Tenofovir ± Entekavir Tedavisinde Olgu Yönetimi

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SAĞLIK BİLİMLERİ ÜNİVERSİTESİ DERİNCE EĞİTİM ARAŞTIRMA HASTANESİ, KOCAELİ

OLGU

- 42 yaşında erkek hasta
- 2004yılında HBsAg pozitifliği saptanıyor
- Fizik muayene doğal
- Öz geçmişinde özellik yok, bulaş öyküsü yok
- Soy geçmişinde özellik yok

Laboratuvar (2004)

- HBc IgM (-)
- HBc IgG (+)
- Hbe Ag (+)
- Anti-Hbe (-)
- Delta antikoru (-)
- HBV DNA ??

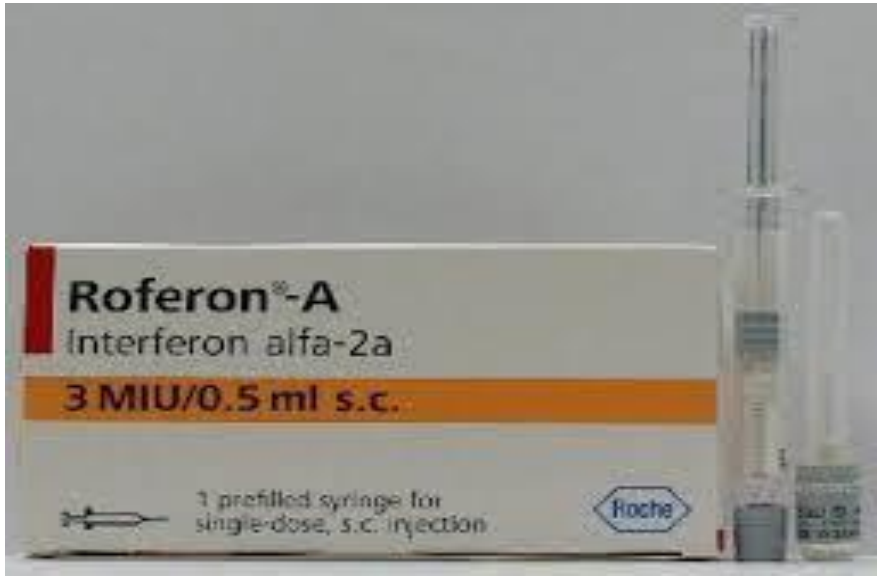
- WBC:9800/mm^3
- Plt: 212000/mm^3
- AST/ALT:30/28 U/L
- INR:1,12
- Total protein:7,4 g/L
- Albumin:4,3 g/L

- Karaciğer Biyopsi:
    - HAİ: 9/18,
    - Fibrozis: 2-3/6

Tedavi (2004)

- Klasik interferon alfa 2a

  - haftada üç kez 3 milyon ünite
- Tedavinin 3. ayında HBV DNA negatif
- Tedavi bir yıla tamamlandı
- Hastanın tedavi sonu HBV DNA negatif



Klasik interferon tedavisi

- Tedavi sonu altıncı ay kontrolünde;
  - HBV DNA:3.560.000 copy/ml
  - AST/ALT: 33/46 U/L
  - HBeAg pozitif,

Tedavi 2005

- Hasta relaps olarak kabul edildi
- Peg interferon alfa 2a haftada bir 180 mikrogram başlandı;
  - 48. hafta HBV DNA negatif
- Peg interferon alfa 2a tedavi sonu 3. ayda;
  - ALT/AST:33/31
  - HBV DNA: 2.580.000 IU/ml

Tedavi (2006)

- Kasım 2006;
- Adefovir 10 mg/gün başlandı
- Adefovir tedavisi altında;
    - 3.ayda 1.623.000 copy/ml
    - 6. ayda HBV DNA:3.390.000 copy/ml
    - AST, ALT üre ve kreatinin normal

Adefovir Tedavisi

Adefovir tedavisinin 12.ay kontrolü;

- HBsAg(+)
- HBeAg (+)
- Anti- Hbe (-)
- HBc IgG (+)
- ALT /AST:32/27
- HBV DNA: 135.000.000 copy/ml

Tedavi (2008)

-Entekavir 1mg/gün tedavisine geçildi

-Entekavir tedavisinin 12. Ay kontrolünde;

- HBVDNA: 121.392.000 copy/ml
- ALT, AST, PTZ, INR, albumin normal
- Kontrol abdominal ultrasonografisinde patoloji saptanmadı

-Entekavir tedavisine devam edildi

Tedavi (2010)

Entekavir tedavisinin 15. ay kontrolünde;

- HBV DNA: 3.000.000 copy/ml
- ALT,AST normal
- Direnç?? (test yaptırılamadı)

Tedavi 2010

- Tenofovir disoproxil fumarat (TDF) 300 mg/gün geçildi

Viread 300mg

Tenofovir tedavisi (2010)

Tenofovir tedavisi	Tedavi başlangıcı	3. ay	6. ay	9.ay	12.AY
HBV DNA (Copy/ml)	3.000.000	490	negatif	1623	1730
ALT/AST	29/28	29/23	29/26	29/23	34/28

Tedavi 2011

- Uyum sorgulandı
- Tenofovir tedavisine entekavir 0.5 mg/gün eklendi

(6) Erişkin hastalar oral antiviral tedavi altındayken;

a) Oral antiviral tedavisi alan hastalarda negatif olan HBV DNA'nın pozitifleşmesi veya HBV DNA'nın 10 kat yükselmesi ile başka bir oral antiviral ajana geçilebilir veya almakta oldukları tedaviye ikinci bir oral antiviral eklenebilir. Başka bir antiviralden lamivudine geçişte ve entekavir veya adefovir tedavisinden tenofovir tedavisine geçişte bu koşullar aranmaz. Lamivudin veya telbivudin tedavisinin 24 üncü haftasında HBV DNA 50 IU/ml (300 kopya/ml) ve üzerinde olan hastalarda diğer oral antiviraller kullanılabilir. Ancak bu tedavilerin 24 üncü haftasında HBV DNA 50 IU/ml (300 kopya/ml) altında ise başka bir oral antiviral ajana geçilemez veya eklenemez.

b) Tenofovir veya adefovir veya entekavir ile tedavi alan hastalarda birinci yılın sonunda halen "HBV DNA pozitif" olması durumunda tedaviye başka bir oral antiviral eklenebilir.

c) Oral antiviral tedavisi alan hastalarda gebelik durumunda oral antiviral değişiminde bu koşullar aranmaz.

ç) Oral antiviral değişimi ya da tedaviye yeni oral antiviral eklenmesi için, düzenlenecek yeni veya mevcut raporda bu durum belirtilir.

Tenofovir + Entecavir	05.07.2011	15.11.2011	25.01.2012	19.02.2012	2013	2014	2015	2016
HBV DNA (copy/ml)	1730	382	68	Negatif	44.1 (IU/ml)	Negatif	Negatif	Negatif

- 2016 yılında HBV DNA negatif olması üzerine hastanın entecavir tedavisi kesilerek tenofovir tedavisinin devamına karar verildi
- Hasta takipten çıktı

KHB’de tedavinin amacı

- KC sirozu, yetmezliği ve hepatosellüler kanseri önlemek
- Hastanın hayat kalitesini yükseltmek
- Anneden bebeğe geçişi, hepatit B reaktivasyonu ve ekstra hepatik tutulumları önlemek
- İdeal amaç; HBV‘nin eradikasyonudur

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Tedaviden beklentiler

İNFLAMATUAR:

- ALT normalleşmesi
- Biyopsiyle karaciğerin inflamasyonunda gerileme

VİROLOJİK:

- Virus replikasyonunun durması
- HBV DNA'nın negatifleşmesi

İMMÜN: Serokonversiyon

- HBe Ag → Anti HBe
- HBs Ag → Anti HBs

KLİNİK İYİLEŞME

Tablo 4. Kronik Hepatit B'de Tedavi Türlerine Göre Virolojik Yanıt Tanımları (89)

İnterferon ve Pegile İnterferon Tedavisi
Virolojik yanıt: Tedavinin 6. ayında, tedavi bitiminde, tedavi bitiminden 6 ay ve 12 ay sonra HBV DNA<2000 İÜ/ml olması.
Kalıcı virolojik yanıt: Tedavi bitiminden en az 12 ay sonra HBV DNA<2000 İÜ/ml olması.
Nükleoz(t)id Tedavisi
Primer yanıtsızlık: Tedavinin 12. haftasında, HBV DNA düzeyinde <1 log İÜ/ml azalma olması.
Virolojik yanıt: HBV DNA'nın PCR ile saptanamayacak düzeye inmesi.
Kısmi virolojik yanıt: Tedavinin 24. haftasında HBV DNA düzeyinde >1 log İÜ/ml azalma olması, fakat RT-PCR ile saptanabilir düzeyde olması.
Histolojik yanıt: Fibroz skorunda kötüleşme olmaksızın nekroinflamatuar aktivite skorunda en az 2 puan düzelme olması.
Tam yanıt: Biyokimyasal ve virolojik yanıtla birlikte HBsAg'nin kaybolması.
Tedavi sonu yanıt: Tedavi bitiminde elde edilen yanıt.

Kronik Hepatit B Virusu İnfeksiyonunun Yönetimi: Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Derneği Viral Hepatit Çalışma Grubu Uzlaşı Raporu,2014

HBV Tedavisinin Gelişimi

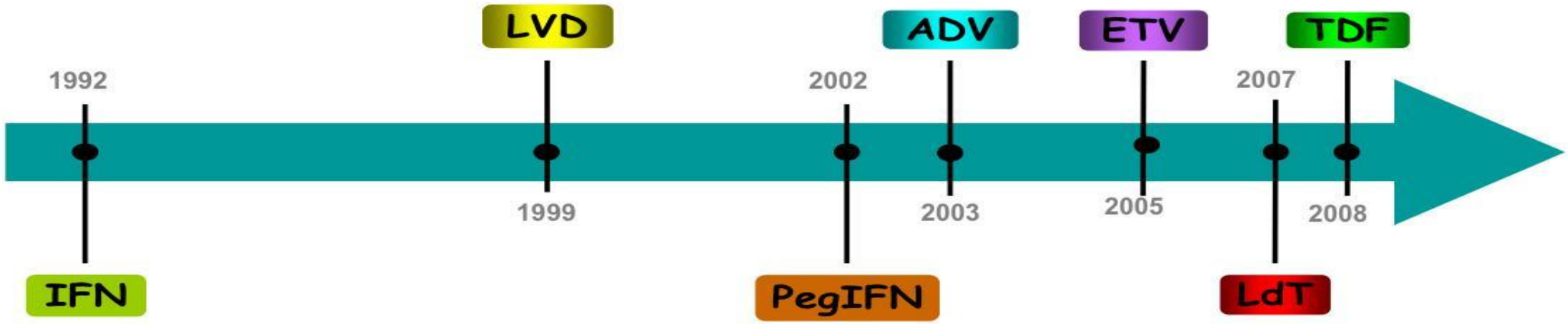

TABLE 1. Approved Antiviral Therapies in Adults and Children

Drug	Dose in Adults*	Use in Children*	Pregnancy Category†	Potential Side Effects†	Monitoring on Treatment‡
Preferred					
Peg-IFN-α-2a (adult) IFN-α-2b (children)	180 mcg weekly	≥1 year dose: 6 million IU/m² three times weekly§	C	Flu-like symptoms, fatigue, mood disturbances, cytopenia, autoimmune disorders in adults, anorexia and weight loss in children	Complete blood count (monthly to every 3 months) TSH (every 3 months) Clinical monitoring for autoimmune, ischemic, neuropsychiatric, and infectious complications
Entecavir	0.5 mg daily‖	≥2 years dose: weight-based to 10-30 kg; above 30 kg: 0.5 mg daily‖	C	Lactic acidosis (decompensated cirrhosis only)	Lactic acid levels if there is clinical concern Test for HIV before treatment initiation
Tenofovir dipovoxil fumarate	300 mg daily	≥12 years	B	Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis	Creatinine clearance at baseline If at risk for renal impairment, creatinine clearance, serum phosphate, urine glucose, and protein at least annually Consider bone density study at baseline and during treatment in patients with history of fracture or risks for osteopenia Lactic acid levels if there is clinical concern Test for HIV before treatment initiation
Tenofovir alafenamide	25 mg daily	—	There are insufficient human data on use during pregnancy to inform a drug-associated risk of birth defects and miscarriage.	Lactic acidosis	Lactic acid levels if clinical concern Assess serum creatinine, serum phosphorus, creatinine clearance, urine glucose, and urine protein before initiating and during therapy in all patients as clinically appropriate Test for HIV before treatment initiation
Nonpreferred					
Lamivudine	100 mg daily	≥2 years dose: 3 mg/kg daily to max 100 mg	C	Pancreatitis Lactic acidosis	Amylase if symptoms are present Lactic acid levels if there is clinical concern Test for HIV before treatment initiation
Adefovir	10 mg daily	≥12 years	C	Acute renal failure Fanconi syndrome Lactic acidosis	Creatinine clearance at baseline If at risk for renal impairment, creatinine clearance, serum phosphate, urine glucose, and urine protein at least annually Consider bone density study at baseline and during treatment in patients with history of fracture or risks for osteopenia Lactic acid levels if clinical concern
Telbivudine	600 mg daily	—	B	Creatine kinase elevation and myopathy Peripheral neuropathy Lactic acidosis	Creatine kinase if symptoms are present Clinical evaluation if symptoms are present Lactic acid levels if there is clinical concern

*Dose adjustments are needed in patients with renal dysfunction.
†In 2015, the U.S. Food and Drug Administration replaced the pregnancy risk designation by letters A, B, C, D, and X with more specific language on pregnancy and lactation. This new labeling is being phased in gradually, and to date only TAF includes these additional data.
‡Per package insert.
§Peg-IFN-α-2a is not approved for children with chronic hepatitis B, but is approved for treatment of chronic hepatitis C. Providers may consider using this drug for children with chronic HBV. The duration of treatment indicated in adults is 48 weeks.
‖Entecavir dose is 1 mg daily if the patient is lamivudine experienced or if they have decompensated cirrhosis.
Abbreviation: TSH, thyroid stimulating hormone.

Tenofovir ± Entekavir

Combination therapy for CHB

NA plus NA

Recommendations

- *De novo* combination t
  barrier to resistance (
  mended (Evidence level I, grade of recommendation 1).
- In treatment-adherent patients with incomplete sup-
  pressio
  either
  the oth
  ered (Evidence level III, grade of recommendation 2).

Yüksek potensli anti virallerle de novo kombinasyon terapileri önerilmiyor

Tedavi deneyimli hastalarda ETV veya TDF/TAF ile uzun süreli tedaviler ile HBV replikasyonu tam olarak süprese edilemezse switch veya kombinasyon terapiler öneriliyor

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- Tedavi öncesi HBV DNA (>10^8 IU/mL)sı yüksek olan Hbe Ag (+) hastalarda dahi de novo tedavilerde potent anti virallerle monoterapi tedavisi öneriliyor
- Potent anti virallerle uzun dönem tedavilerde minimal residüal viremiler (HBV DNA <69 IU/mL) olsa bile monoterapi ile devam etmek;
    - etkili ve güvenli
    - HCC ve siroz ile ilişki saptanmamış
- Bunun istinası
- Dekompanze sirozlu hastalarda tam virolojik yanıt sağlanamazsa (HBV DNA <20IU/mL) HCC riskinde anlamlı artış olduğu
- Kompanze sirozlu hastalarda HCC riskinde anlamlı artış saptanmamış

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MANAGEMENT OF PERSONS WITH PERSISTENT LOW-LEVEL VIREMIA ON NA THERAPY

6A. The AASLD suggests that persons with persistent low-level viremia (<2,000 IU/mL) on entecavir or tenofovir monotherapy continue monotherapy, regardless of ALT

Quality and Certainty of Evidence: Very Low

Strength of Recommendation: Conditional

Guidance: *Persons on TAF with persistent low-level viremia (<2,000 IU/mL) should continue monotherapy, regardless of ALT.*

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

6B. The AASLD suggests 1 of 2 strategies in persons with virological breakthrough on entecavir or tenofovir monotherapy: either switch to another antiviral monotherapy with a high barrier to resistance or add a second antiviral drug that lacks cross-resistance (Table 8)

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

Management of patients with NA failure

Recommendations

- Prevention of resistance should rely on the use of first line therapy with high barrier to resistance NAs (Evidence level I, grade of recommendation 1).
- Compliance to NA therapy should be checked in all cases of treatment failure (Evidence level II-1, grade of recommendation 1).
- Management of treatment failure should be based on NAs cross-resistance data (Evidence level II-2, grade of recommendation 1).
- Treatment adaptation should be performed as soon as virologic failure under NAs is confirmed (Evidence level II-1, grade of recommendation 1).

Tedavi başarsızlığının yönetimi

- Direnci önlemek için tedaviye mutlaka yüksek potensli ilaçlarla başlamak lazım
- Uyum mutlaka sorgulanmalı ve ilaçlarını düzgün kullandığından emin olmak lazım
- Tedavi başarısızlığında mutlaka çapraz dirençlere dikkat edilmeli
- Direnç konfirme edildikten sonra sonra yeni tedaviler planlanmalı

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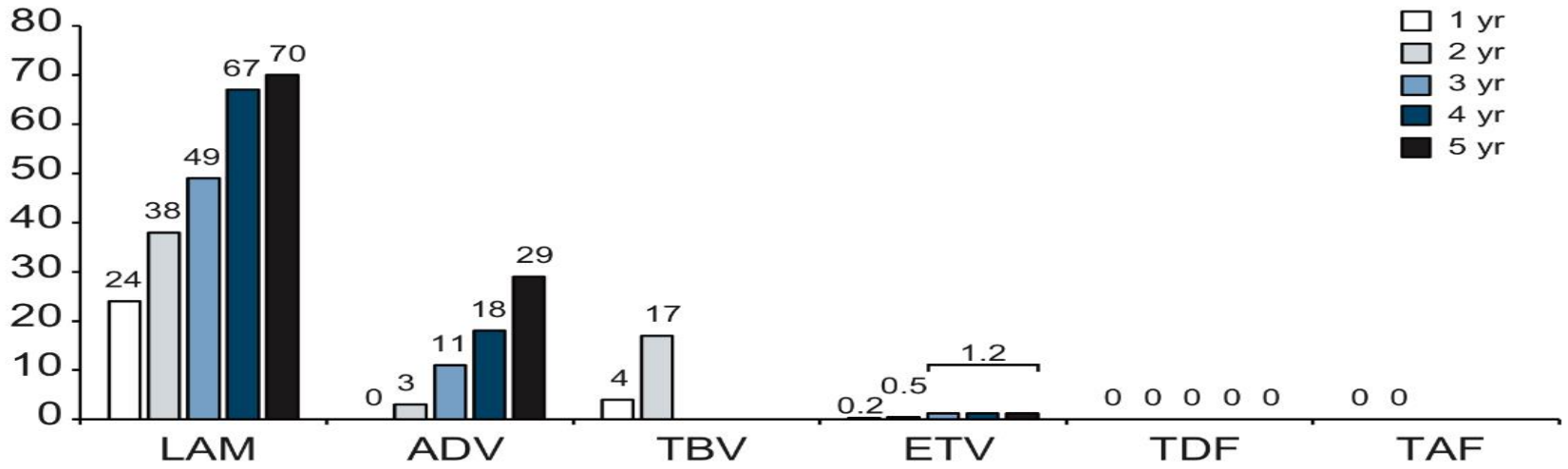

Fig. 3. Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV), tenofovir (TDF) and tenofovir alafenamide (TAF) in pivotal trials in nucleos(t)ide-naïve patients with chronic hepatitis B. (Collation of currently available data – not from head-to-head studies). No evidence of resistance has been shown after 8 years of TDF treatment.[69]

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Table 6. Cross-resistance data for the most frequent resistant HBV variants.

HBV variant	LAM	LDT	ETV	ADV	TDF/TAF*
Wild-type	S	S	S	S	S
M204V	R	S	I	I	S
M204I	R	R	I	I	S
L180M + M204V	R	R	I	I	S
A181T/V	I	I	S	R	I
N236T	S	S	S	R	I
L180M + M204V/I ± I169T ± V173L ± M250V	R	R	R	S	S
L180M + M204V/I ± T184G ± S202I/G	R	R	R	S	S

The amino acid substitution profiles are shown in the left column and the level of susceptibility is given for each drug: S (sensitive), I (intermediate/reduced susceptibility), R (resistant).

ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; ADV, adefovir.

* *In vitro* data for tenofovir, *in vivo* data for TDF, no clinical data for TAF.

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Table 7. Management of patients who develop NA resistance.

Resistance pattern	Recommended rescue strategies
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	If LAM-naïve: switch to ETV or TDF or TAF If LAM-resistance: switch to TDF or TAF If HBV DNA plateaus: add ETV*** or switch to ETV
TDF or TAF resistance**	If LAM-naïve: switch to ETV If LAM-R: add ETV*
Multidrug resistance	Switch to ETV plus TDF or TAF combination

ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; ADV, adefovir; TBV, telbivudine.

* The long-term safety of these combinations is unknown.

** Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine the cross-resistance profile.

*** Especially in patients with ADV resistant mutations (rA181T/V and/or rN236T) and high viral load, the response to TDF (TAF) can be protracted.

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TABLE 8. Antiviral Options for Management of Antiviral Resistance

Antiviral Resistance by Genotypic Testing	Switch Strategy (Preferred)	Add Strategy: 2 Drugs Without Cross-Resistance
Lamivudine resistance	Tenofovir* (TDF or TAF)	Continue lamivudine; add tenofovir (TDF or TAF) (or alternative emtricitabine-tenofovir)
Telbivudine resistance	Tenofovir* (TDF or TAF)	Continue telbivudine; add tenofovir (TDF or TAF)
Adefovir resistance	Entecavir or Tenofovir* (TDF or TAF)	Continue adefovir; add entecavir
Entecavir resistance	Tenofovir* (TDF or TAF)	Continue entecavir; add tenofovir (TDF or TAF) or alternative emtricitabine-tenofovir
Tenofovir resistance	Entecavir*	Continue tenofovir (TDF or TAF) and add entecavir
Multidrug resistance	Tenofovir	Combined tenofovir (TDF or TAF) and entecavir*

*Efficacy similar between switching to an antiviral with high genetic barrier to resistance and adding 2 drugs without cross-resistance with follow-up to 5 years. Thus, switching is the preferred strategy except if HBV is multidrug resistant.

World J Gastroenterol. 2018 May 7;24(17):1919-1924. doi: 10.3748/wjg.v24.i17.1919.

Development of tenofovir disoproxil fumarate resistance after complete viral suppression in a patient with treatment-naïve chronic hepatitis B: A case report and review of the literature.

Cho WH[1], Lee HJ[1], Bang KB[1], Kim SB[2], [1]

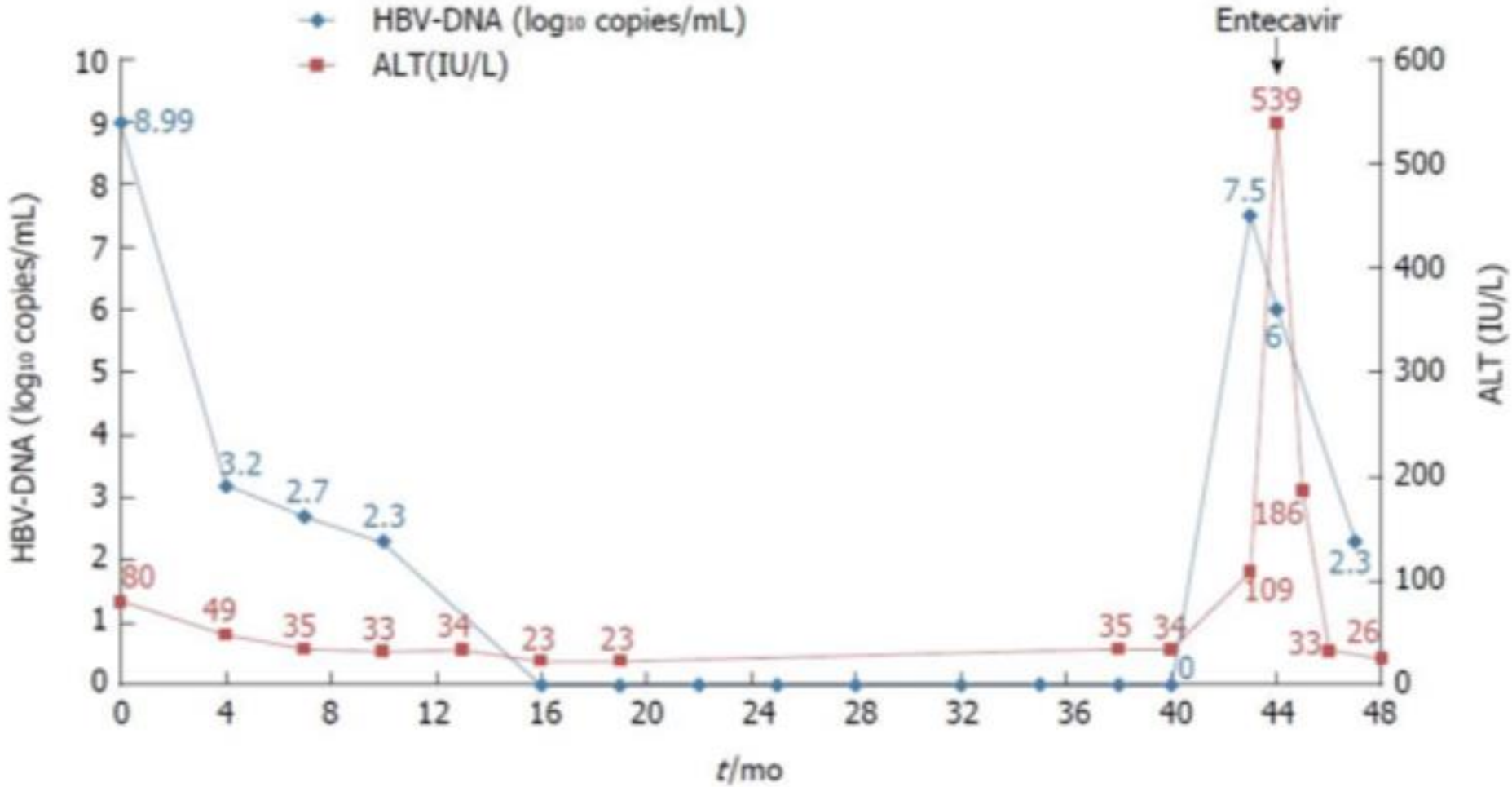
Author information

Naif kronik hepatit B hastası TDF direnci bildirilmiş

Abstract

Tenofovir disoproxil fumarate (TDF) is a potent nucleotide analogue that is recommended as first-line therapy for patients with chronic **hepatitis B**. The results of a longitudinal study of TDF treatment demonstrated no development of **resistance**. We observed one treatment-naïve chronic **hepatitis B** (CHB) patient who developed TDF **resistance** after complete viral suppression during long-term TDF treatment. A 37-year-old HBeAg-positive man received TDF 300 mg/d for 43 mo. The **hepatitis B** virus (HBV) DNA titer was 8 $\log_{10}$ copies/mL at baseline and became undetectable at 16 mo after treatment. However, the HBV DNA titer rebounded to 7.5 $\log_{10}$ copies/mL at 43 mo after treatment. We performed full sequencing to find mutation sites associated with virologic breakthrough. The results showed 9 mutation sites, most of which had not been well-known as mutation sites. We changed the therapy from **tenofovir** to entecavir with a regimen of 0.5 mg once daily. After 4 mo, the HBV DNA titer decreased to 267 copies/mL, and the liver enzyme levels were normalized.

KEYWORDS: Chronic **hepatitis B**; Mutation; **Resistance**; **Tenofovir**



(http://www.wjgnet.com/1007-9327/full/v24/i17/WJG-24-1919-g003.htm)

43 yaş erkek hasta Hbe Ag pozitif
Entecavir 0.5 mg 4 ay sonra 268 copy/ ml

Figure 3 Clinical cours mo of
antiviral treatment with T reatment
initiation.

J Viral Hepat. 2015 Aug;22(8):675-81. doi: 10.1111/jvh.12368. Epub 2014 Nov 24.

Tenofovir-based alternate therapies for chronic hepatitis B patients with partial virological response to entecavir.

Liu L[1,2], Yip B[3], Trinh H[4], Pan CQ[5], Han SH[6], Wong CC[7], Li J[8], Chan S[9], Krishnan G[10], Wong CC[11], Nguyen MH[2].

Author information

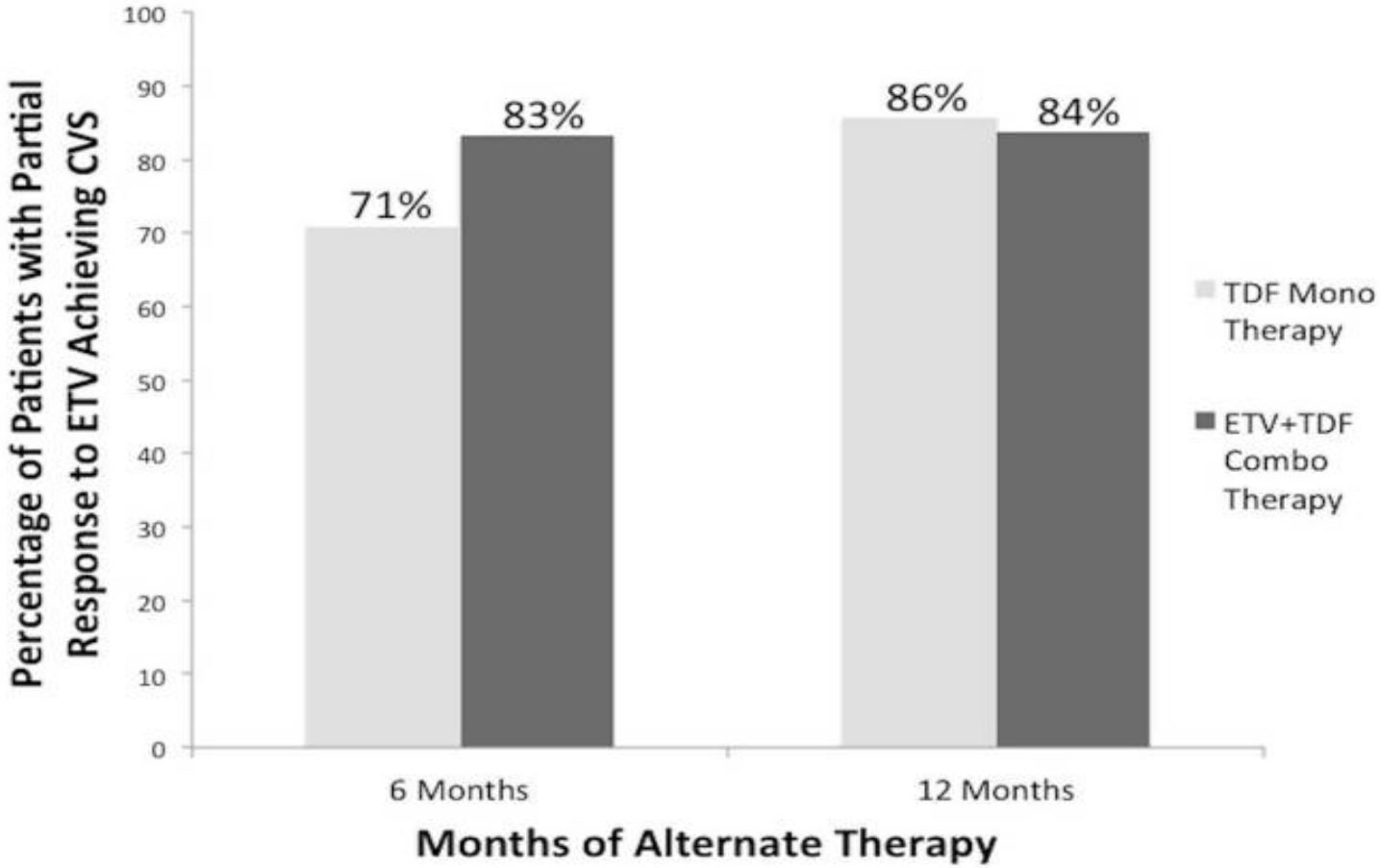
Abstract

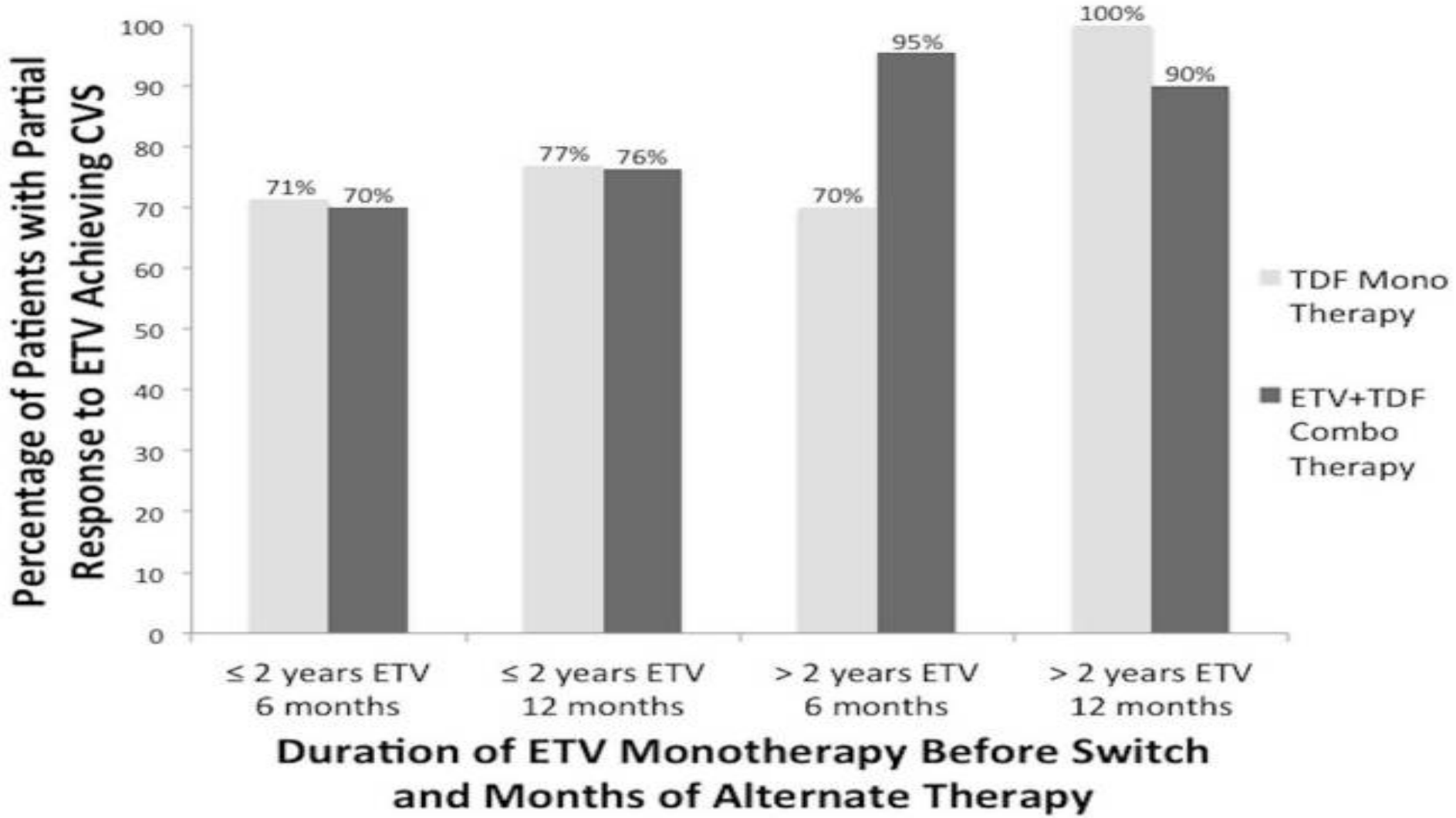
Entekavire kısmi virolojik yanıtlı kronik hepatit B li hastaların tenofovir temelli alternatif tedavilerin incelendiği bir çalışma

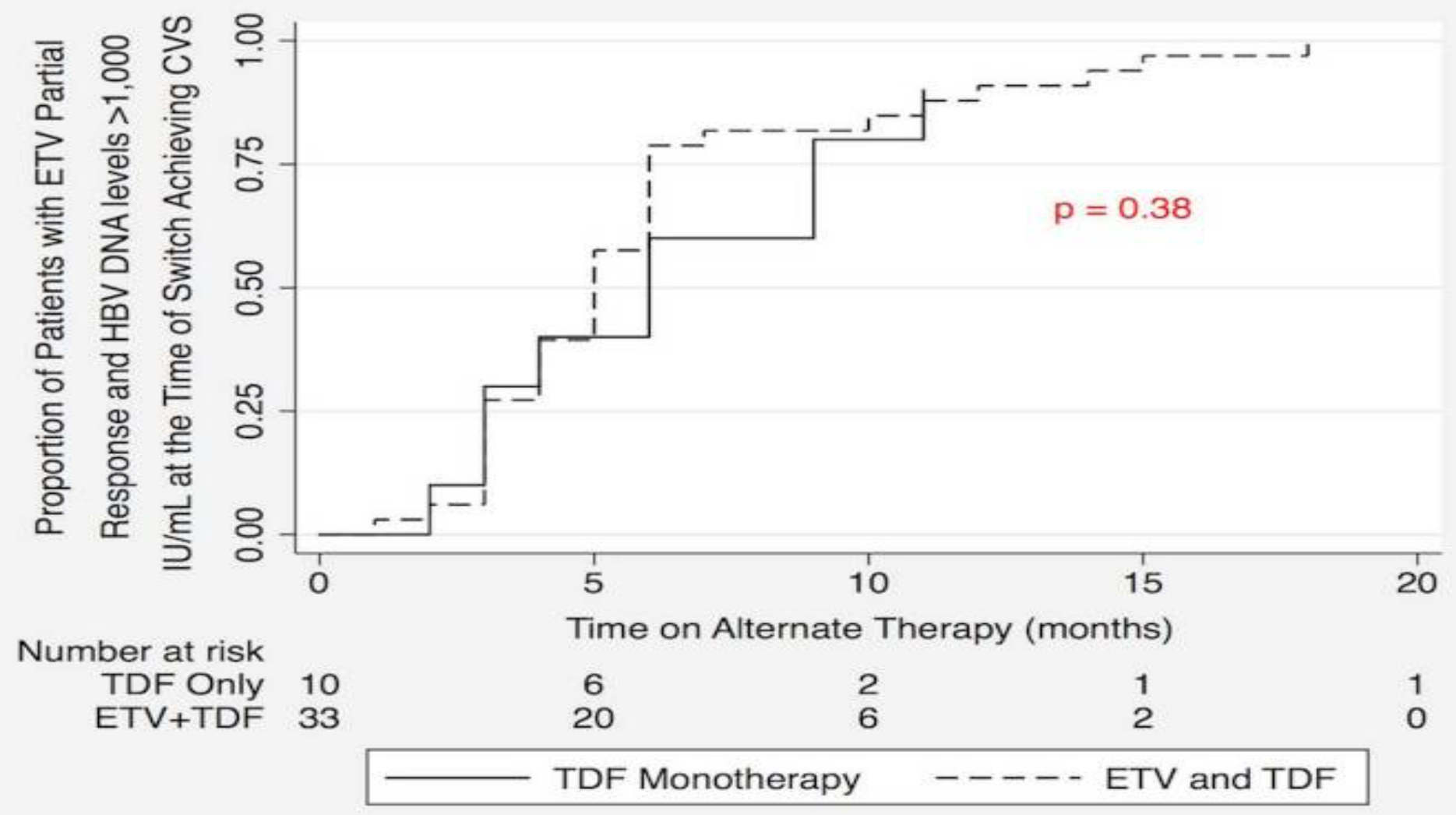
B (CHB); however, data on how to ess of two alternate TDF--in CHB patients with ETV partial virological response. We conducted a retrospective study of 68 patients who had partial virological response to ETV, defined as having detectable HBV DNA following at least 12 months of ETV, and were switched to TDF monotherapy (n = 25) or ETV+TDF (n = 43). Patients were seen in seven US liver/community-based clinics and started on ETV between 2005 and 2009. The majority of patients were male; the vast majority were Asian and had positive hepatitis B e antigen (HBeAg). Patients in both groups had similar pretreatment characteristics. Complete viral suppression (

Toplam Entekavir alan ve kısmi yanıtlı 68 hasta
25 tenofovir monoterapisi
43 tenofovir + entekavir kombinasyon terapisi verilmiş.

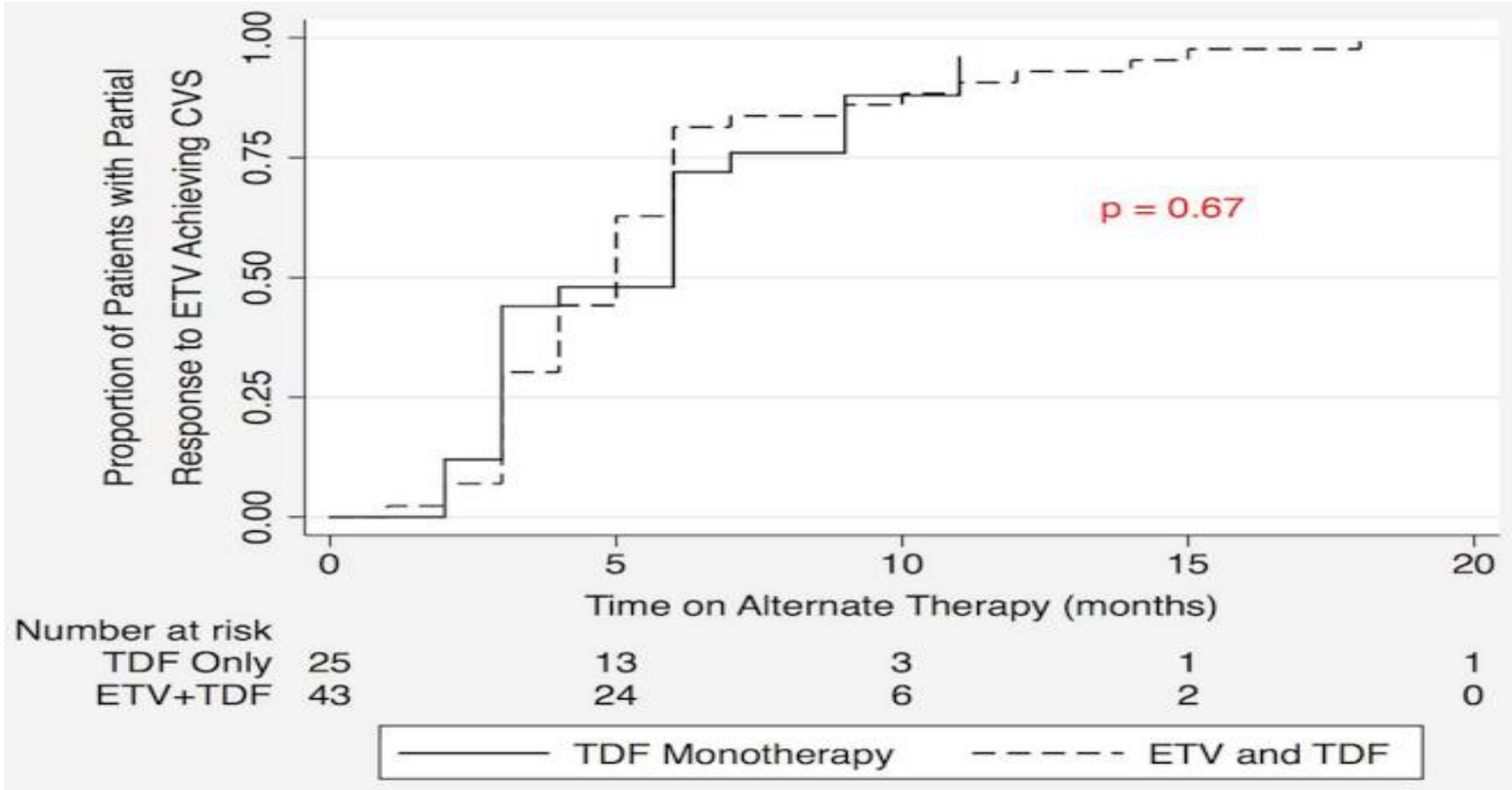
were similar after 6 months (71% vs 83%, P =
there was no statistically significant differenc
HBV DNA levels at **switch** (>1000 IU/mL) we
ETV+TDF was not an independent predictor of CVS compared to TDF monotherapy (OR = 1.19, P = 0.63). In conclusion, TDF monotherapy and ETV+TDF are comparable in achieving CVS in CHB patients with partial virological response to ETV. Long-term alternate therapy with one pill (TDF monotherapy) vs two pills (ETV+TDF) could lead to lower nonadherence rates and better treatment outcomes.


Percentage of Patients with Partial Response to ETV Achieving CVS
100
90
80
70
60
50
40
30
20
10
0
71%
83%
86%
84%
6 Months
12 Months
Months of Alternate Therapy
TDF Mono Therapy
ETV+TDF Combo Therapy


Percentage of Patients with Partial Response to ETV Achieving CVS
100
90
80
70
60
50
40
30
20
10
0
71%
70%
77%
76%
70%
95%
100%
90%
TDF Mono Therapy
ETV+TDF Combo Therapy
≤ 2 years ETV 6 months
≤ 2 years ETV 12 months
> 2 years ETV 6 months
> 2 years ETV 12 months
Duration of ETV Monotherapy Before Switch and Months of Alternate Therapy



Kaplan Meier analysis of complete viral suppression (CVS) rates comparing tenofovir (TDF) monotherapy and entecavir (ETV) + TDF combination therapy as alternate therapies in patients with a partial virological response to ETV and HBV DNA levels >1,000 IU/mL at the time of switch



Kaplan Meier analysis of cumulative complete viral suppression (CVS) rates comparing tenofovir (TDF) monotherapy and entecavir (ETV) + TDF combination therapy as alternate therapies in patients with a partial virological response to ETV

Clinical Practice Guidelines

Monitoring of patients treated with ETV, TDF or TAF
Recommendations

- All patients treated with NA should be followed with periodical assessments including ALT and serum HBV DNA (Evidence level I, grade of recommendation 1).
- Patients at risk of
  all patients regar
  should undergo p
  at least estimated
  serum phosphate levels (Evidence level II-2, grade of recommendation 1).
- Patients on TDF at risk
  underlying renal or bon
  for a switch to ETV o
  LAM exposure (Evidence
  mendation 1).

Böbrek fonksiyon bozukluğu olanlarda herhangi bir antiviralle tedavi edilebilir
Serom fosfat ve eGFR takibi ile

Tenofovir tedavisi altında böbrek ve kemik bozuklukları gelişirse ETV veya TAF geçimesi öneriliyor

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Clinical Practice Guidelines

Table 5. Indications for selecting ETV or TAF over TDF.*

1. Age >60 years
2. Bone disease
Chronic steroid use or use of other medications that worsen bone density
History of fragility fracture
Osteoporosis
3. Renal alteration**
eGFR <60 ml/min/1.73 m^2
Albuminuria >30 mg/24 h or moderate dipstick proteinuria
Low phosphate (<2.5 mg/dl)
Hemodialysis

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ⩾15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

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5. The AASLD suggests no preference between entecavir or tenofovir (TDF) regarding potential long-term

Böbrek ve kemik komplikasyonlarının uzun dönem potensiyel riskleri ile ilgili TDF ve ETV arasında öncelik tavsiyesi yok

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

Technical Remarks

1. The existing
ferences in r
or bone mir
persons treated with tenofovir (TDF) or entecavir. However, renal events, such as acute renal failure or hypophosphatemia, have been reported in TDF-treated persons.

Mevcut çalışmalarda böbrek ve kemik bozuklukları açısından entecavir yada tenofovir arasında ciddi fark olmamakla birlikte renal fonksiyon bozukluğu ve hipofosfatemi bildiren vakalar mevcut

2. In persons on TDF,
serum creatinine, ph
urine protein should
initiation and period
annually and more frequently if the patient is at high risk for renal dysfunction or has a preexisting renal dysfunction).

TDF alan hastalar serum kreatinin, fosfate, idrar glukozu ve protein açısından takip edilmeli

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3. In the absence of oth
sis or osteomalacia,
for or against monit
in HBV-infected pers
4. ***Guidance:*** *In cases of suspected TDF-associated renal dysfunction and/or bone disease, TDF should be discontinued and substituted with TAF or entecavir, with consideration for any previously known drug resistance.*
5. Dosage of NAs should be adjusted based on renal function and creatinine clearance, as recommended by manufacturers.

Eğer osteoporozis yada osteomalazi için diğer risk faktörleri yoksa TDF de kemik mineral density takibi ile ilgili yeterli kanıt yok

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Renal Adjustment Dose

- Body weight and Creatinine Clearance calculations

Half-life (Normal/ESRD, hr)	17 / very prolonged
Reference Dose Normal Renal Function	300 mg q24h
CrCl > 50-90	300 mg q24h
CrCl 30-49	300 mg q48h
CrCl 10-29	300 mg q72-96h
CrCl < 10	No data
Hemodialysis	300 mg after every 3rd dialysis or every 7 days if no dialysis
CAPD	No data
CRRT	No data

- CrCl = Creatinine clearance level (mL/min)
- CAPD = Continuous Ambulatory Peritoneal Dialysis
- CRRT = Continuous Renal Replacement Therapy

Top

Tenofovir-associated nephrotoxicity in patients with chronic hepatitis B: two cases

Hyeki Cho[1], Yuri Cho[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Kook-Hwan Oh[2], Kyoungbun Lee[3], Syifa Mustika[4] Jung-Hwan Yoon[1], and Yoon Jun Kim[1]

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Tenofovir disoproxil fumarate (TDF) is effective against chronic hepatitis B (CHB) infection and its use is increasing rapidly worldwide. However, it has been established that TDF is associated with renal toxicity in human in has rarely b who were b nal tubular d treatment. Th nd to have membranoproliferative glomerulonephritis with acute tubular injury. The renal function improved in both patients after discontinuing TDF. We discuss the risk factors for TDF-associated renal toxicity and present recommendations for monitoring renal function during TDF therapy. **(Clin Mol Hepatol 2016;22:286-291)**

Keywords: Tenofovir; Acute Kidney Injury; Drug-Related Side Effects and Adverse Reactions; Chronic Hepatitis B; Kidney Tubules

1. vaka: TDF tedavisinin 5. ayında tubuler disfonksiyon ve akut tubuler nekroz gelişmiş TDF kesilip EVT geçilmiş, böbrek fonksiyonları düzelmiş
2. Vaka TDF tedavisinin 17. gününde akut membranoprofiletarif glomerulonefrit TDV kesilip EVT geçilmiş, böbrek fonksiyonları düzelmiş

Clin Ther. 2017 Sep;39(9):1870-1880. doi: 10.1016/j.clinthera.2017.07.015. Epub 2017 Aug 7.

Comparison of the Efficacy of Tenofovir Versus Tenofovir plus Entecavir in the Treatment of Chronic Hepatitis B in Patients With Poor Efficacy of Entecavir: A Systematic Review and Meta-analysis.

Chen J[1], Zhao SS[2], Liu XX[1], Huang ZB[3], Huang Y[4].

Author information

Abstract

PURPOSE: This study aimed to compare the efficacy between tenofovir diso (TDF) and TDF plus entecavir (ETV) combination therapy in patients with chronic hepatitis B (CHB) with a poor response to ETV.

METHODS: We searched the China National Knowledge Infrastructure (CNKI), PubMed, EMBASE, and SCOPE libraries for articles using the keywords chronic hepatitis B virus or CHB or HBV, entecavir or ETV, and tenofovir or TDF.

FINDINGS: Five studies (from CNKI and PubMed) with a total of 408 patients met the inclusion criteria: 212 patients in the TDF group and 196 patients in the TDF plus ETV group. The rates of viral suppression between the 2 groups were comparable at weeks 24 and 48 of treatment (P = 0.546 vs P = 0.818). In addition, the subanalysis revealed that no significant differences were observed in the rates of viral suppression between the 2 groups at week 24 (subgroup 1 [partial response to ETV]: P = 0.822; subgroup 2 [resistance to ETV]: P = 0.294) and week 48 (subgroup 1: P = 0.797; subgroup 2: P = 0.545). No significant differences were found in alanine aminotransferase normalization, hepatitis B e antigen loss, hepatitis B e antigen seroconversion, virologic breakthrough, and tolerability between the 2 groups at weeks 24 and 48. Therefore, the results suggest that TDF monotherapy should be chosen for patients with CHB with a poor response to ETV for reasons of economy and convenience.

IMPLICATIONS: We conclude that TDF monotherapy is comparable to TDF-ETV combination therapy for patients with a poor response to ETV; thus, TDF monotherapy may be a better choice for these patients. However, because of the limited citations in this meta-analysis, complete and systematic evidence is needed to evaluate the differences in efficacy and tolerability between TDF and TDF-ETV. Larger and longer randomized clinical trials and further studies should be conducted to verify the results.

TDF 212 HASTA
TDF+ETV 196 HASTA
Viral süpresyon açısından 24 ve 48 haftalarda iki grup arasında fark görülmemiş

CONCLUSIONS

Our meta-analysis found that TDF monotherapy at weeks 24 and 48 was comparable to TDF plus ETV combination therapy for patients with a poor response to ETV. Therefore, TDF monotherapy may be a better choice for these patients when considering economic benefit and convenience. However, because of the limited sample sizes, larger and longer RCTs and additional studies should be conducted to verify the result.

Tenofovir versus Tenofovir plus Entecavir in the Treatment of Chronic Hepatitis B in Patients with Poor Efficacy of Nucleoside/Nucleotide Analogs

- Çalışma:
- 266 kronik hepatit B hastası
- Daha önce nükleotid, nükleozid analoğu kullanmış primer, parsiyel yanıtsız veya virolojik kırılması olan ve tedavisi tenofovire yada tenofovir+ Entecavir olarak değiştirilmiş hastalar
- En az 48 hafta virolojik yanıt ve virolojik kırılma açısından incelenmiş

Çalışma sonucu

- Hastaların yaş ortalaması 37
- Hbe Ag(+) %87.1
- HBV DNA ortalaması 4240 IU/ ml
- 192 hasta TDF ve 74 hasta TDF+ETV ile en az 48 hafta
- Virolojik yanıt olarak HBV DNA<60 IU/mL
- Virolojik yanıt oranları
    - TDF %87.6
    - TDF + ETV %91.4(*P*=.062)
-

- Multivariete analizlerinde iki grup arasında virolojik yanıt üzerinde bazal HBV DNA nın önemli olduğu saptanmış
- Sub analizlerde bazal HBV DNA >4000 IU/Ml olan hasta grubu TDF + ETV kolunda daha fazla kümelenmiş
- Bazal HBV DNA >4000 IU/mL virolojik yanıt;

  - TDF + ETV : %95.1
  - TDF : %70.5 *P*<.001

- Bazal HBV DNA <4000 IU/mL virolojik yanıt;

  - Hem TDF + ETV hem TDF kolunda %94

İki grup arasında; 24 ve 48. haftalarda

- ALT normalizasyonu,
- Hbe Ag kaybı,
- Hbe Ag serokonversiyonu
- Virolojik breakthrough,
- Tolerabilite açısından fark yok.

Tartışma

- Virolojik yanıt üzerinde kombinasyon tedavisinin monoterapiye göre belirgin üstün olduğu saptanmamış
- Bazal HBV DNA yüksek olanlarda kombinasyon tedavisi düşünülmelidir

b) Oral antiviral tedavisi alan hastalarda negatif olan HBV DNA'nın pozitifleşmesi veya HBV DNA'nın 10 kat yükselmesi ile başka bir oral antiviral ajana geçilebilir veya almakta oldukları tedaviye ikinci bir oral antiviral eklenebilir.

c) Tenofovir veya entekavir ile tedavi alan hastalarda birinci yılın sonunda halen "HBV DNA pozitif" olması durumunda bu iki antiviral arasında geçiş yapılabilir veya bu iki antiviral birlikte kullanılabilir.

Sağlık Uygulama Tebliğ, 2014


TEŞEKKÜRLER...