ↔	Sofosbuvir ↔; efavirenz ↔	Ledipasvir ↓; efavirenz ↓*	Daclatasvir ↓ [b]	No pharmacokinetic data*	No data	Grazoprevir ↓; elbasvir ↓; efavirenz ↓
Rilpivirine	Simeprevir ↔; rilpivirine ↔	Sofosbuvir ↔; rilpivirine ↔	Ledipasvir ↔; rilpivirine ↔	No data	Paritaprevir ↑; rilpivirine ↑	No data	Grazoprevir ↔; elbasvir ↔ ; rilpivirine ↔
Etravirine	No data	No data	No data	Daclatasvir ↓ [b]	No data	No data	No data
Raltegravir	Simeprevir ↔; raltegravir ↔	Sofosbuvir ↔; raltegravir ↔	Ledipasvir ↔; raltegravir ↔	No data	PrOD ↔; ↑ raltegravir	PrO ↔; raltegravir ↑	Grazoprevir ↔; elbasvir ↔ ; raltegravir ↑
Cobicistat-boosted elvitegravir	No data	Cobicistat ↑*; sofosbuvir ↑ (okay with TAF not TDF)	Cobicistat ↑; ledipasvir ↑* (okay with TAF not TDF)	No data	No data	No data	No data
Dolutegravir	No data	No data	Ledipasvir ↔; dolutegravir ↔	Daclatasvir ↔; dolutegravir ↑	Paritaprevir ↓; dolutegravir ↑	No data	Grazoprevir ↔; elbasvir ↔ ; dolutegravir ↑
Maraviroc	No data	No data	No data	No data	No data	No data	No data
Tenofovir disoproxil fumarate	Simeprevir ↔; tenofovir ↔	Sofosbuvir ↔; tenofovir ↔	Ledipasvir ↔; tenofovir ↑	Daclatasvir ↔; tenofovir ↔	PrOD ↔; tenofovir ↔	Pro ↔; tenofovir ↔	Grazoprevir ↔; elbasvir ↔ ; tenofovir ↑

Tedavi sonlandırma durumları

4. haftada HCV RNA pozitif → 6. haftada yinele;

→ 1 log artış var → sonlandır

→ artış yok ama pozitif → **??**