ÇOK MU İDDİALI OLDU?

KRONİK HBV'DE YENİLİKLER

Prof.Dr. Mustafa Kemal ÇELEN

KLİMİK DİYARBAKIR TOPLANTISI

Kronik Hepatit B

- Aşılama amacına ulaştı mı?
- Ülkemizde epidemiyolojik değişimler oldu mu?
- KHB hastalarının dermografik özellikleri
- SUT değişikliği…
- OAV mi? PEG-INF mu?
- KC-S, HCC & KC transplantasyonu…
- Vertikal Bulaş…
- Tedavi de yenilikler?

Aşılama-1998

Aşılama çalışmaları başarılı, ancak…

- E
-
- Diş tedavis
- Güneydoğu Bölgesinde
- Eğitim düzeyinin düşük olması

Günümüzde 16 yaş altı olup KHB olan çok sayıda hasta var. **Peki neden?**

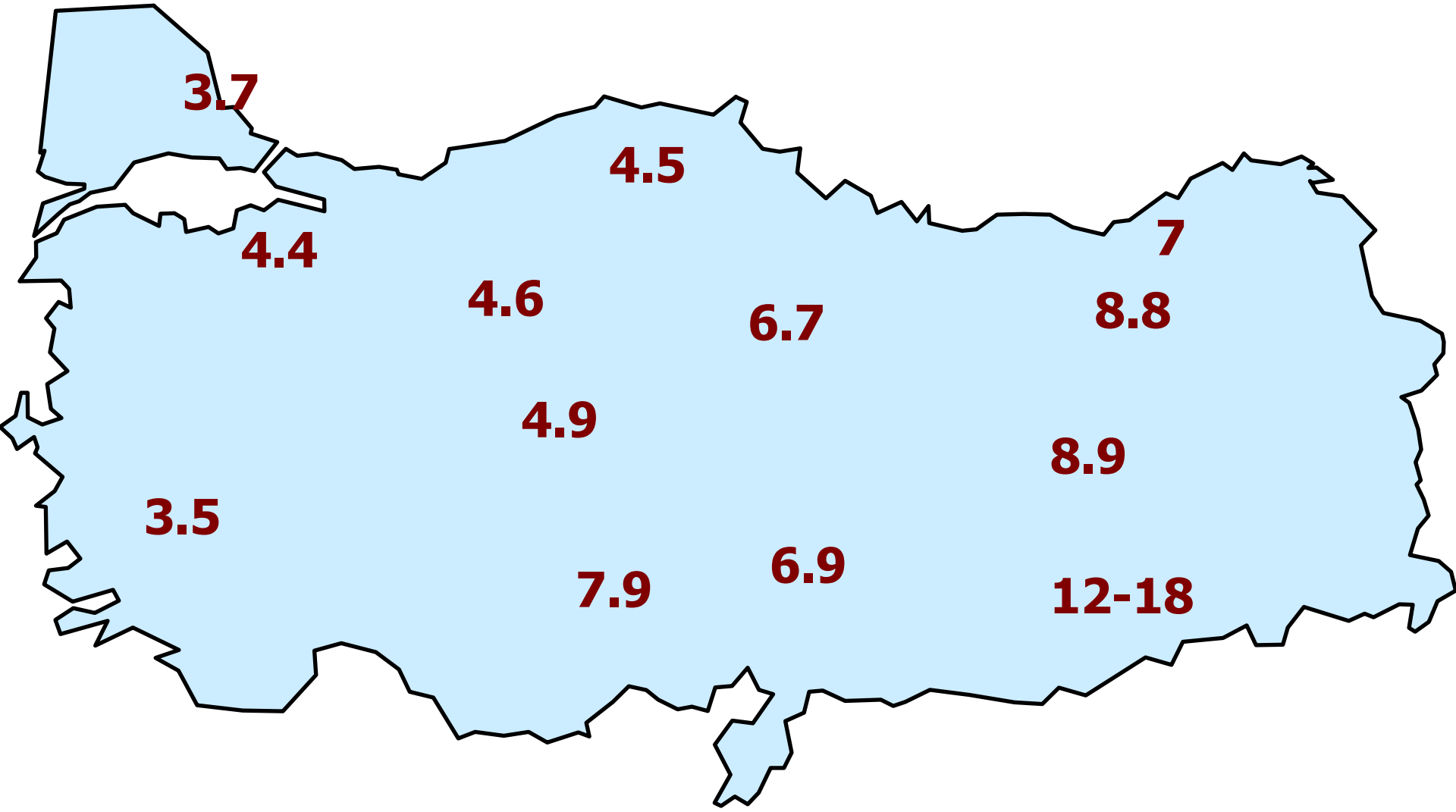
Önemli risk faktörleri olarak kabul edilmektedir

Epidemiyoloji

- Epi
- Dem
- Logo

Toplumdaki hastalık, kaza ve sağlıkla ilgili durumların dağılımını, görülme sıklıklarını ve bunları etkileyen belirteçleri inceleyen bir tıp bilimi dalıdır.

Türkiye’de farklı bölgelerdeki B tipi sarılık taşıyıcılık oranları (yüzde olarak)



Aile içi yakın temas sonucu

Ülkemizde HBsAg pozitifliği

- 1985-1999 yılları arasında

  HBsAg pozitifliği %5.2

- 2000-2005 yılları arasında

  HBsAg pozitifliği %2.97

Mıstık R. Turkiye'de viral hepatit epidemiyolojisi, Viral Hepatit Derg 2007

TKAD

- 5.471 kişi 23 farklı merkezde taranmış
- HBsAg pozitifliği %4
- Anti-HBs pozitifliği %32
- Anti-HBc IgG (+) %30.6
- Anti-HBe pozitifliği %92.1
- *Yaş ile ilişkisi*

  50-59 yaş %5.3

  18-30 yaş %2.7

Kızılay Verilerine Göre

Kan donörlerinde H

1997 yılından beri kan merkezlerinde uygulanan donör sorgulama formu nedeni ile risk taşıdığı düşünülen kişilerden kan alınmamasına bağlı rölatif bir azalma

- 1985 yılında %6.7
- 1988 yılında %5.3
- 1995 yılında %4.7
- 2004 yılında %2.12
- 2009 yılında %1.21

Taşlı O. Turkiye'de kan bankacılığının yeniden yapılanmasında Türk Kızılay'ının rolü 2010

VHSD Saha çalışmasının sonuçları

- GDA Bölgesinde %3.6
- Karadeniz %2.4
- İç Anadolu %2.2
- Akdeniz Bölgesi %2.1
- Marmara %2.0
- Ege Bölgesi %1.4

The characteristics of patients with chronic hepatitis B in Turkey

Mustafa Kemal Celen[1], Suda Tekin Koruk[2], Bilgehan Aygen[3], Tuba Dal[4], Oğuz Karabay[5], Selma Tosun[6], İftihar Koksal[7], Hüseyin Turgut[8] , Yusuf Onlen[9], Ismail Balik[10], Necmettin Yildirim[11], Mehmet Sinan Dal[12], Celal Ayaz[1], Fehmi Tabak[13]

Med Glas (Zenica) 2014; 11(1):94-98

- HEP-NET veri tabanına kayıtlı **7871 HBsAg (+)**
- 13 merkez katıldı

Table 1. Distribution of hepatitis B patients according to the regions of Turkey and the mean age

Regions of Turkey	No (%) of patients	Mean (standard deviation) age
Southeastern Anatolia	2361 (30)	26.2±11.3
Aegean	1480 (18.8)	38.1±15.2
Central Anatolia	1390 (17.6)	33.1±10.4
Marmara	1189 (15.1)	39.4±14.9
Black Sea	752 (9.6)	38.7±15.2
Eastern	389 (4.9)	27.1±10.8
Mediterranean	310 (4)	39.3±8.9
Total	7871	35 (14)

- %60.9 erkek
- Vakaların %40.4 aile hikayesi yok
- %30.8'i kan bağışı esnasında saptanmış
- %22.4 vakada aile içi HBsAg pozitifliği mevcut
- Aile içi bulaş vakalarının %63'ünde Anne-çocuk pozitifliği mevcut
- HBeAg pozitifliği %18.9

Tedavi durumu?

- %29 takip edilmekte
- %71'i tedavi deneyimli
- Bu vakaların %38.9 kombine tedavi deneyimine sahip
- Tedavi deneyimli vakaların %37.8 interferon tedavisi almış

Epidemiology and Risk Factors of Hepatitis Delta Infection in Turkey

Celal Ayaz[1], Suda Tekin Koruk[2], Aysun Yalci[3], Tansu Yamazhan[4], Bilgehan Aygen[5], Selma Tosun[6], Tuba Dal[7], Mustafa Kemal Celen[1] and Fehmi Tabak[8]

JOURNAL OF PURE AND APPLIED MICROBIOLOGY, December 2013.

- HEP-NET projesinde mevcut 7366 HBsAg (+)
- 15 merkez

- Anti-HDV pozitifliği %2.8

- GDA bölgesinde Anti-HDV pozitifliği %4.5

Ko-infeksiyon, HAV!

- Takip edilen HBsAg pozitif hastaların ko-infeksiyon açısından durumu ne?
- Anti-HAV Ig G ????
- Gerçek hayatta ne sıklıkta değerlendirilmektedir?
- Yaş aralığının bir önemi var mı?

The Evaluation of Exposure to Hepatitis A Virus in HBsAg-positive persons

JOURNAL OF PURE AND APPLIED MICROBIOLOGY, August 2014.

Mustafa Kemal Celen[1], Kamuran Turker[2], Nefise Oztoprak[3], Alper Sener[4], Nazan Tuna[5], Nevin Ince[6], Ilknur Erdem[7], Nese Saltoglu[8], Davut Ozdemir[9], Tuba Dal[10], Mustafa Karahocagil[11], Fatma Sirmatel[12], Fusun Zeynep Akcam[13], Fatma Eksi Polat[2], Mehmet Cabalak[14], Suzan Sacar[4], Selma Tosun[15] and Fehmi Tabak[8]

- 14 merkez
- 4793 HBsAg pozitif hasta değerlendirildi
- Vakaların %54.2'sinde HAV serolojisine bakılmış

Yaş aralığı & Anti-HAV seronegatifliği ?

Age groups	HAV IgG positive	HAV IgG negative	Total
<19	203 (%73.8)	72 (%26.2)	275
20-25			645
26-29			681
30-35			742
36-44			944
45-64	1256 (%99.5)	7 (%0.5)	1263
65 +	243 (%100)	0 (%0)	243
Total	4483 (%93.5)	310 (%6.5)	4793

Genç-adelosan HBV taşıyıcılarının Anti-HAV Ig G açısından taranmalı ve gereğinde aşılanmalı…

The Prevalence and Epidemiological Characteristics of Hepatitis B Virus and Hepatitis C Virus Coinfection in Turkey

Bilgehan AYGEN,[a]
Mustafa Kemal ÇELEN,[b]
İftihar KÖKSAL,[c]
Selma TOSUN,[d]
Oğuz KARABAY,[e]
Tansu YAMAZHAN,[f]
Orhan YILDIZ,[a]
Celal AYAZ,[b]
Fehmi TABAK[g]

ABSTRACT Objective: We aimed to determine prevalence and epidemiological characteristics of cases coinfected with hepatitis B virus (HBV)/hepatitis C virus (HCV) in Turkey. **Material and Methods:** The data for this study was obtained from Turk-Hepatitis Registry (HEP-NET) Project, which includes real-life cohort of hepatitis patients from 15 centers in Turkey, and is supported by Viral Hepatitis Society. In the project, 10,165 hepatitis cases were evaluated in 10 hospitals. **Results:** According to initial visit results, HBV/HCV coinfection was detected in 99 patients. The ratio was 974/100 000. The mean age of the cases was 40.9+21.7 years, 56.6% of them were males and 43.4% were females,. The major risk factors were dental therapy, any surgical procedure, hemodialysis and blood transfusion. The mean alanine aminotransferase (ALT) levels were 70.9±49.1 IU/L in coinfected patients. In 12% of cases HBeAg was positive. The median HCV RNA level was found 0 IU/mL (minimum: 50-maximum: 2.18x107 IU/mL), and the median HBV DNA level was found 2.50x102 IU/mL (minimum: 12-maximum: 1.70x108 IU/mL). In 8.1% of the patients both HCV RNA and HBV DNA were positive, and in 87.5% of cases HCV infection was dominant. The most important risk factor was hemodialysis (25%) in this group. **Conclusion:** This is the most detailed study which evaluates the prevalence of HBV/HCV coinfection in Turkey. HBV/HCV coinfection prevalence was not higher than HBV or HCV monoinfections. In cases where both HCV RNA and HBV DNA were positive, HCV was predominant.

SUT

Kronik Hepatit B Tedavisi
(Değişik: RG- 25/07/2014)

İlk tedaviye başlamak için; HBV-DNA:10.000 kopya/ml VEYA 2.000 IU/ml ve HAI ≥6 veya fibrozis ≥2

Erişkin hastalarda; günde 100 mg lamivudin veya 600 mg telbivudin veya 245 mg tenofovir veya 0,5 mg entekavir ile başlanır.

12-18 yaş grubu hastalarda lamivudin veya tenofovir kullanılabilir

- 2-18 yaş Lamivudin
- 12-18 yaş Lamivudin, Tenofovir
- 16-18 yaş Lamivudin, Tenofovir, Entekavir

SUT

Kronik Hepatit B Tedavisi
(Değişik: RG- 25/07/2014)

You can do, what you want!!!

Ora talarda gebelik durumunda oral antiviral değişiminde bu

Kullanılan antivirale karşı yan etki geliş ksızın başka bir antivirale geçilebilir.

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.

Peki neden ?

2013, 21 Ocak

- Akılcı İlaç Derneği
- Bakanlık
- SGK
- İlaç Firmaları
- 42.000 hasta
- 110 Milyarlık Bütçe
- 20.000 TDF, 10.000 ETV, 12.000 diğerlerleri

Uluslararası Kılavuzlar Ne Öneriyor?

AASLD PRACTICE GUIDELINE UPDATE

Chronic Hepatitis B: Update 2009

Anna S. F. Lok[1] and Brian J. McMahon[2]

Based on these new findings, the recommendation for first-line oral antiviral medications has been changed to tenofovir or entecavir, and adefovir has been moved to second-line oral antiviral medication.

Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance [67,70,78,85,92,123] (Fig. 1). Thus, they can be confidently used as first-line monotherapies [1] (**A1**).

APASL guidelines for HBV management

Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update

considered [5]. In general, the first-line therapy should be either ETV or TDF, and the second-line therapy should be LdT, ADV, and LAM. Nonetheless, pharmacoeconomic

Diğer Uluslararası Uygulamalar

4.1 Therapeutic indications | Go to top of the page

Zeffix is indicated for the treatment of chronic hepatitis B in adults with:

• compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis. Initiation of lamivudine treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier is not available or appropriate (see in section 5.1).

NHS National Institute for Health and Clinical Excellence

Drug treatment for chronic hepatitis B

Implementing NICE guidance

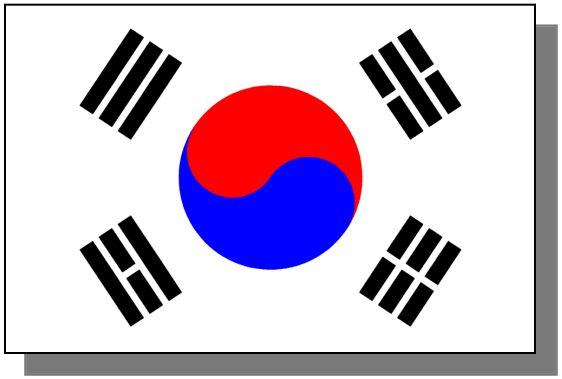
Updated 2009

Telbivudine is not recommended for the treatment of chronic hepatitis B.

People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

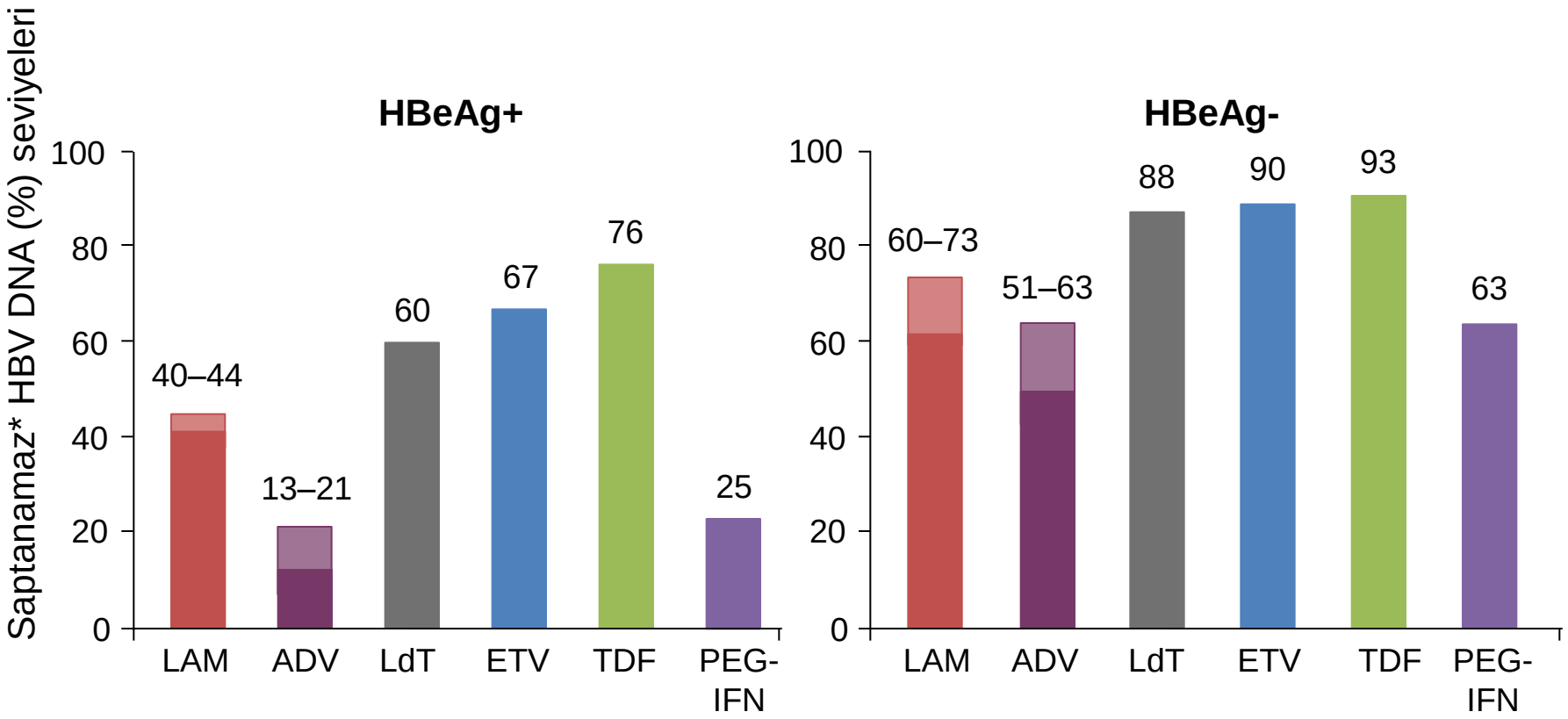
Reimbursement for Naive patients:

HBV DNA>10^5copies/ml (eAg+), HBV DNA>10^4copies/ml (eAg -) AND AST or ALT>2xULN, if LCor HCC pt, HBV DNA>10^4copies/ml and AST or ALT> ULN should be treated. Treatment choice should be ADV, TDF, ETV0.5mg or LtD.



Kılavuz Önerilerin I. Rasyoneli; Etkili Viral Baskılama

1 Yıllık Tedavi Ardından Saptanamaz HBV DNA Seviyeleri



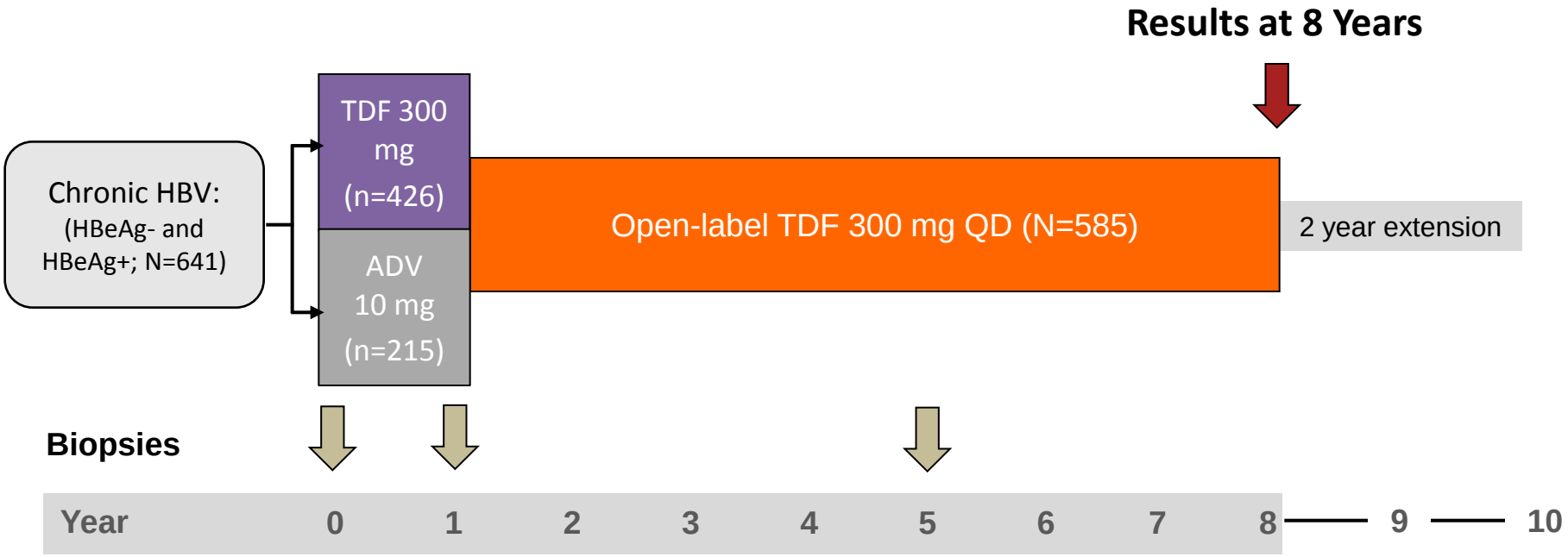
Bire bir karşılaştıran çalışmalar değil; hasta popülasyonu ve çalışma tasarımları farklı

Adapted from Lok AS, et al. Hepatology 2007;45:507–39;
Adapted from Lok AS, et al. Hepatology 2009;50:661–2.

*By PCR-based assay (LLD ~50 IU/mL) except for some LAM studies.
ADV: adefovir; ETV: entecavir; LAM: lamivudine; PEG-IFN: pegylated interferon; LdT: telbivudine; TDF: tenofovir disoproxil fumarate

Eight Year Treatment with TDF for CHB

Phase 3, randomized, double-blind, controlled trials in which adult patients received ADV or TDF for 1 year followed by open-label TDF for a study duration of up to 10 years*



* Emtricitabine (FTC) could be added for confirmed viremia on/after Week 72

Emtricitabine (FTC) is not licensed for use to treat CHB

Marcellin, AASLD, 2014, Oral #229
Marcellin P, et al. *Lancet.* 2013;381:468-75.
Data on File – protocol amendment to extend to 10 years

Kronik Hepatit B Tedavisinde Kullanılan Orijinal ve Jenerik Tenofovir Preperatları

Necati Örmeci[1], Hasan Özkan[1], Atila Karaalp[2]
[1] Ankara Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı, Gastroenteroloji Bilim Dalı, Sıhhiye, Ankara.
[2] Marmara Üniversitesi Tıp Fakültesi Tıbbi Farmakoloji Anabilim Dalı, Maltepe, İstanbul.

Metot

Bu çalışma serbest eczanelerden temin edilen beş farklı TDF preperatı (tablet) ile gerçekleştirilmiştir. Referans olarak kabul edilen ***VİREAD®*** ürün, çeşitli ilaç firmalarınca üretilmiş olan 4 farklı TDF jenerik preperatıyla karşılaştırılmıştır.

Ormeci N. HEBİPA 2014 PS 295

TDF tabletlerinde içerik tekdüzeliği sonuçları

Ticari İsim	Referans ve Test Tenofovir DF (mg)				
	1	2	3	Ort.Miktar (mg)	SD
Referans (Viread®)	300,6304	300,6304	303,2095	301,4901	1,22
Jenerik-1	**320,8329**	**324,0567**	**314,6002**	319,8300	3,93
Jenerik-2	293,1082	298,0514	293,1082	294,7559	2,33
Jenerik-3	314,6002	320,8329	311,5914	315,6748	3,85
Jenerik-4	**293,1082**	306,0034	**317,6091**	305,5736	10,01

Ormeci N. HEBİPA 2014 PS 295

In vitro dissolüsyon testi sonuçları

Zaman (dakika)	Referans (Viread®)	Jenerik-1	Jenerik-2	Jenerik-3	Jenerik-4
5	304,2841	283,2212	224,7636	303,6393	153,8399
10	309,6571	283,2663	263,8791	313,5256	225,8382
15	312,666	305,3587	285,1562	310,5168	267,3178
30	318,039	306,4333	305,1438	311,5914	299,3409
45	312,666	308,1527	298,0514	309,6571	317,3942
60	316,7495	306,6482	290,3143	299,9857	323,412
f2	**Referans**	**% 76,26**	**% 42,44**	**% 100**	**% 27,74**

SONUÇ

*Aynı blister içindeki tabletlerde miktar açısından değişkenlik olması, sırasıyla **etkinlikte azalmaya** ve olası virolojik kırılmalara ya da **gerekenden daha fazla ilaç** olması nedeniyle istenmeyen etkilere yol açabilir.*

*İn vitro ilaç çözünürlükteki bu azalma, in vivo olarak bu ilaçların mide barsak sisteminde istenilen oranlarda çözünmediklerini ifade etmektedir. İlacın çözünmesinde azalma **emilimde azalmaya**, dolayısıyla antiviral etkisinde azalmaya yol açabilir.*

Ormeci N. HEBİPA 2014 PS 295

FOUR-YEAR STUDY OF ENTECAVIR EFFICACY AND SAFETY IN NUCLEOS(T)IDE-NAÏVE HBeAg POSITIVE CHRONIC HEPATITIS B PATIENTS

Mustafa Kemal Celen[1], Tuba Dal[2], Celal Ayaz[1], Kadim Bayan[3], Duygu Mert[4], Ozcan Deveci[1] and Ebru Kursun Oruc[5]

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SUMMARY – Entecavir is a guanosine analogue with activity against hepatitis B virus. The aim of this 4-year trial was to evaluate entecavir treatment in nucleos(t)ide-naïve HBeAg-positive chronic hepatitis B patients. Forty-nine patients received entecavir and nine of them withdrew from the trial at the end of week 96. The initial mean value of alanine aminotransferase was 79.4±41.5 IU/L, and at the end of the 4-year study period, 90% of patients had alanine aminotransferase values within the normal range. At week 96, 91.7% of patients had HBV DNA <300 copies; at month 48, 90% of patients had HBV DNA <50 IU/mL. HBeAg loss was recorded in 7.1% of patients at week 96 and in 12.5% at month 48. The rate of HBeAg seroconversion was 4.8% at week 96 and 7.5% at month 48. The rate of HBsAg seroconversion was 2.1% at week 96 and 2.5% at month 48. Entecavir as a potent and safe agent leading to continuous viral suppression proved to be safe and well tolerated therapy.

Key words: *Guanine – therapeutic use; Hepatitis B, chronic; Antiviral agents – therapy*

EFFICACY AND SAFETY OF TELBIVUDINE VERSUS TENOFOVIR TREATMENT BASED ON THE ROADMAP CONCEPT: RESULTS FROM A RANDOMIZED, CONTROLLED TRIAL IN HBEAG-NEGATIVE CHRONIC HEPATITIS B PATIENTS

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AASLD 2014

PREMISE

- Chronic hepatitis B (CHB) is a common global health problem with more than 350 million people in the world infected with hepatitis B virus (HBV)[1]
- In the long term, CHB may progress to decompensated cirrhosis and hepatocellular carcinoma[2]
- However, early virological response at Week 24 is associated with better long-term treatment outcomes in CHB[3,4]
- The Roadmap strategy, a therapeutic algorithm with conditional intensification of telbivudine (LdT) and tenofovir disoproxil fumarate (TDF) based on early virological response, appears to be a highly effective approach to CHB treatment[1]
- This study evaluated the efficacy and safety of LdT versus TDF treatment in patients with hepatitis B e antigen (HBeAg)-negative CHB following the Roadmap concept of response-guided therapy

METHODS

2.1 Study design

- A prospective, randomized, double-arm, open-label, non-inferiority study
- Patients were randomized (1:1) to either LdT 600 mg or TDF 300 mg once daily

Treatment arms

- Arm 1: LdT 600 mg once daily for 104 weeks
  - Patients with HBV DNA <300 copies/mL at Week 24 will continue to receive LdT monotherapy
  - Patients with HBV DNA ≥300 copies/mL at Week 24 will initiate an add-on therapy of TDF 300 mg once daily for the remaining weeks of treatment
- Arm 2: TDF 300 mg once daily for 104 weeks
  - Patients with HBV DNA <300 copies/mL at Week 24 will continue to receive TDF monotherapy
  - Patients with HBV DNA ≥300 copies/mL at Week 24 will initiate an add-on therapy of LdT 600 mg once daily for the remaining weeks of treatment

2.2 Primary endpoint

- The rate of HBV DNA <300 copies/mL (51 IU/mL) at Week 52
- The primary analysis was performed for the modified intent-to-treat (mITT) population. The mITT population consisted of all patients who did not discontinue before Week 24 and did not receive an add-on therapy at Week 24 and those with missing values were considered using failure imputation rule

2.3 Secondary endpoints

- Antiviral efficacy by rate of patients achieving HBV DNA undetectability at different time points, alanine aminotransferase (ALT) normalization, rates of virological breakthrough and resistance, and estimated glomerular filtration rate (eGFR) assessment
- Safety analysis, such as adverse events (AEs), serious AEs (SAEs) and AE of special interest (AESI) during the study period

RESULTS

- In total, 241 patients were randomized; 121 in the LdT arm and 120 in the TDF arm
- A total of 115 patients in the LdT arm and 117 patients in the TDF arm were included in the mITT population used for efficacy analysis
- The baseline characteristics were similar in the treatment groups (Table 1)

Table 1. Demographics and baseline characteristics

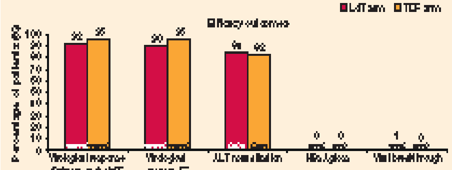
	LdT arm (N=121)	TDF arm (N=120)
Age (years), mean (SD)	42.1 (11.63)	42.2 (12.57)
Male, %	71.1	69.2
Caucasian, %	96.7	99.2
BMI, mean (SD)	26.79 (4.10)	26.74 (4.06)
Genotype D, %	95	91.7
Genotype A, %	5	1.7
HBV DNA (log_{10} copies/mL), mean (SD)	6.2 (1.47)	6 (1.37)
ALT (IU/L), mean (SD)	79.9 (64.09)	79.2 (95.11)
CK (IU/L), mean (SD)	119.6 (64.29)	150.1 (229.2)

ALT, alanine aminotransferase; BMI, body mass index; CK, creatine phosphokinase; HBV DNA, hepatitis B virus DNA; LdT, telbivudine; SD, standard deviation; TDF, tenofovir disoproxil fumarate

3.1 Efficacy outcomes

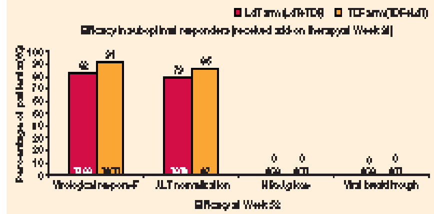
- The primary efficacy endpoint for non-inferiority (margin: -10%) was met, with 92% LdT and 95% TDF patients achieving HBV DNA level <300 copies/mL at Week 52 (Figure 1)
- Overall, 80% of patients in the LdT arm and 89.7% in the TDF arm had HBV DNA level <300 copies/mL at Week 24
- 90% of patients in the LdT arm and 95% in the TDF arm had HBV DNA level <169 copies/mL at Week 52 (Figure 1)
- More than 80% of patients in either arm achieved ALT normalization at Week 52
- Hepatitis B surface antigen (HBsAg) loss was not detected in any patient at Week 52
- In the LdT monotherapy arm, two patients were identified with genotypic resistance

Figure 1. Efficacy of LdT versus TDF at Week 52



- A high proportion of patients who had HBV DNA ≥300 copies/mL at Week 24 and received add-on treatments had decreased HBV DNA level to <169 copies/mL at Week 52 (Figure 2)
- Neither virological breakthrough nor HBsAg loss was reported in the add-on treatment arms

Figure 2. Efficacy at Week 52 in suboptimal responders who received add-on therapy



3.2 Renal function assessment between LdT versus TDF

- LdT was associated with a consistent increase of eGFR from baseline (Figure 2)
- The change in eGFR from baseline, calculated by modification of diet in renal disease (MDRD) formula, was significantly greater in the LdT monotherapy arm compared with the TDF monotherapy arm at different time points (Figure 3)
- Compared with the TDF monotherapy arm, twice as many patients from the LdT monotherapy arm with an abnormal eGFR (60 to <90 mL/min/1.73m²) at baseline reverted to normal eGFR at Week 104; 28/59 (50.6%) versus 11/40 (27.5%) patients for LdT versus TDF, respectively

Figure 3. Evolution of renal function over 104 weeks of treatment

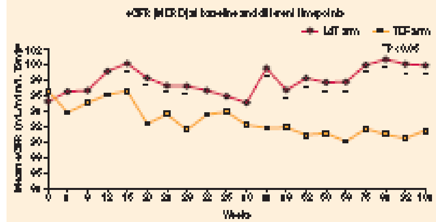
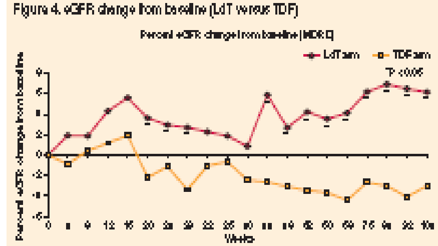


Figure 4. eGFR change from baseline (LdT versus TDF)



Events	LdT arm			TDF arm		
	LdT monotherapy n=98	LdT+TDF n=22	Overall N=120	TDF monotherapy n=109	TDF+LdT n=11	Overall N=120
SAE	[illegible]	[illegible]	[illegible]	[illegible]	1 (9.1%)	[illegible]
Death	0	0	0	0	0	0
AE	[illegible]	15 (68.2%)	[illegible]	[illegible]	[illegible]	[illegible]
AE causing discontinuation	1 (1.0%)	0	1 (0.8%)	[illegible]	0	[illegible]
Total number of patients with AESI	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CK increased	[illegible]	7 (31.8%)	[illegible]	[illegible]	1 (9.1%)	[illegible]
Myalgia	[illegible]	[illegible]	[illegible]	0	0	0
ALT increased	[illegible]	0	[illegible]	[illegible]	1 (9.1%)	[illegible]
Proteinuria	[illegible]	0	[illegible]	[illegible]	0	[illegible]
Muscular weakness	1 (1.0%)	0	1 (0.8%)	0	0	0
Musculoskeletal pain	1 (1.0%)	0	1 (0.8%)	0	0	0
Paresthesia	1 (1.0%)	0	1 (0.8%)	0	1 (9.1%)	1 (0.8%)
Renal failure	0	0	0	1 (0.9%)	0	1 (0.8%)
Acute renal failure	0	0	0	1 (0.9%)	0	1 (0.8%)
Blood creatinine increased	0	0	0	1 (0.9%)	0	1 (0.8%)

CONCLUSIONS

- This is the first head-to-head, prospective, randomized clinical trial in HBeAg-negative CHB patients comparing the efficacy and safety of LdT versus TDF
- The 1-year result of the response-guided therapy based on LdT has a similar antiviral efficacy compared to TDF
- LdT was well tolerated for the treatment of HBeAg-negative CHB patients
- LdT was associated with an improvement in eGFR compared with TDF

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Disclosures
The financial disclosures of all the authors will be included.

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BRIEF ARTICLE

Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection

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= 24). All infants received 200 IU of hepatitis B immune globulin (HBIG) within 24 h postpartum and 20 μg of recombinant HBV vaccine at 4, 8, and 24 wk. Perinatal transmission rate was determined by hepatitis B surface antigen and HBV DNA results in infants at week 28.

RESULTS: At week 28, none of the infants of TDF-treated mothers had immunoprophylaxis failure, whereas 2 (8.3 %) of the infants of control mothers had immunoprophylaxis failure (P = 0.022). There were no differences between the groups in terms of adverse events in mothers or congenital deformities, gestational age, height, or weight in infants. At postpartum week 28, significantly more TDF-treated mothers had levels of HBV DNA < 250 copies/mL and normalized alanine aminotransferase compared with controls (62% *vs* none, P < 0.001; 82% *vs* 61%, P = 0.012, respectively).

CONCLUSION: TDF therapy during the second or third trimester reduced perinatal transmission rates of HBV and no adverse events were observed in mothers or infants.

TDF monoterapisi yeterli mi?

EASL THE INTERNATIONAL LIVER CONGRESS™ 2014
LONDON, UNITED KINGDOM, APRIL 9 - 13 / 2014

TENOFOVIR MONO-RESCUE THERAPY IN MULTI-DRUG RESISTANT CHB : A INTERIM RESULT OF PROSPECTIVE COHORT STUDY

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BACKGROUND

Tenofovir disoproxil fumarate (TDF) has demonstrated high antiviral efficacy of treatment-naive or lamivudine - resistant (LAM-R) chronic hepatitis B (CHB) virus infection in the western world.[1, 2] However, TDF mono-resue therapy for the patients with multiple nucleos(t)ide analogue resistance have been studied rarely.

OBJECTIVES

We investigated how effectively TDF mono-rescue therapy can control in CHB patients with multiple nucleoside/ nucleotide resistance by evaluating the viral kinetics and response .

MATERIALS & METHODS

In patients who were treated by TDF monotherapy from December 2012 to December 2013, 418 patients were enrolled with LAM-R and multiple - drug resistance (MD-R) including LAM - R + Adefovir–R (ADV-R), LAM-R + Entecavir–R (ETV-R), LAM-R + ADV-R + ETV-R. HBV DNA was measured using the real-time PCR assay on a Cobas TaqMan 48 analyzer (Roche Molecular systems, Branchburg, NJ) with the lower detection limit of 20 IU/mL. Viral response was defined as HBV DNA level with less than 20 IU/mL.

681 patients were reviewed

- Partial viral response (n=149)
- Reactivation after stopping nucleos(t)ide (n=65)
- Previous treatment of interferon (n=10)
- Pregnancy (n=12)
- Adverse event of nucleos(t)ide (n=27)

418 patients were eligible and analyzed in this study

- LAM-R (n= 302)
- LAM-R + ADV-R (n=40)
- LAM-R + ETV-R (n=69)
- LAM-R + ADV-R + ETV-R (n=7)

RESULTS

Table 1. Baseline characteristics

	LAM-R	MD-R
Age (mean ± SD, years)	52 ± 21	51 ± 11
Male, n (%)	204 (67.5)	82 (70.7)
Liver cirrhosis, n (%)	96 (31.8)	46 (39.7)
HBe antigen positive, n (%)	199 (65.9)	69 (59.5)
HBV DNA (mean ± SD, $\log_{10}$ IU/mL)	3.6 ± 1.7	2.6 ± 1.6
ALT (mean ± SD U/L)	66.0 ± 123.9	43.5 ± 103.5

Abbreviation: SD, standard deviation

Table 2. Mean $\log_{10}$ HBV DNA level (IU/mL ± SD)

	HBV DNA				
	Baseline	Month 3	Month 6	Month 9	Month 12
LAM-R	3.6 ± 2.0	1.8 ± 0.9	1.5 ± 0.6	1.4 ± 0.7	1.4 ± 0.6
LAM-R + ADV-R	3.0 ± 1.9	1.6 ± 0.7	1.6 ± 1.4	1.5 ± 0.3	1.4 ± 0.3
LAM-R + ETV-R	2.4 ± 1.4	1.5 ± 1.0	1.6 ± 1.4	1.4 ± 0.5	1.4 ± 0.5
LAM-R + ADV-R + ETV-R	1.6 ± 0.4	1.1 ± 1.4	1.3 ± 0.0	1.3 ± 0.0	1.3 ± 0.0

Figure 1. Mean HBV DNA ($\log_{10}$ IU/mL). The effectiveness of TDF mono-rescue therapy for MD-R didn't show the significant difference compared with LAM-R when HBV DNA level was analyzed using linear Mixed Model.

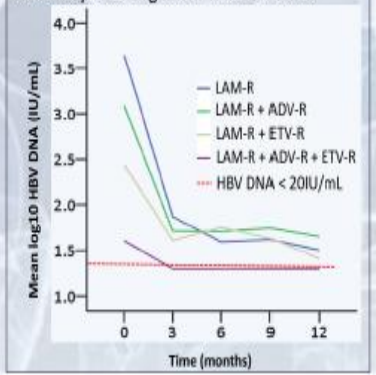
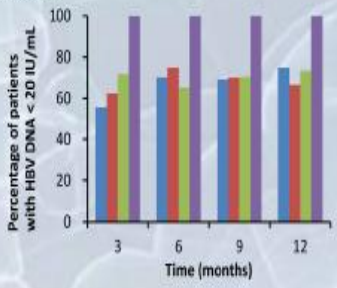


Figure 2. Percentage of patients with HBV DNA < 20 IU/mL for the 12 months follow-up duration.



	Number of subjects			
LAM-R	300	224	139	96
LAM/ADV-R	40	28	20	12
LAM/ETV-R	67	49	37	15
LAM/ADV/ETV-R	7	3	3	2

CONCLUSIONS

- TDF mono-rescue therapy in patients with MD-R is as effective as in patients with LAM-R
- The further follow up study were required for the evaluation of efficacy and safety of TDF mono-rescue therapy for CHB patients with MD-R.

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Summary & Conclusion

Summary

TDF vs. TDF+ETV for 48 weeks in CHB patients with documented ADVr and persistent viremia

- No significant difference between the two groups in terms of
  - The proportion of patients with VR (about 63% at 48 week)
  - Serum HBV DNA reduction
- Minimal incidence of virological breakthrough
- Marked decrease in detectable resistance mutations
- No ad
- Both t
  - No
  - No

Conclusions

- Compared to the combination therapy with TDF and ETV, monotherapy with TDF provided similar rate of virological response during 48 weeks of treatment in CHB patients with documented ADV-resistance mutations and persistent viremia during previous any treatment.
- Both TDF monotherapy and TDF+ETV combination in the week

O halde ADV direnci olan .... TDF monoterapisi uygundur denilebilir mi?

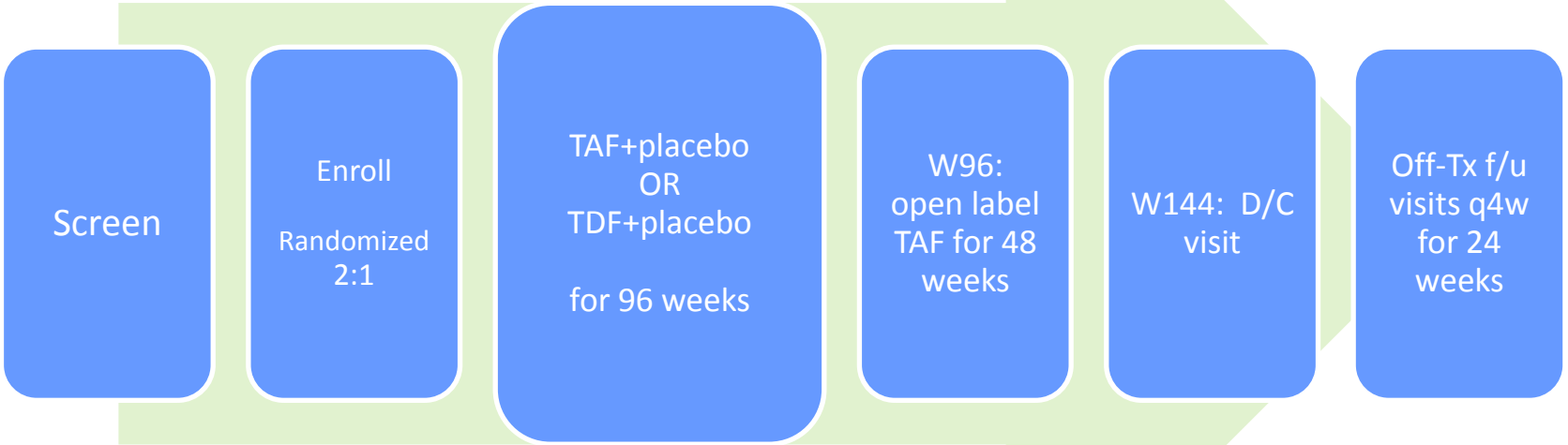
screening (rtA181V or rtA181T or rtN236T) by restriction fragment mass polymorphism (RFMP) or direct sequencing

- Serum HBV DNA ≥ 60 IU/mL despite continued preceding oral antiviral treatment
- No previous exposure to TDF
- Lamivudine (LAM) and/or ETV experience was allowed
- No concomitant chronic viral infection (HCV or HIV) or malignancy
- Serum creatinine < 1.5 mg/dL

EASL 2014

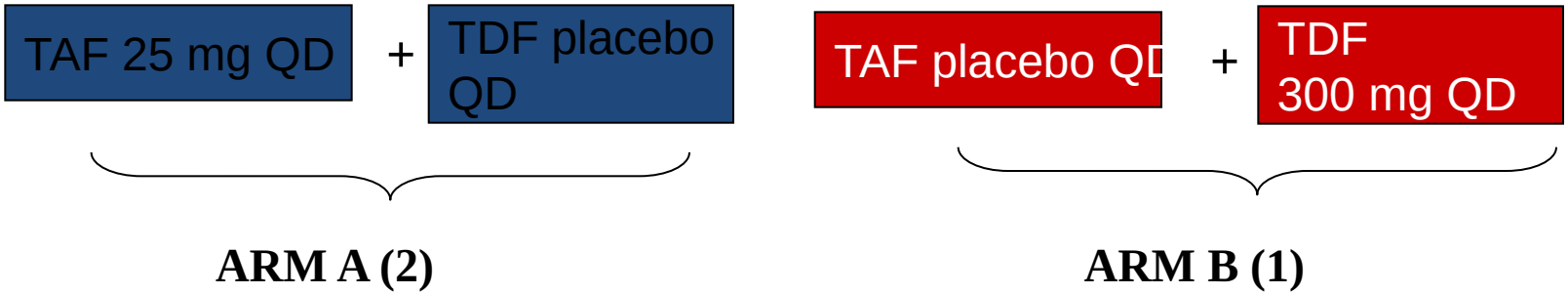
TAF (TENOFOVİR ALAFENAMİD)

- Double blind (until Week 96) – 2 treatment arms (A/B)
- Followed by open label TAF(until Week 144)
- 24 week off-Tx Follow-up (for both ET pts and those who complete W144)



Study Design

- Treatments arms (until Week 96)



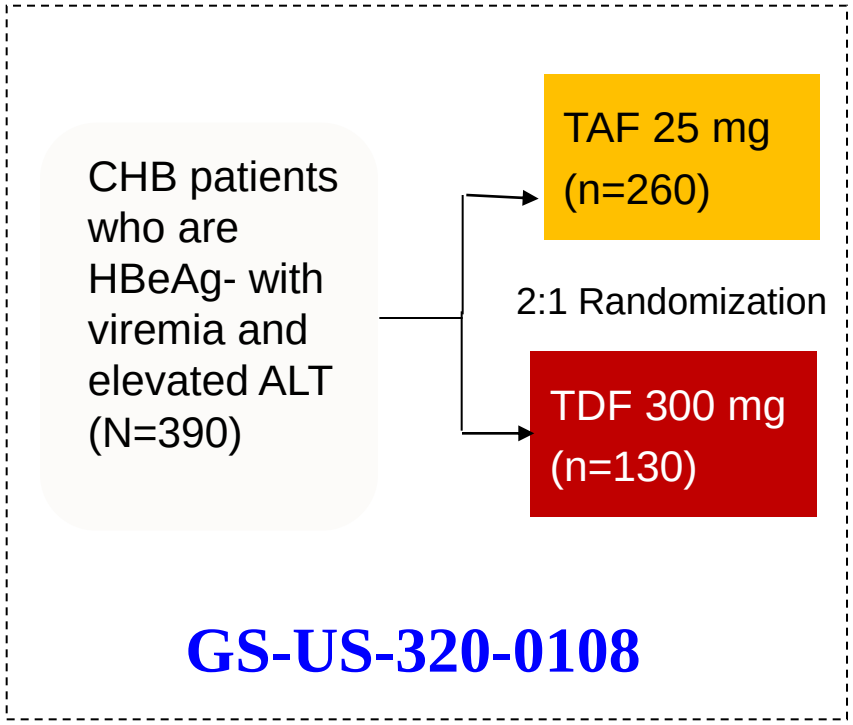
- Subjects will be randomized 2 (A) :1 (B) to receive either blinded TAF 25 mg and TDF matched placebo or TDF 300 mg and TAF matching placebo for 96 weeks
- Subjects will take 2 pills a day during blinded period (until Week 96)
- Stratification by plasma HBV DNA level and oral antiviral Treatment Status (treatment naïve vs. treatment experienced)

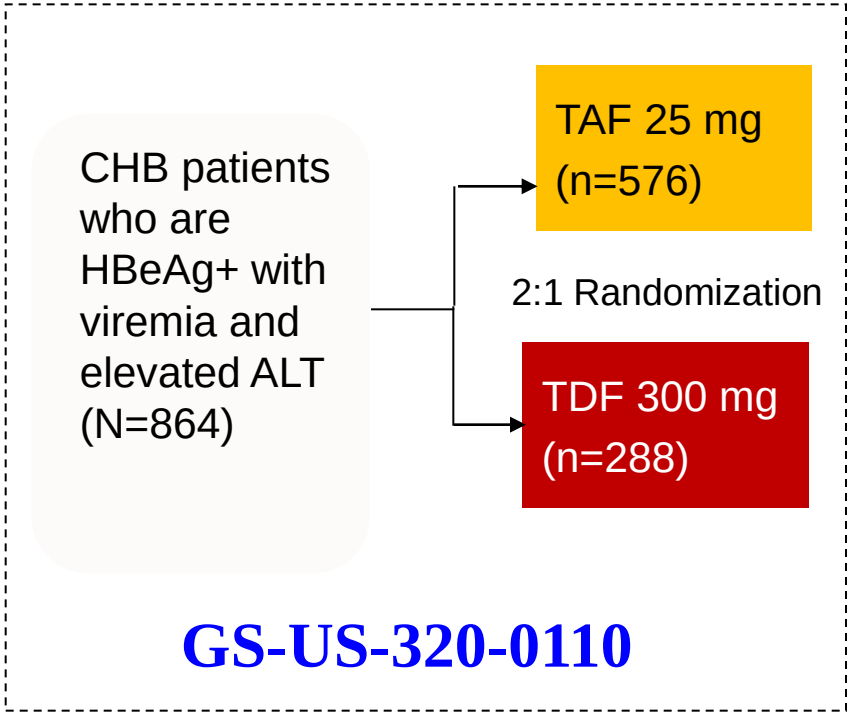
Study Design

- The primary analysis will occur at Week 48
- DMC – meets every 24 weeks (6 months) during the blinded period and every 48 weeks (1 year) during the open label period
  - will review safety and DXA data

Study population

- Prospective, randomized, double-blind trials





Timelines & Enrollment goals

Targets:

- First site activated: Aug 2013 (N America)
- First subject screened: Aug 2013 (N America)
- First subject enrolled: Sep 2013 (N America)
  - Jan 2014 (Europe)
  - Dec 2013 (Asia Pacific)
- Estimated enrollment end:
  - 31-Dec-14 (110)
  - 31-Aug-14 (108)

- 864 subjects to be enrolled on 110
- 390 subjects to be enrolled on 108

Enhanced Levels of Interleukin-8 Are Associated with Hepatitis B Virus Infection and Resistance to Interferon-Alpha Therapy

Int. J. Mol. Sci. **2014**

Kai Yang, Shi-He Guan *, Hao Zhang, Ying Pan, Yuan-Yuan Wu, Ai-Hua Wang and Bei-Bei Sun

- **IL-8** salınımındaki artış fibrozisi artırmaktadır
- Yüksek düzeyde IL-8
- ALT yükselmesi ve Albümin düşüklüğü ile ilişkili bulunmuştur
- İnterferon yanıtsızlığı ile ilişkili bulunmuştur

Peg-INF + NA kombinasyonu

- İki INF ve 5 OAV ajanımız mevcut
- INF immunmodulatör etkili olmasına karşın ancak OAV'lerin çeyreği kadar etkili
- OAV: Potent & Direnç & Yan etki
- Ardışık ve kombinasyon tedavilerinde fark yok
- INF+ LdT kombinasyonunda periferik nöropati riski mevcut
- Sonuç hasta bazlı olarak değerlendirilmeli…

Wong GL. Combination therapy of interferon and nucleotide/nucleoside analogues for chronic hepatitis B. J Viral Hepat. 2014

HCC takibinde maliyet…

- AFP mi?
- USG mi?
- AFP + USG mi?
- CT ?
- MR ?

Sangmala P Economic evaluation and budget impact analysis of the surveillance program for hepatocellular carcinoma in thai chronic hepatitis B patients. Asian Pac J Cancer Prev. 2014

SONUÇ OLARAK

- Aşı…
- Yeni tedaviler…
- OAV…
- PEG-INF
- Maliyet etkinlik
- Kombinasyon tedavileri
- Tedavi Süreleri