



HEPATİT B TEDAVİSİ ALAN HASTADA İLACA BAĞLI YAN ETKİ

Dr. Ercan YENİLMEZ

Sultan Abdulhamid Han EAH, İstanbul



Olgu 1

Tedavi başlangıç değerleri

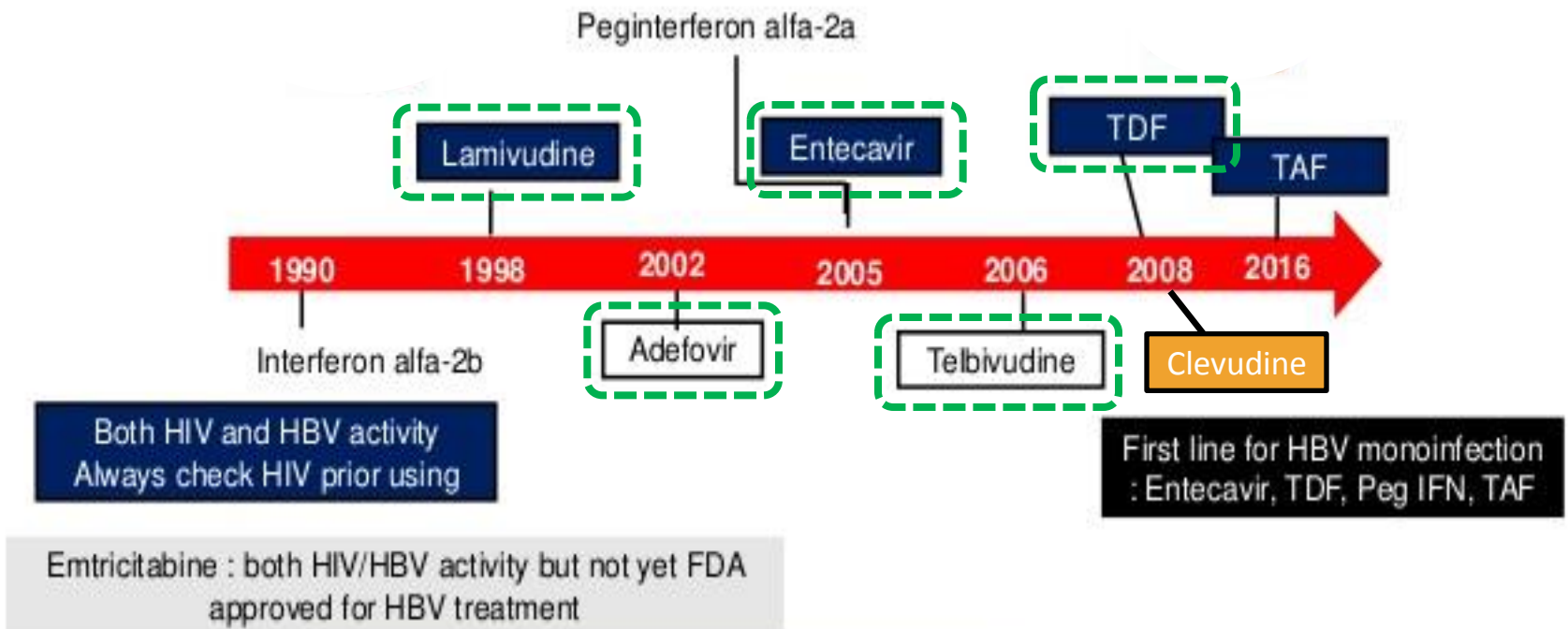
- 2 yıldır HBV (2012)
- Yaş 57, Bayan
- HBV aile öyküsü (+)
- AST: 49 U/L
- ALT: 64 U/L
- HBsAg (+)
- Hbe Ag (-), AntiHBe (+)
- HBV DNA PCR: 2890 IU/mL (Önceki 2.130 IU/mL)
- Delta Ag/Ab - HDV PCR: negatif
- Üre/Kr: 39/1,1 mg/dL
- eGFR: 70 ml/dk/1,73m2
- AFP: 1,17 – 2,2 ng/mL
- TSH T4: normal
- PT/aPTT: normal
- Anti-HCV: negatif
- Anti HIV: negatif
- Psikiyatri normal

BİYOPSİ

HAİ:7/18, Fibrozis: 3/6 (ISHAK)

TEDAVİ?

HBV Treatment Landscape





Olgu 1

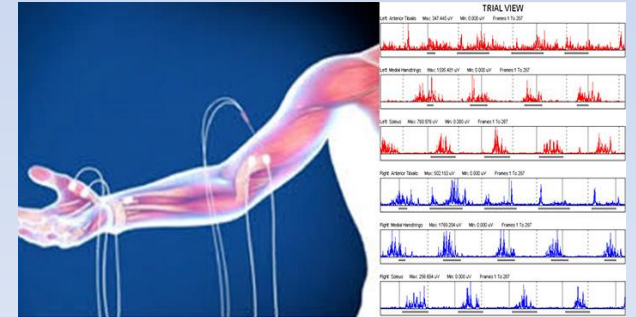


- (2017) 62 yaş, bayan
- Şiddetli **eklem – kas ağrıları**
- Şikayetlerin başlangıcı ilaç başladıktan 6-8 ay sonra
- Kadın doğum, ortopedi ve fizik tedavi plk. müracaatları
- Kaplıca ve sıcak uygulamalar gerilemekte
- İki üç aylık ağrısız dönemler
- Ağrıları dayanılmaz boyutta



Olgu 1

- ✓ Kas ağrısı
- ✓ Nöroloji
 - ✓ CK 20 kat (~3000 U/L)
 - ✓ LDH 3 kat (~1800 U/L)
 - ✓ MRG normal
 - ✓ EMG:
 - ✓ uyluk proksimal kaslarında güç kaybı
 - ✓ fleksiyonda miyopatik deşarj



Olgu 1

A- Hangi tedaviyi alıyor ?

B- Tanımız ne?



Nükleozid/Nükleotid analoglarına bağlı yan etki

	Telbivudin	Lamivudin	Tenofovir	Adefovir	Entekavir
Kas toksisitesi	++ (9-12.9%)	++ (4.1%)			
Periferal nöropati	++ (1.9-7.3%)	+			
Nefrotoksisite			++ (2.6%)	++ (3-12%)	
Laktik asidoz	+				+

+ Vaka bildirimleri

++ Placebo kontrollü prevalans çalışmaları

Lung-Yi Mak, Wai-Kay Seto, Ching-Lung Lai & Man-Fung Yuen. DNA polymerase inhibitors for treating hepatitis B: a safety evaluation. Expert Opinion on Drug Safety, DOI: 10.1517/14740338.2016.1139573

How To 

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Clinical features and risk factors of creatine kinase elevations and myopathy associated with telbivudine

X. J. Zou, X. Q. Jiang and D. Y. Tian *Department of Infectious Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

- CK yüksekliği sık (%12.9)¹
- Miyopati (%2.35)²
- Miyozit (%0.3–0.88)³
- Rabdomiyoliz (olgu bildirimleri)
- Periferik nöropati
 - IFN kombinasyonunda (%17)

Table 1 Baseline characteristics of patients and the status of CK elevations and myopathy

Variable	Status n (%)
Number of patients	200
Duration of telbivudine therapy [medium (range)] (months)	24 (12–42)
Age (mean $\pm$ SD) (years)	32.1 $\pm$ 11.1
Male gender	150 (75)
HBeAg positive	142 (71)
Number of patients with CK elevations	122
Grade 1 (1–3 $\times$ ULN)	77 (63.12)
Grade 2 (3–7 $\times$ ULN)	30 (24.59)
Grade 3 (7–10 $\times$ ULN)	9 (7.37)
Grade 4 (>10 $\times$ ULN)	6 (4.92)
Number of patients with myopathy	9
Muscle symptoms	4 (44.44)
Myositis	5 (55.56)
Rhabdomyolysis	0 (0)

¹Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al.; GLOBE Study Gro-up. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in pati-ents with chronic hepatitis B. *Gastroenterology* 2009; 136: 486–95

²Brown CA, Smith F, Laessig KA. Creatine kinase elevations and muscle toxicities associated with chronic telbivudine use in prospective clinical trials. *Hepatology* 2007; 46(Suppl 1): 655.

³Matthews SJ. Telbivudine for the management of chronic hepatitis B virus infection. *Clin Ther* 2007 29(12): 2635–2653.

İlaç	Potansiyel yan etkiler
Entekavir	Laktik asidoz; dekompanse sirozda*
Tenofovir disoproksil fumarat	Nefropati, Fanconi sendromu, osteomalazi, laktik asidoz
Tenofovir alafenamid	Laktik asidoz
Lamivudin	Pankreatit, Laktik asidoz
Adefovir	Akut böbrek yetmezliği, Fankoni sendromu, Laktik asidoz
Telbivudin	Kreatinin kinaz artışı ve miyopati Periferel nöropati Laktik asidoz

Approved Antiviral Therapies in Adults, AASLD 2018

Patofizyoloji

HBV DNA polimeraz
inhibisyonu

Nükleoz(t)id analogları

mtDNA polimeraz γ inhibisyonu

Intrasellüler mtDNA seviyesinde
azalma

Mitokondrial disfonksiyon

Bozulmuş oksidatif fosforilasyon

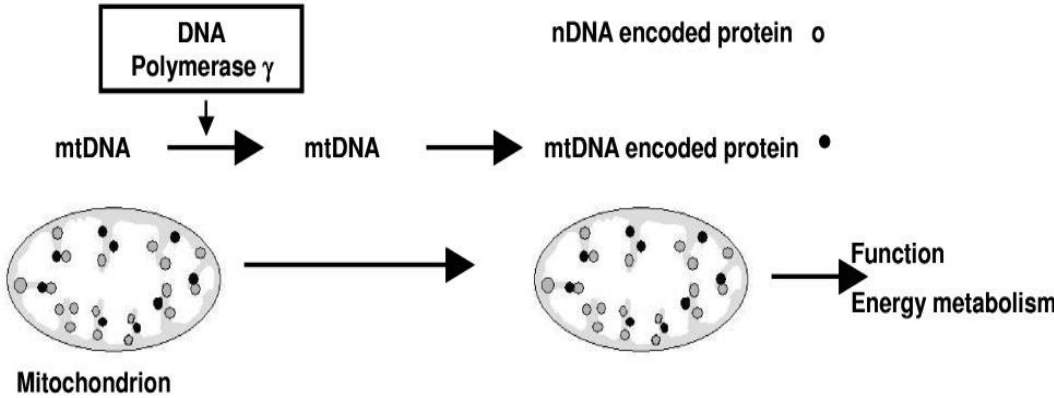
Artmış reaktif oksijen ürünleri

Intrasellüler protein lipid hasarı

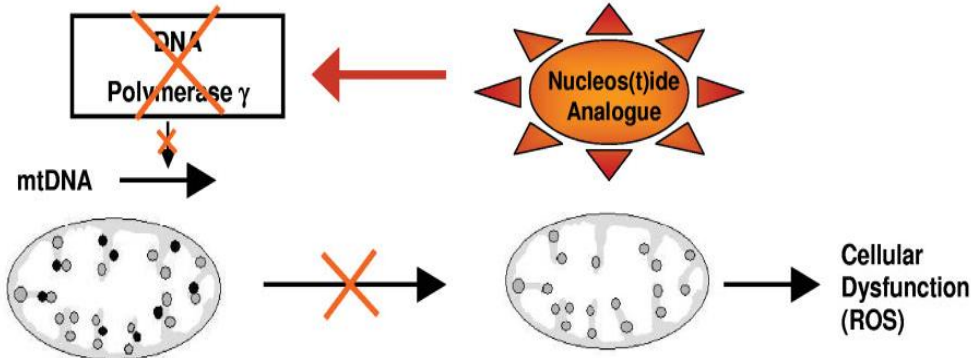
Laktik asidoz ve hc ölümü

A

Class effect of NAs

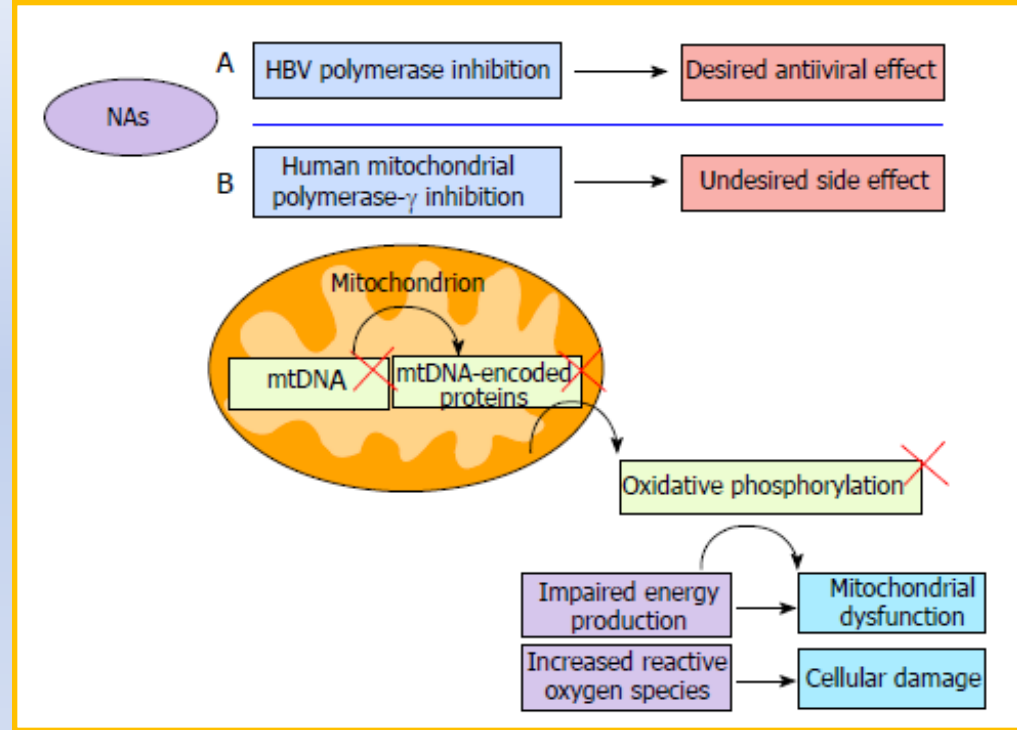


B



NA' lerin sınıf etkisi

- Hematolojik bozukluklar
- Periferel nöropati
- İskelet ve kardiyak miyopati
- Pankreatit
- Hepatik yetmezlik
- Laktik asidoz



Kayaaslan B, Guner R. Adverse effects of oral antiviral therapy in chronic hepatitis B. World J Hepatol. 2017 Feb 18;9(5):227-241

Telbivudin Miyotoksisiyesi - Tanı

- Klinik
 - Kırgınlık, güçsüzlük, miyalji
 - İştahsızlık
 - Simertrik proksimal kas kuvvetinde azalma
- Laboratuvar
- EMG
- Histopatoloji
 - Miyofiber dejenerasyon/nekroz
 - Sitoplazmik cisimcikler
 - Lenfosit infiltrasyonu

Tedavi

- Telbivudin kesilmesi***
- Hidrasyon
- Alkalizasyon
- Düşük doz steroid
- Koenzim Q 10
- L-asetilkarnitin
- Hemofiltrasyon



A- Telbivudini kesmem, ETC (0.5 / 1 gr) başlarım ?

B- Telbivudini keserim, ETC (0.5 / 1 gr) başlarım ?

C- Telbivudini keserim, TDF başlarım ?

D- Telbivudini keserim, tedavisiz takip ederim ?

Literature review of patients who developed severe adverse events during telbivudine treatment

Patient number	Age (years)	Adverse effect	Liver condition	Tx time (months)	Peak CK (U/L)	Peak lactate (mmol/L)	Prognosis	Reference
1	27	Myopathy	CHB	3	3243	–	Resolved	[4]
2	67	Myopathy	CHB	20	4775	–	Resolved	[14]
3	25	Myopathy	CHB	6	1614	–	Resolved	[15]
4	28	Myopathy	CHB	9	788	–	Resolved	[16]
5	25	Myopathy	CHB	13	2992	–	Resolved	[16]
6	68	Myopathy	CHB	2	237	–	Resolved	[17]
7	35	Rhabdomyolysis, lactic acidosis	CHB	11	3683	> 12.0	Resolved	[6]
8	26	lactic acidosis	CHB	12	4151	11.3	Resolved	[18]
9	30	Rhabdomyolysis, lactic acidosis, organ failure	CHB	11	8050	> 20.0	Resolved	This paper
10	48	Rhabdomyolysis, metabolic acidosis, organ failure	Cirrhosis	9	3246	–	Death	[5]

Jinxin Zheng et al., Rhabdomyolysis, lactic acidosis, and multiple organ failure during telbivudine treatment for hepatitis B: a case report and review of the literature. J Med Case Rep. 2017; 11: 331

Telbivudini keserim, tedavisiz takip ederim ?

Clinical Practice Guidelines



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EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection[☆]

European Association for the Study of the Liver*

NA discontinuation Recommendations

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1).
- NAs can be discontinued in non-cirrhotic HBeAg-positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted (Evidence level II-2, grade of recommendation 2).
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (≥ 3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2).

Limited sustained response and lack of HBsAg decline after stopping long-term nucleos(t)ide analogue therapy in HBeAg negative patients with chronic hepatitis B:

Results of the prospective, randomized, open-label phase IV STOP study

Kin Seng Liem^{1,2}, Scott Fung¹, David K. Wong¹, Colina Yim¹, Seham Noureldin¹, Feng Fei Huang¹, Hemant Shah¹, Jordan J. Feld^{1,3}, Bettina E. Hansen^{1,2,4}, Harry L.A. Janssen¹

1 Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, Toronto, Canada.

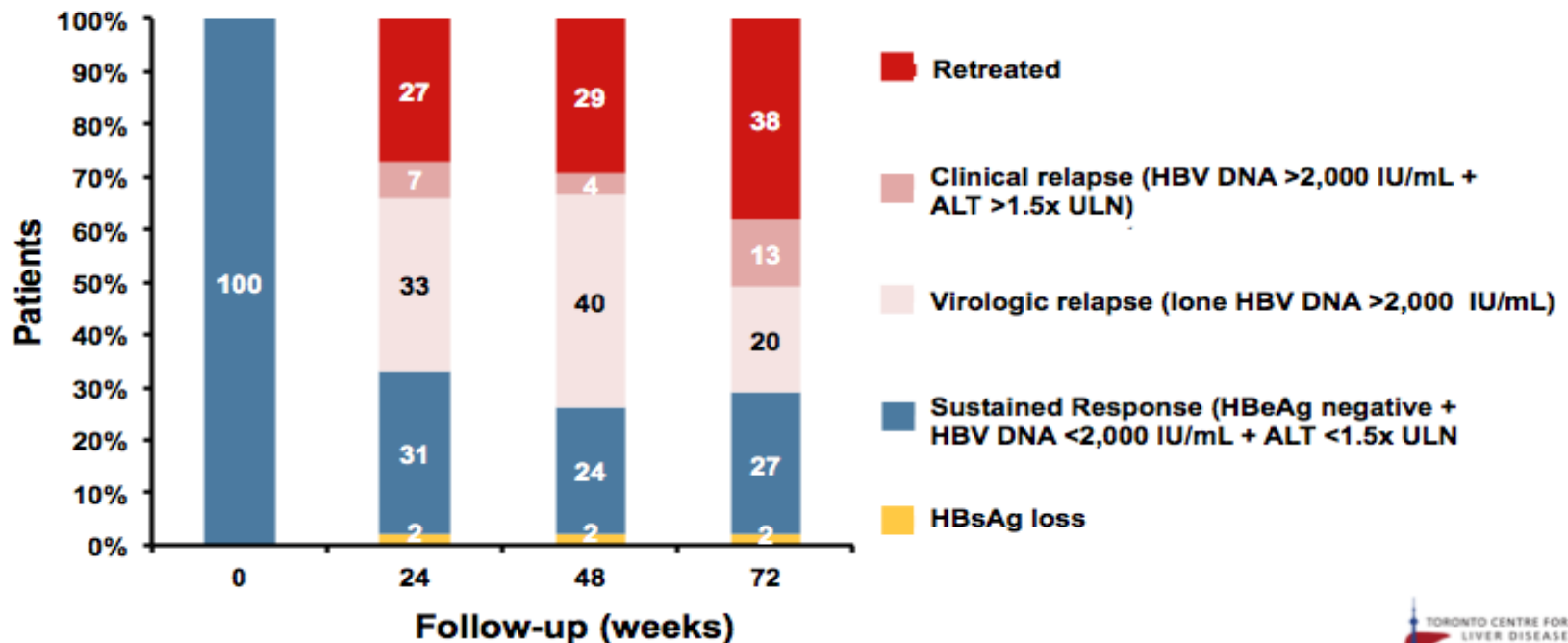
2 Department of Gastroenterology and Hepatology, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.

3 McLaughlin-Rotman Centre for Global Health, Toronto, Canada.

4 Institute of Health Policy Management and Evaluation, University of Toronto, Toronto, Canada.

AASLD 2018 Nov 9-13 SF

Sustained response, retreatment & HBsAg loss in stop arm (n=45)



Olgu 1

Tedavi STOP

	HBV DNA (IU/mL)	ALT (U/L)	AST (U/L)	CK (U/L)	LDH (U/L)
Haziran 2017	-	44	70	2980	1766
Temmuz 2017	-	35	42	133	590
Ağustos 2017	-	45	51	120	338
Eylül 2017	19800	242	183	92	220
Ekim 2017	102	38	41	55	232
Kasım 2017	-	32	26	62	280

TDF Tedavisi

Sonuç olarak;

- Telbuvudin kesildikten 1 ay sonra hastanın semptomları geriledi
- CK yüksekliği 3. ayda normale döndü
- 3. ayda HBV reaktivasyonu gelişti
- TDF tedavisi başlandı
- Halen TDF ile takipleri devam etmekte





Olgu 2

- 59 yaşında erkek hasta
- 12 yıldır Kr.HBV tedavisi altında
- 2012'de LAM direnci
- Biyopsi: HAI:6/18, F:5/6 (2012)
- CHILD A (Kompanse siroz)
- TDF almakta
- 5 yıldır DM (OAD)
- HBeAg (-), HBV DNA (-)
- AST, ALT normal
- Üre normal, kreatinin: 1.2~1.4 mg/dl



Olgu 2

Başvuru şikayeti

- Bir haftadır halsizlik, son 3 gündür bulantı – kusma
- FM: Ateş 36.3°C, TA: 160/100 mm/hg
- +2 pretibial ödem



Olgu 2

Renal toksisite..

ABY...

TDF?

	WBC	CRP	ALT	AST	Üre	Kr	eGFR	N	Prot (spot)
26.09.17	7.600	<2	32	21	92	3.82	15.5	7.3	Prot (+2), Glu (+1)
02.10.17					76	3.52	17.1	7.32	Prot (+2), Glu (+1)
10.10.17							2.5	7.36	Prot (+1), Glu (+1)
15.11.17							2.7		Prot (Eser) Glu (eser)
17.01.18							3.6		
18.04.18									
21.08.18									



- 24 saatlik idrar protein: 264 mg/dl
- Renal USG: böbrek boyutlarında artış, parankimde bilateral grade 1-2 ekojenite artışı

Olgu 2



- Peg-IFN-alfa, LAM (R) deneyimli
- 2012'de LAM direnci
- Biyopsi: HAI:6/18, F:5/6 (2012)
- CHiLD A (Kompanse siroz)

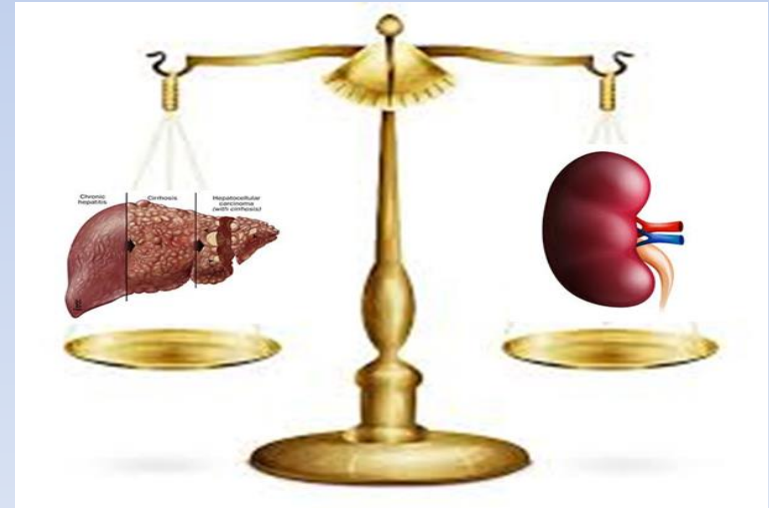
A- TDF keserim, tedavisiz takip ederim ?

B- TDF keserim, ETV başlarım ?

C- TDF keserim, TAF beklerim ?

D- Direnç çalışırım ?

E- TDF devam ederim, diğer nedenleri araştırırım?



TDF keserim, tedavisiz takip ederim ?

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- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (≥ 3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2).

Entecavir monotherapy improves renal function in patients developing renal side effects during long-term tenofovir treatment without compromising virological response: a multicenter real-life study in 103 patients

Mauro Vigano, Alessandro Loglio, Mattia Cappelletti *et al.*



- 49% siroz, 75% LMV, 46% LMV-resistance (R), 71% adefovir dipivoxil (ADV) öyküsü
- TDF'ye bağlı renal toksisite gelişen hastalar
- TDF k
- 94 ha
- 72% F
- 27.ayda
- LAM direnci olmayanların **tamamında virolojik yanıt** korunuyor,
- LAM dirençli 46 olgunun 4'ünde (%8.7) entekavir direnci mevcut

ETV'ye geçelim mi?
Suçlu TDF mi?

Nükleozid/Nükleotid analoglarına bağlı yan etki

	Telbivudin	Lamivudin	Tenofovir	Adefovir	Entekavir
Kas toksisitesi	++ (9-12.9%)	++ (4.1%)			
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Nefrotoksisite			++ (2.6%)	++ (3-12%)	
Laktik asidoz	+				+

+ Vaka bildirimleri

++ Placebo kontrollü prevalans çalışmaları

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REVIEW ARTICLE

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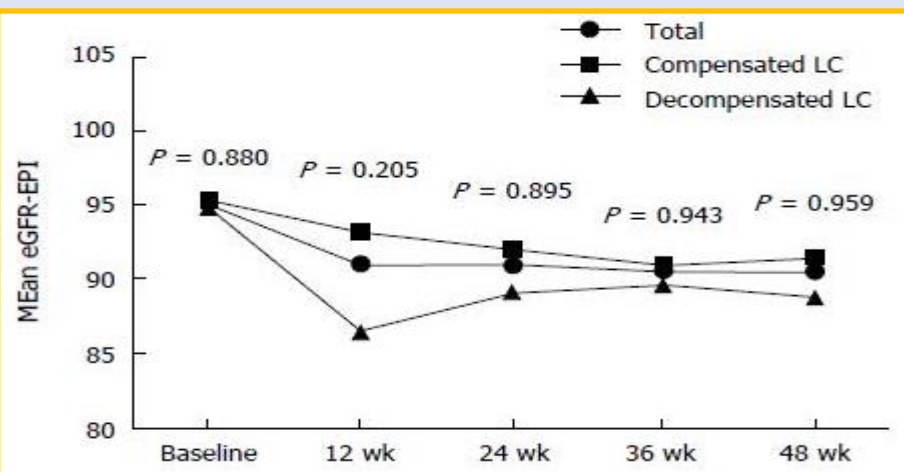
Long-term safety and efficacy of nucleo(t)side analogue therapy in hepatitis B

Safety of TDF and ETV in real-world setting

Study	Follow-up (years)	N	NAs	AEs Discontinuation	Lactic acidosis	Renal-related events	
						TDF	ETV
USA ²¹	5	658	ETV	8 (1.2%)	2 (0.3%)	-	2 (0.3%)
China ²³	5	222	ETV	0 (0%) ^a	0 (0%)	-	N/A
Spain ²²	4	611	TDF/ETV	0 (0%)	0 (0%)	7 (1.7%)	4 (2.1%)
USA ³⁸	N/A	160	TDF/ETV	0 (0%)	0 (0%)	3 (3.8%)	11 (13.8%)
Spain ¹⁷	3	158	TDF/ETV	0 (0%)	0 (0%)	2 (2%)	2 (3%)
France ²⁸	3	440	TDF	23 (5%)	0 (0%)	7 (1.6%)	-
Germany ²⁹	3	400	TDF	11 (2.8%)	0 (0%)	5 (1.3%)	-

Observational Study

Safety and efficacy of tenofovir in chronic hepatitis B-related decompensated cirrhosis



	All (n = 174)	Mean eGFR (CKD-EPI equation)		P value
		Compensated LC (n = 117)	Decompensated LC (n = 57)	
Baseline	95.2 ± 17.8	95.4 ± 14.8	94.8 ± 23.0	0.880
Week 12	91.1 ± 16.2	93.2 ± 13.0	86.6 ± 21.1	0.205
Week 24	91.1 ± 17.5	92.2 ± 14.2	89.2 ± 22.0	0.895
Week 36	90.6 ± 16.6	91.1 ± 14.4	89.7 ± 20.3	0.943
Week 48	90.7 ± 18.4	91.6 ± 14.9	88.9 ± 23.8	0.959

Effects of Entecavir and Tenofovir on Renal Function in Patients with Hepatitis B Virus-Related Compensated and Decompensated Cirrhosis

Jihye Park¹, Kyu Sik Jung¹, Hye Won Lee^{1,2}, Beom Kyung Kim^{1,2,3}, Seung Up Kim^{1,2,3}, Do Young Kim^{1,2,3}, Sang Hoon Ahn^{1,2,3}, Kwang-Hyub Han^{1,2,3}, and Jun Yong Park^{1,2,3}

¹Department of Internal Medicine, Yonsei University College of Medicine, ²Yonsei Liver Center, Yonsei University Health System, and ³Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

Table 2. Changes in Renal Markers

Marker	Group (n)	Baseline	Week 48	Week 96	LS mean±SE change (%) from baseline to week 96	p-value*
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Table 3. Changes in Renal Markers Following Treatment

	TDF	ETV	p-value*
All patients (n=235)	n=73	n=162	

Table 5. Independent Risk Factor for Decreases in eGFR >20% (CKD-EPI Equation)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Tenofovir (vs entecavir)	1.195 (0.410–3.485)	0.745	1.393 (0.434–4.472)	0.578
Male sex	1.355 (0.465–3.946)	0.578		
Age	0.977 (0.924–1.034)	0.426		
History of hypertension	2.957 (1.104–7.918)	0.003	2.378 (0.769–7.356)	0.133
History of diabetes mellitus	5.855 (2.168–15.813)	0.001	5.692 (1.823–17.776)	0.003
Use of diuretics	8.104 (2.612–25.147)	0.001	20.170 (5.043–80.672)	<0.001
Use of NSAID	2.985 (0.990–9.002)	0.052		
eGFR (CKD-EPI)	1.060 (1.014–1.108)	0.009	1.043 (1.002–1.084)	0.038
Compensated cirrhosis (vs decompensated cirrhosis)	2.418 (0.887–6.592)	0.084		

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance

5. The AASLD suggests no preference between entecavir or tenofovir (TDF) regarding potential long-term risks of renal and bone complications

Guidance: TAF is associated with lower rates of bone and renal abnormalities than TDF.

Technical Remarks

1. The existing studies do not show significant differences in renal dysfunction, hypophosphatemia, or bone mineral density between HBV-infected persons treated with tenofovir (TDF) or entecavir. However, renal events, such as acute renal failure or hypophosphatemia, have been reported in TDF-treated persons.

Olgu 2

- Şikayetleri başlamadan önceki hafta boyunca günde bir iki kez **naproksen sodyum** ve/veya **flurbiprofen** kullanımı
- NSAID kullanımına bağlı ABY olarak değerlendirildi
- Hasta renal biyopsiyi kabul etmedi
- Hastaya düşük doz 1mg/kg/gün dozunda steroid tedavisi
- 1 ay içinde doz azaltılarak sonlandırıldı.
- TDF renal dozda devam edildi.

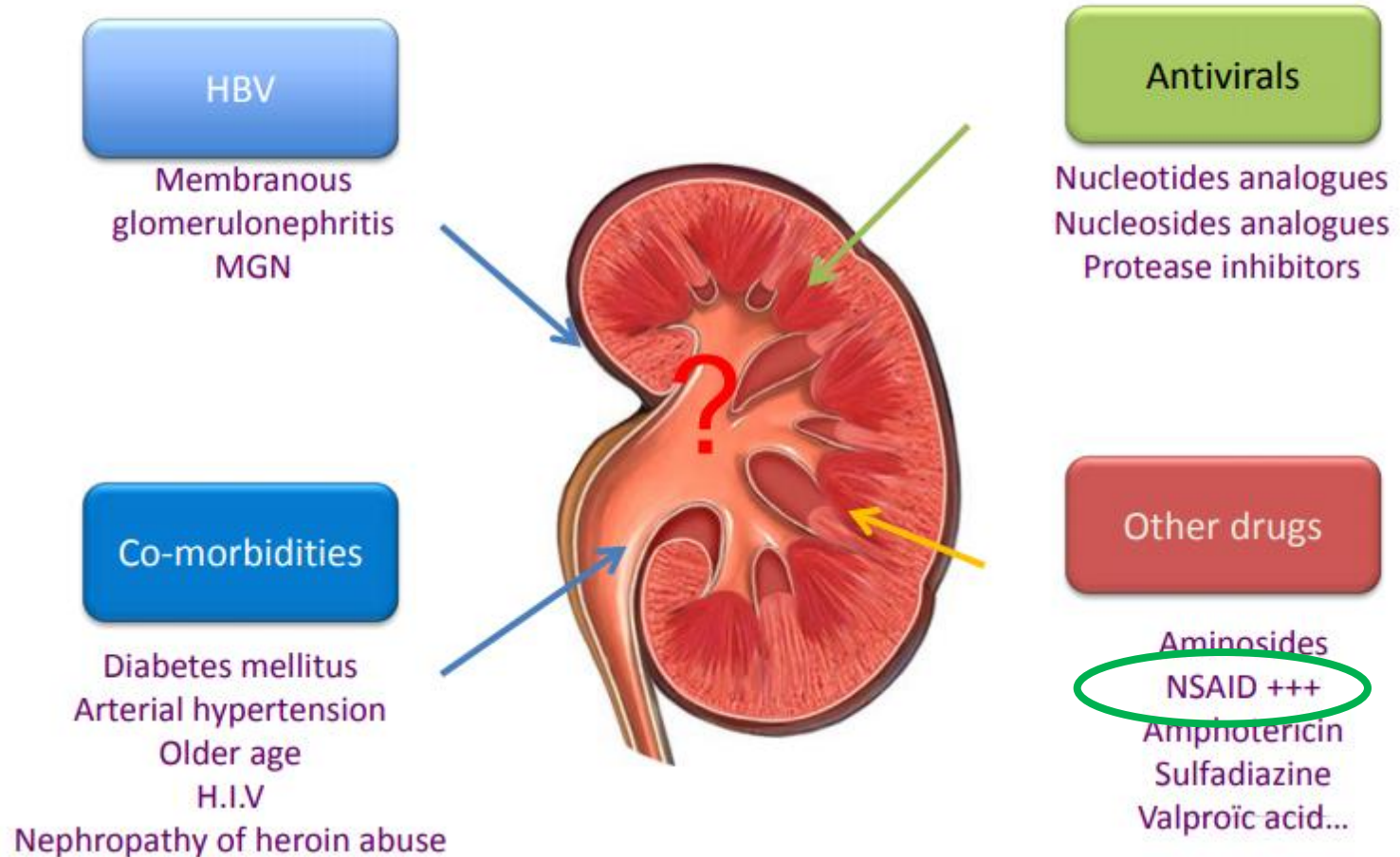


Olgu 2

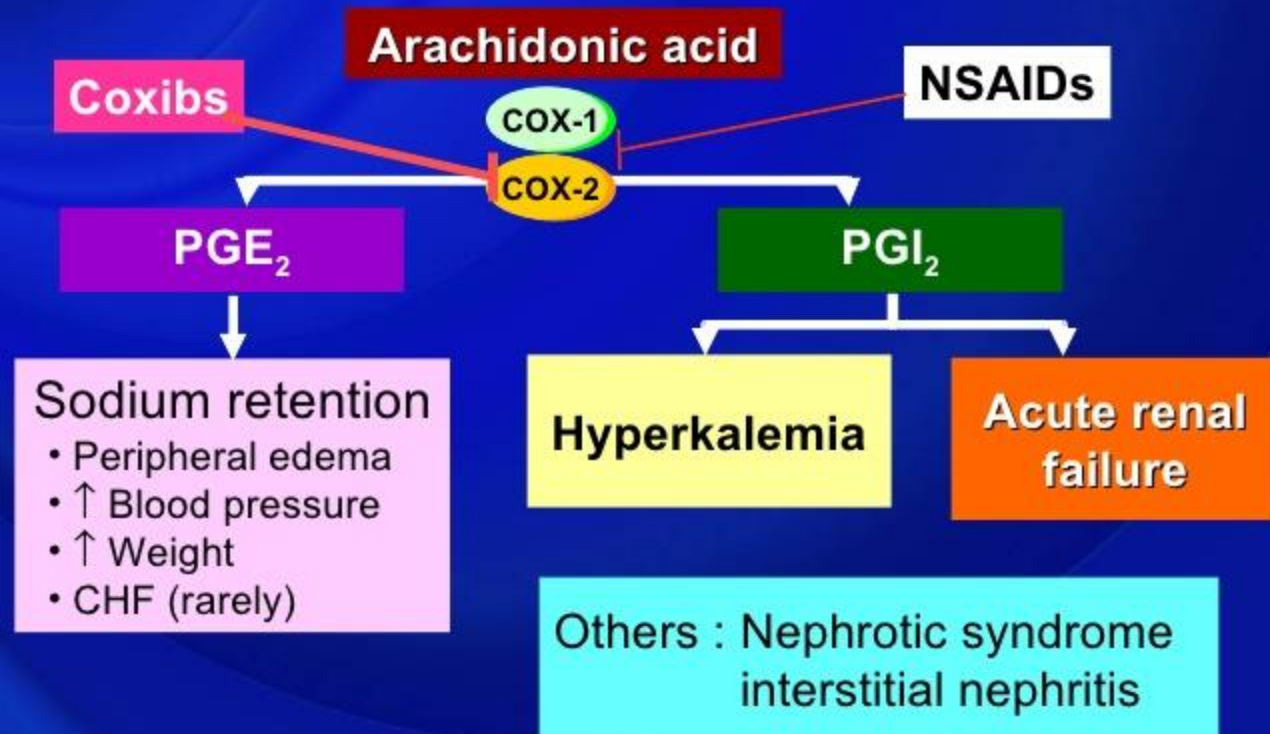
	WBC	CRP	ALT	AST	Üre	Kr	eGFR	Na	K	P	Glu	pH	TİT (Spot)
26.09.17	7.600	<2	32	21	92	3.82	15.5	153	5.9	2.2	118	7.3	Prot (+2), Glu (+1)
02.10.17					76	3.53	17.1	149	5.4	2.3		7.32	Prot (+2), Glu (+1)
10.10.17					52	2.52	26.8	144	4.8	2.5		7.36	Prot (+1), Glu (+1)
15.11.17					55	2.24	30.9	139	4.1	2.7			Prot (Eser) Glu (eser)
17.01.18					46	1.99	35.7			3.6			
18.04.18					42	1.41	54.5						
21.08.18					44	1.24	63.7						Glu: eser +

- Hastanın şikayeti yok, HBV DNA: negatif

Main Pathologic Conditions And Treatments That May Cause Kidney Injury In Chronic Hepatitis B Patients



NSAIDs & Renal Effect



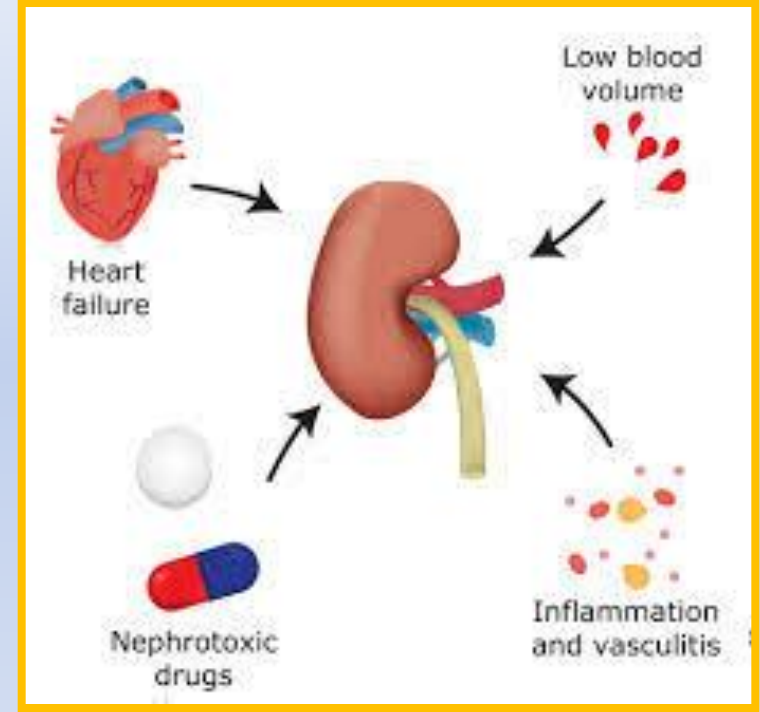
Brater. Am J Med. 1999;107:65S.

NSAID nefropatisi

- Sağlıklı kişide, NSAID'ların böbrek yetmezliği yapması konusundaki deliller çok kısıtlıdır

NSAID alanlarda nefropati için riskli olgular

- 60 yaş üzeri arteriyosklerotik hastalar
- Kronik böbrek yetmezliği
- HT; Diüretik – Ace inh kullanımı
- **Karaciğer** ve konjestif kalp **yetmezliği**, nefrotik sendrom gibi renal hipoperfüzyon halleri



EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection[☆]

European Association for the Study of the Liver^{*}

NA tedavisi alanlarda yüksek renal risk;

- Dekompanse siroz
- Kreatinin klirensi (eGFR) <60 ml/min
- Hipertansiyon
- Proteinüri
- Kontrolsüz diyabet
- Aktif glomerulonefrit
- Eş zamanlı nefrotoksik ilaç kullanımı (NSAID, aminoglikozid, kontrast madde)
- Solid organ transplantasyonu



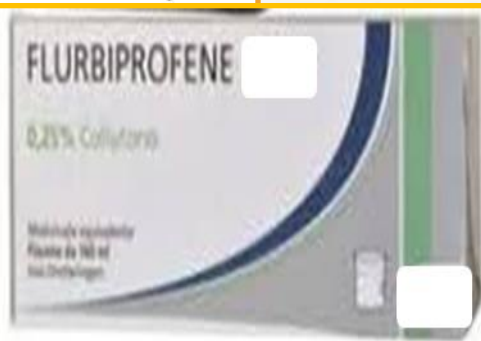
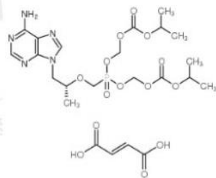
1 Interaction Found

Clear All



⊗

Tenofovir disoproxil fumarate



tenofovir df + flurbiprofen

tenofovir DF, flurbiprofen. Either increases levels of the other by decreasing renal clearance. Modify Therapy/Monitor Closely. Toxicity may result from coadministration of tenofovir DF with other drugs that are also primarily excreted by glomerular filtration and/or active tubular secretion including high-dose or multiple-dose NSAIDs; alternatives to NSAIDs should be considered.

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**Take
home message*

- Kr. Hepatit hastalarında antienflamatuvar ve diğer ilaçların kullanımına dikkat !
- TDF'ye bağlı böbrek toksisitesi HBV'de nadir
- Kesin tanı zor, iyi anamnez***
- Böbrek toksitesi açısından etyolojinin ve risk faktörlerinin bilinmesi önemli
 - Tanı
 - Yönetim
 - Tedavi seçimi; ETV, TDF, TAF...



TEŞEKKÜRLER...