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Treatment of chronic hepatitis B in clinical practice with entecavir or tenofovir

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Abstract

Results from phase III clinical trials clearly demonstrate the efficacy and safety of entecavir and tenofovir in the controlled environment of randomized clinical studies. There are several studies with both drugs performed in clinical practice (also called "real life studies"). Despite the pros and cons, studies performed in real life conditions represent everyday practice and add important information about long term treatment effectiveness and safety in this clinical setting. This review shows that patients treated with first line nucleos(t)ide analogs at referral centres, with good clinical follow-up and adherence to international guidelines, can achieve high treatment response rates with a very low rate of adverse events.

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Key words: Hepatitis B; Clinical practice; Entecavir; Tenofovir; Real life

Core tip: Patients treated with entecavir or tenofovir in routine clinical practice at referral centres, with good clinical follow-up and adherence to international guidelines, can achieve high treatment response rates with a very low rate of adverse events.

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INTRODUCTION

The hepatitis B virus (HBV) is estimated to have infected more than 2 billion people worldwide, of whom 400 million are chronically infected today and are at an increased risk of liver-related complications, including cirrhosis, liver failure, hepatocellular carcinoma (HCC) and death^[1,2]. In most regions of America, HBV prevalence is relatively low, with hepatitis B surface antigen (HBsAg) positivity ranging from < 2% to 7% compared with Asia, Africa and the Middle East, where chronic hepatitis B (CHB) prevalence rates reach 5%-20% of the general population^[2,3]. Indications for treatment have been established by several international guidelines^[3,4]. Treatment end-points are complete viral suppression (undetectable levels of HBV DNA replication), hepatitis B e antigen (HBeAg) clearance and seroconversion in HBeAg-positive patients, and if possible HBsAg clearance and development of antiHBs antibody^[3,4]. Patients achieving these serologic end-points may discontinue treatment after an additional 6-12 mo period of consolidation therapy according to the cited guidelines. The goal of HBV treatment is to improve survival by preventing disease progression to decompensated cirrhosis

and HCC^[3,4].

Treatment induced suppression of HBV DNA to undetectable levels reduce the risk of disease progression improving liver fibrosis, and can result in fibrosis and cirrhosis regression^[5,6]. Also, HBV DNA clearance is associated with increased rates of HBeAg and HBsAg seroconversion, the ultimate goal of HBV therapy. Since HBV DNA is integrated in the host genome, HBV persists in the covalently closed circular DNA form in the hepatocyte even if HBV DNA is not detectable in the serum. This HBV persistence may result in reactivation and hepatocarcinogenesis. Long-term treatment nucleos(t)ide analogs (NUC) is required in HBeAg negative and positive patients who cannot maintain off-treatment virologic suppression.

Pegylated interferon alpha (PEG-IFN alpha), entecavir (ETV) and tenofovir disoproxil fumarate (TDF) had been selected as the first-line therapy to initiate treatment in naïve CHB infected patients^[3,4]. Other NUCs like lamivudine (LAM), adefovir (ADV) and telbivudine (LdT), are no longer recommended as first-line therapy since long-term therapy success with these drugs has been reduced with the emergence of drug-resistant mutants^[3,4]. ETV and TDF were approved by different regulatory agencies in most countries between 2005 and 2009 on the basis of phase III clinical trials results. Since their approval, observational studies have been performed in everyday clinical practice (also known as “real life studies”), with their long term use adding valuable information to the efficacy and safety profiles of these two drugs. The aim of this review is to analyze the currently available data of long term ETV and TDF use in clinical practice as first-line treatments for NUC naïve chronic HBeAg positive and negative HBV patients.

RESULTS FROM CLINICAL TRIALS

Results from phase III clinical trials (CT) are critical for the approval of new drugs. Their main objective is to demonstrate the efficacy and safety of the drug being evaluated in comparison with the current standard of care, in a controlled setting. These trials are conducted on large patients groups under standardized conditions. “Ideal” young patients without comorbidities are included, and usually, patients with advanced liver disease are excluded. These strict inclusion/exclusion criteria are developed to facilitate analyzing the results and getting the new drug approved for its use in clinical practice. Also, patients treated within CT are strictly monitored and assist more frequently to clinical consultation and to laboratory monitoring than in routine clinical practice. Once approved, treating physicians use the same drug in “real life” patients, some of whom would have been excluded from these trials.

Entecavir

Entecavir is a potent inhibitor of HBV replication, which has been commercially available since 2005. In phase III

randomized clinical trials (RCT) ETV showed increased virologic, biochemical and histologic response rates when compared with LAM. ETV at a dose of 0.5 mg/d in treatment-naïve patients suppressed HBV DNA to undetectable levels by year 1 in 67% of HBeAg-positive and in 90% of HBeAg-negative patients compared with 36% and 72% in the LAM arms, respectively^[7,8]. Recent reports showed that when administered for 2 to 5 years, ETV resulted in better HBV DNA suppression and higher HBeAg seroconversion rates^[9-11]. ETV treatment for 3 years in HBeAg-negative and for 5 years in HBeAg-positive patients resulted in 95% and 94% HBV DNA undetectable levels, respectively^[10,11]. In HBeAg-positive patients, treatment for 96 wk resulted in 31% HBeAg seroconversion rates^[9]. In the ETV-901 study, continuing treatment in those patients who remained HBeAg positive at week 96 resulted in 23% HBeAg seroconversion rates and 1.4% HBsAg loss^[11].

ETV has a high genetic barrier to resistance and a strong resistance profile, and has a very favorable safety profile. Recently reported results of more than 6 years of therapy showed that in NUC naïve patients the cumulative probability of genotypic resistance to entecavir was very low (1.2%) and that treatment was well tolerated^[12,13]. Also, analysis of liver biopsies from the two phase III entecavir studies (ETV-022 and ETV-027) and the open-label rollover study (ETV-901) have shown that ETV treatment can improve fibrosis of the liver and can cause fibrosis and cirrhosis regression^[5]. Patients receiving treatment for at least 3 years had ≥ 2 point decrease in the Knodell necroinflammatory score and no worsening of the Knodell fibrosis score in 96% of the cases, and ≥ 1 -point improvement in the Ishak fibrosis score in 88% of the cases^[5]. Reversal of advanced fibrosis/biopsy-proven cirrhosis was demonstrated in nine of 10 patients with baseline Ishak fibrosis scores of 4-6 who underwent serial liver biopsies up to year 6.

Tenofovir

TDF is also a potent inhibitor of HBV replication, which has been commercially available since 2008. In phase III RCT TDF showed increased virologic and biochemical response rates when compared with ADV. TDF at a dose of 300 mg/d in treatment-naïve patients suppressed HBV DNA to undetectable levels by year 1 in 76% of HBeAg-positive and in 93% of HBeAg-negative patients compared with 13% and 63% in the ADV arms, respectively^[14]. As previously shown with ETV, extending treatment with TDF is associated with increasing HBV DNA suppression and higher HBeAg seroconversion rates^[15-17]. After 4 years of treatment, 96% of HBeAg positive and 99% of HBeAg negative patients achieved undetectable HBV DNA levels^[15-17]. In HBeAg positive patients, HBeAg loss occurred in 41% of patients and HBeAg seroconversion in 29%; the cumulative probability of HBsAg loss was 11%^[15,16]. Longer treatment with TDF is associated with higher HBV DNA negativization rates (98%-99%), and higher

HBeAg and HBsAg negativization and seroconversion rates^[18].

As with ETV, long-term treatment with TDF has been associated with histologic improvement. Sustained viral suppression with TDF treatment over 5 years was associated with histological improvement in 87% of patients and 51% fibrosis regression; 74% of patients with cirrhosis (Ishak score 5 or 6) at baseline no longer had cirrhosis^[6]. TDF was well tolerated over this treatment period^[15-18], and no resistance with long term treatment has been reported to date^[19,20].

RESULTS FROM CLINICAL PRACTICE STUDIES

Results from phase III RCT clearly demonstrate the efficacy and safety of ETV and TDF in the controlled environment of randomized clinical studies. There are several studies with both drugs performed in clinical practice (also called “real life studies”). Some had been published in full text in peer review journals, and some had been only presented at the liver meetings organized by the American Association for the Study of Liver Diseases and the European Association for the Study of Liver. These studies contain a heterogeneous mixture of patients treated for different periods of time who are differentiated from those in clinical trials as based on a number of criteria and may, therefore, be more reflective of the treatment population and the real efficacy and safety of the drug (Table 1)^[21]. Results from these studies are discussed in the following section and summarized in Table 2.

Entecavir

There are several studies of ETV treatment in clinical practice from different regions of the world. Most of them are from Europe and Asia, and a minority from America and Oceania. The Oriente study analyzed the results from 190 NUC-naïve patients treated for a year in 25 centres in Spain. The cohort was 73% male, 84% Caucasian, 30% HBeAg positive and 34% of the patients who underwent biopsy had advanced fibrosis/cirrhosis. At week 48, 83% of the patients (61% HBeAg-positive; 92% HBeAg negative) achieved a virological response, 26% of the HBeAg-positive patients lost HBeAg and 22% achieved seroconversion to antiHBe and 2% showed HBsAg clearance^[22]. The European network of excellence for vigilance against viral resistance (VIRGIL) performed a multicentre cohort study at over 10 European referral centres between 2005 and 2010 including 243 NUC-naïve patients^[23]. At week 144, 90% of HBeAg positive patients and 99% of HBeAg negative patients achieved a virologic response, and 34% of the HBeAg-positive patients lost HBeAg. In a single-centre cohort study from the King's College in the United Kingdom 3 treatment strategies were compared. One hundred and fifty four patients were treated with ETV monotherapy for a median of 28 mo: 76%

of patients achieved HBV DNA undetectable levels, 8% of the HBeAg positive patients cleared HBeAg and 1% cleared HBsAg^[24].

A retrospective/prospective, multicentre study was conducted at 19 Italian centres and included 418 consecutive NUC-naïve patients treated with ETV^[25]. In their last evaluation, 100% of HBeAg positive patients and 99% of HBeAg negative patients achieved HBV DNA undetectable levels after 60 mo of treatment. In HBeAg positive patients, HBeAg seroconversion occurred in 31 patients (cumulative rate of 55%) and HBsAg loss in 15 patients (cumulative rate of 34%). One patient developed resistance to ETV (L180M, M204V, S202G) over the treatment period and was successfully treated with TDF^[25].

A single centre study from Italy included 100 patients, 85 of whom were NUC-naïve treated with ETV for 36 mo. Overall, 94% of the patients achieved HBV DNA negativization, 33% of HBeAg positive patients cleared HBeAg and 15% cleared HBsAg^[26]. Another multicentre study from Italy included 300 patients, 287 being NUC-naïve treated for 24 mo. At the end of follow up, cumulative rates of undetectable HBV DNA was 89%, 39 patients were HBeAg positive and 17 achieved negative HBeAg with antiHBe seroconversion in 15 cases (38.4%), and HBsAg loss was observed in 5 patients^[27]. Unfortunately, both studies presented their overall results, including both NUC-naïve and NUC-experienced patients.

The results from a previously reported multicentre study performed in Argentina were recently updated^[21,28]. One hundred and sixty nine consecutive patients were treated with ETV for a median 181 wk. Overall, 156 (92%) patients became HBV DNA undetectable, 92 (88%) of HBeAg positive and 64 (98%) of HBeAg negative patients. Cumulative clearance of HBV DNA by week 192 and 240 was 100% in both HBeAg positive and negative patients. Seventy four (71%) patients cleared HBeAg, 23 (14%) patients cleared HBsAg (19 HBeAg positive and 4 HBeAg negative, $P = 0.025$), and 22 (13%) patients developed protective titers of antiH-Bs. One patient developed virological breakthrough due to ETV resistance (M204V, S202G) over the treatment period^[29]. In a follow up study, post-treatment outcomes of patient from this study were evaluated in clinical practice^[30]. Thirty-five patients (20%) discontinued ETV treatment due to sustained virological response; 33 of these patients developed HBeAg seroconversion and 18 HBsAg seroconversion. Nine patients (26%), all HBeAg positive at baseline, developed virological relapse after a median 48 wk off treatment, 3 of them showed HBeAg reversion and 4 lost antiHBe. No patient with HBsAg seroconversion relapsed^[30]. These results confirmed that ETV, after 12 mo consolidation therapy, can be discontinued in real life. Patients have to be followed since there is still a risk of virological relapse.

A single-centre prospectively followed cohort from Hong Kong analyzed 222 NUC-naïve patients receiv-

Table 1 Baseline characteristics of patients included in entecavir studies^[2,1]

Characteristic, n (%) ¹	ETV-022	ETV-027	Oriente	Virgil	King's College Cohort	Italian cohort	Argentinean cohort	Hong Kong cohort	Japan cohort	China cohort	China cohort 2	Taiwan cohort	Taiwan cohort 2	United States cohort	United States cohort 2	Australia	
Ref.	[7]	[8]	[22]	[23]	[24]	[25]	[29]	[32]	[33]	[34]	[35]	[36]	[37]	[38]	[39]	[40]	
n	354	325	190	243	154	418	169	222	474	230	1768	98	248	169	136	163	
Age, yr (mean ± SD or range)	35 ± 13 ²	44 ± 11 ²	44 (35-54) ³	43 ± 14 ²	42 ³	58 (18-82) ⁴	51 ± 13 ²	47 (21-77) ⁴	47 (17-82) ⁴	42 ± 12 ²	36 (16-70) ⁴	48 ± 13 ²	39 (17-77) ⁴	39 ± 12 ²	39 ± 12 ²	52 (24-86) ⁴	
Male	274 (77)	248 (76)	139 (73)	177 (73)	122 (79)	316 (76)	113 (77)	157 (71)	321 (67)	196 (85)	1414 (80)	67 (68)	172 (69)	100 (59)	83 (61)	113 (69)	
Race																	
White	140 (40)	193 (59)	60 (84)	114 (47)	NR	NR	143 (85)	NR	NR	NR	NR	NR	NR	7 (4)	10 (7)	NR	
Asian	204 (58)	122 (38)	18 (9)	70 (29)	NR	NR	26 (15)	NR	NR	NR	1768 (100)	NR	NR	162 (96)	126 (93)	NR	
Other	2 (<1)	2 (<1)	6 (3)	59 (24)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Region	Europe 24%, North America 13%, South America 14%, Australia and Asia 49%	Europe 48%, North America 13%, South America 9%, Asia 11%, Australia and Asia 33%	Europe	Europe	Europe	Europe	South America	Asia	Asia	Asia	Asia	Asia	Asia	North America	North America	North America	Oceania
Genotype																	
A	94 (27)	33 (10)	NR	40 (22)	NR	NR	NR	NR	12 (3)	NR	NR	NR	NR	0	0	NR	
B	68 (19)	46 (14)	NR	14 (8)	NR	NR	NR	NR	67 (16)	NR	NR	NR	NR	-61	-57	NR	
C	111 (31)	57 (18)	NR	25 (14)	NR	NR	NR	NR	336 (81)	NR	NR	NR	NR	-39	-41	NR	
D	37 (10)	157 (48)	NR	91 (50)	NR	NR	NR	NR	0 (0)	NR	NR	NR	NR	0	0	NR	
HBeAg negative	6 (3)	322 (99)	133 (70)	157 (65)	106 (69)	347 (83)	65 (39)	132 (59)	252 (53)	117 (51)	602 (34)	57 (58)	0 (0)	0 (0)	0 (0)	10 (6.1)	
HBV DNA, log ₁₀ IU/mL ¹	9.62 (2.01) ^{2,5}	7.6 (1.8) ^{2,5}	5.94 (4.64-7.39) ³	6.2 ± 1.7 ³	4.6 (0.2) ⁶	6.0 (1.5-9) ⁴	6.88 (1.81) ²	7.1 (4.0->8.8) ⁴	6.7 (2.6->9.0) ⁴	6.3 ± 1.4 ³	6.74 (1.04-9.69) ⁴	6.0 ± 1.5 ³	7.6 (2.2-13.1) ⁴	7.58 (3.77-9.70) ⁴	7.48 (3.8-9.9) ⁴	NR	
ALT, IU/L ¹	140.5 (114.3) ²	141 (114.7) ²	71.5 (44-108) ³	NR	NR	92 (11-2241) ⁴	139 (231) ²	92 (17-2168) ⁴	70 (8-2121) ⁴	68 (3-2631) ⁴	NR	138 (21-4190) ⁴	201 (27-2415) ⁴	62 (14-839) ⁴	67 (14-1077) ⁴	NR	
Cirrhosis	26/329 (8)	15/303 (5)	0 ⁷	57 (24)	52 (34)	202 (49)	38 (23)	0	102 (22)	74 (32)	NR	13 (14)	39 (16)	NR	NR	26(16)	

¹Unless otherwise specified; ²Mean ± SD; ³Median (interquartile range); ⁴Median (range); ⁵log₁₀ copies/mL; ⁶Mean ± SE; ⁷Advanced fibrosis in 34%. ALT: Alanine transaminase; NR: Not reported; NUC: Nucleos(t)ide analogue; VIRGIL: Vigilance against viral resistance; ETV: Entecavir.

ing ETV (0.5 mg daily) for up to 4 years^[31,32]. The cumulative rate of patients achieving HBV DNA undetectable levels was 90% by year 4. HBeAg seroconversion occurred in 53% of HBeAg positive patients, and of HBsAg positive patients seroconversion developed only in one patient (0.5%). Only one case of resistance (rtI180M, rt204Y, and rtI184S/C/G/A) was reported in this cohort, representing a 0.6% cumulative resistance rate up to year 4^[32]. This low rate, by comparison with previously mentioned results, probably evidences the less frequent occurrence of HBsAg loss (mainly if not exclusively reported in HBeAg positive patients) in genotypes B and C (the most frequent in Asia) compared with genotypes A and D (the most frequent in Europe)^[21].

A retrospective analysis from Japan included 474 patients who received ETV treatment for up to 4 years^[33]. The cumulative rate of patients achieving HBV DNA undetectable levels was 96% by year 4. HBeAg seroconversion occurred in 42% of HBeAg positive patients, and of HBsAg positive patients seroconversion developed only in one patient (0.2%). In this cohort, 5 patients showed virological breakthrough during the treatment period, including 2 patients who developed ETV-resistant mutations^[33]. Two hundred and thirty NUC-naïve patients treated for up to 5 years were retrospectively evaluated in China^[34]. Incremental increases were observed in undetectable HBV DNA rates, with

Table 2 Summary of efficacy results from real-life studies of entecavir in nucleos(t)ide analogue-naïve patients *n* (%)^[21]

Study	Median follow-up (range)	Patients (<i>n</i>)	Cut-off (assay limit) (IU/mL)	HBV DNA undetectable ¹	HBeAg seroconversion ^{1,2}	HBsAg loss ¹
ORIENTE ^[22]	52 wk (46-53 wk)	190	50	115 (82)	12 (21)	2 (1)
VIRGIL ^[23]	19 mo (3-45 mo)	243	80	126 (74)	13 (15)	3 (1)
King's College cohort ^[24]	28 mo (NR)	154	12	NR	NR	NR
Italian cohort ^[25]	58 mo (2-80 mo)	418	12	93 (99)	527 (31 patients)	337 (15 patients)
Argentinean cohort ^[29]	181 wk (108-248 wk)	169	6	34 (100)	71 (68)	23 (14)
Hong Kong cohort ^[32]	3 yr (12-60 mo)	222	12	51 (90)	16 (53)	1 (0.5) ³
Japan cohort ^[33]	2.37 yr (0.5-7.2 yr)	473	12	70 (96)	93 (42)	1 (0.2)
China cohort ^[34]	27.5 mo (3-73 mo)	230	100	NR	17 (15)	1 (0.4)
China cohort 2 ^[35]	191 wk (1-233 wk)	1768	50	1327 (83)	NR	NR
Taiwan cohort ^[36]	144 wk	98	NR	93 (95)	5 (12)	0
Taiwan cohort 2 ^[37]	25.3 mo (12-69 mo)	248	6	33 (82)	64 (28)	NR
United States cohort ^[38]	25 mo (6-68 mo)	169	100	75 (44)	12 (8)	NR
United States cohort 2 ^[39]	36 mo	136	100	115 (85)	41 (30)	0
Australia cohort ^[40]	26 mo (3-46)	163	12	134 (82)	66 (43)	1 (0.6)

¹Unless otherwise specified; ²Median (interquartile range); ³Advanced fibrosis in 34%.

100% being undetectable at 5 years of treatment. Fifteen percent achieved HBeAg/antiHBe seroconversion, and only one patient cleared HBsAg (0.4%). Only one patient developed ETV resistance mutations (rtL180M + rtT184A + rtM204V), and was subsequently treated with ETV+ADV combination therapy^[34].

In a sub-study of the randomized, observational study of entecavir to assess long-term [(REALM) outcomes associated with nucleoside/nucleotide monotherapy for patients with chronic HBV infection] trial, 1768 NUC-naïve patients were treated with ETV in a 'real-world' clinical practice setting in China^[35]. The preliminary results of the virologic efficacy and limited safety data were recently presented. At week 144, 84% of ETV-treated patients had HBV DNA undetectable levels. Unfortunately HBeAg and HBsAg clearance rates were not reported. Importantly, in this large cohort of patients prospectively followed, ETV demonstrated to be very safe with no serious adverse events reported. In Taiwan 98 patients were treated with ETV, in a study comparing its efficacy with LdT^[36]. Short term treatment, up to 48 wk, showed HBV DNA was undetectable in 95% of patients and the HBeAg seroconversion rate was 27%. None of the patients achieved HBsAg clearance. No resistance was reported. In the real-world study "Taiwan Retrospective study of Entecavir Treatment: a Multi-center E Antigen positive Treatment-Naïve Trial of Chronic Hepatitis B" (TREATMENTCHB), 248 HBeAg positive patients were treated with ETV^[37]. Undetectable serum HBV DNA levels were achieved in 52% (111/213), 79% (101/128), and 82% (33/40) of patients at 1, 2, and 3 years of treatment, respectively. Of 248 patients, 99 (40%) achieved HBeAg loss at the time of data analysis. The rate of HBeAg seroconversion was 28% (64/231; 17 missing data of antiHBe antibody). The cumulative rates of HBeAg loss were 20%, 38%, and 49% at years 1, 2, and 3 of treatment, respectively. HBsAg loss rate were not reported^[37].

A retrospective cohort study was performed including 333 consecutive treatment-naïve HBeAg positive

patients treated with oral NUC monotherapy with LAM, ADV, ETV, or TDF for up to 12 mo at three gastroenterology clinics in the United States, where 96% of the cohort were Asians^[38]. One hundred and sixty nine of them received treatment with ETV. At the time of evaluation 44% achieved HBV DNA undetectable levels and the HBeAg seroconversion rate was only 8%. In the entire cohort, a total of 118 patients switched therapy during the course of treatment: 38 switched to combination therapy and 80 switched to alternative monotherapy. The HBeAg seroconversion rates improved with time, being 21% at year 2, 28% at year 3, 38% at year 4, and 38% at year 5. There is no data about ETV patients treated outcome. A subgroup of this study, those receiving only ETV was reported^[39]. One and hundred thirty six patients received treatment for up to 36 mo. Complete viral suppression rates at months 24 and 36 were 66% and 85%, respectively. The cumulative HBeAg seroconversion rates were 20% at month 24 and 30% at month 36. No patients achieved HBsAg loss or HBsAg seroconversion in this study. The results from this study suggest that, unlike the majority of the studies reported, achieving HBeAg seroconversion in real-life settings appears to be much more difficult than in registration trial settings. In this case, it might be related to lower ALT levels. Also, the low rate of HBsAg loss in this predominately Asian cohort may be associated with the predominance of HBV genotypes B and C as previously mentioned.

A study from Australia included 163 NUC-naïve patients treated with ETV for up to 36 mo^[40]. It showed that 134 patients (82%) achieved complete virologic suppression (HBV DNA levels < 12 IU/mL). Authors reported that the annual HBeAg positive to negative seroconversion rate was 14%; after 36 mo 66 patients (43%) achieved this serologic endpoint. In this cohort only one patient (HBeAg negative) cleared HBsAg. A recent review also from Australia showed similar results: 81%-89% HBV DNA suppression rates^[41]. Unfortunately they do not report HBeAg and HBsAg clearance rates.

Results from these 13 studies, including 4434 pa-

Table 3 Baseline characteristics of patients included in tenofovir studies *n* (%)^[21]

Characteristic ¹	Study 103	Study 102	King's College Cohort	United States cohort	European cohort	German cohort
Reference <i>n</i>	[14] 176	14 250	[24] 60	[38] 28	[42] 302	[43] 184
Age, yr (mean ± SD or range)	34 ± 11 ²	44 ± 11 ²	403	36 ± 9 ²	55 (19-80)	44 ± 14 ²
Male	119 (68)	193 (77)	30 (50)	16 (58)	222 (74)	127 (69)
Race			NR		NR	
White	92 (52)	161 (64)		1 (4)		140 (76)
Asian	64 (36)	63 (25)		27 (96)		
Other	20 (11)	26 (10)				
Region	Europe 55%, North America 27%, Australia and Asia 18%	Europe 63%, North America 21%, Australia and Asia 16% ⁴	Europe	North America	Europe	Europe
Genotype			NR		NR	NR
A	94 (27)	33 (10)				
B	68 (19)	46 (14)		18 (65)		
C	111 (31)	57 (18)		10 (35)		
D	55/173 (32)	156/243 (64)				
HBeAg negative	0 (0)	250 (100)	46 (77)	0 (0)	241 (80)	127 (69)
HBV DNA, log ₁₀ IU/mL ¹	8.64 (1.076) ^{2,5}	6.86 (1.31) ^{2,5}	4.2 (0.3) ⁶	7.74 (3.34-8.66) ³	5.9 (1.4 -> 9) ³	6.9
ALT, IU/L ¹	142 (102.81) ²	127.5 (101.21) ²	NR	52.5 (8-468) ³	88 (11-3733) ³	
Cirrhosis	34/172 (20)	47/250 (19)	14 (23)	NR	105 (35)	20 (11)

¹Unless otherwise specified; ²mean ± SD; ³median (range); ⁴Australia or New Zealand; ⁵log₁₀ copies/ml; ⁶mean ± SE. ALT: Alanine transaminase; NR: Not reported; HBeAg: Hepatitis B e antigen.

Table 4 Summary of efficacy results from real-life studies of tenofovir in nucleos(t)ide analogue-naïve patients *n* (%)

Study	Median follow-up (range)	Patients (<i>n</i>)	Cut-off (assay limit) (IU/mL)	HBV DNA undetectable ¹	HBeAg seroconversion ^{1,2}	HBsAg loss ¹
King's College cohort ^[24]	12 mo	60	12	33 (76)	2 (7)	0
United States cohort ^[38]	12 mo (6-23 mo)	28	100	23 (82)	7 (5)	0
European cohort ^[42]	33 mo (0-66 mo)	302	12	91 (97)	18 (36) ³	8 (13)
German cohort ^[43]	24 mo	184	69	170 (92)	NR	NR

¹Unless stated otherwise; ²among those hepatitis B e antigen (HBeAg) (+) at baseline; ³Kaplan-Meier estimate. NR: Not reported; HBV: Hepatitis B virus; NUC: Nucleos(t)ide analogue; HBsAg: Hepatitis B surface antigen.

tients, showed that ETV is as effective in clinical practice as in clinical trials. Extending treatment duration is associated with increasing rates of HBV DNA complete suppression, HBeAg seroconversion and HBsAg loss. Different response rates between studies, mainly regarding serological response, may be associated with particular virological and host factors of each geographic region.

Tenofovir

There are fewer studies published with TDF than with ETV. Also, the population included in these studies tended to be heterogeneous, patients were treated for different periods of time (generally for shorter periods of time than with ETV) (Table 3), and may also be more reflective of the treatment population and the real efficacy and safety of the drug^[22]. Results from these studies are discussed in the following section and summarized in Table 4.

The King's College Cohort from London (already discussed in the ETV section) included 60 patients receiving first-line TDF treatment^[24]. Since TDF was approved after ETV, these patients received a shorter duration of

treatment at the time of the analysis (9 mo compared with 28 mo). At 12 mo of treatment, 76% of TDF treated patients cleared HBV DNA, 7% achieved HBeAg seroconversion and no patient cleared HBsAg. In another previously mentioned study, 333 consecutive treatment-naïve CHB patients treated with oral NUC monotherapy with LAM, ADV, ETV, or TDF for up to 12 mo were evaluated at three gastroenterology clinics in the United States^[38]. Twenty eight of them received treatment with TDF. At 12 mo of treatment, 82% of TDF treated patients cleared HBV DNA, 5% achieved HBeAg seroconversion and no patient cleared HBsAg.

Two large studies evaluating TDF use in clinical practice were recently reported^[42,43]. A multicentre cohort study conducted at 19 European centres retrospectively and prospectively monitored 302 NUC-naïve patients followed for a median of 33 mo and the 3 years follow up study was presented^[42]. Virological response rates increased over time from 84% at year 1 to 95% at year 3 in the overall population, from 66% to 86% in HBeAg positive patients and from 74% to 98% in HBeAg negative ones. The cumulative probability of HBeAg seroconversion steadily increased to 36% at year 3, with 8 patients

(13%) clearing HBsAg, and 5 of these stopping TDF successfully. Virologic breakthrough was reported in 2% of patients, with no potentially resistance-associated mutations identified to date. A prospective observational study including 400 TDF-naïve patients was performed in Germany and the 2 year data is available (GEMINIS study)^[43,44]. Forty-six percent of the patients ($n = 184$) were NUC-naïve. At the time of evaluation, overall 92% of NUC-naïve patients achieved HBV DNA undetectable levels, 81% of HBeAg positive and 91% of HBeAg negative patients; 20% achieved HBeAg seroconversion, and there was 5% loss in HBsAg in HBeAg positive patients. No virologic breakthrough and no resistance have been reported to date.

SAFETY AND TOLERABILITY IN CLINICAL PRACTICE

Entecavir

ETV should be administered on an empty stomach (at least 2 h after a meal and 2 h before the next meal) and is generally well tolerated. The most commonly reported treatment related adverse events in phase III clinical trials were headache, fatigue, dizziness, and nausea at comparable rates to LAM^[7,8]. In the ETV-901 rollover study 1051 patients were enrolled from 10 prior Phase II/III studies and were treated with ETV for at least a 5 year period^[13]. Most of the reported adverse events (AEs) were mild to moderate, 19% were grade 3-4 events, with only 4% of them possibly related to ETV. These grade 3-4 AEs were myalgias (5%), neuropathy (hypoparesis and hyperparesthesia, polyneuropathy) (4%), increased lipase (2%), increased serum creatinine ($< 1\%$), increased serum lactate or decreased serum bicarbonate ($< 1\%$), hypophosphatemia ($< 1\%$), muscular weakness ($< 1\%$), pancreatitis ($< 1\%$) and creatinine phosphokinase elevation ($< 1\%$)^[45,46]. It was reported an overall discontinuation rate due to AEs was extremely low ($< 1\%$).

Are these results from phase III trials applicable to treatment in real life settings? After reviewing the experience from these studies (including 4434 patients), it seems that the ETV Safety profile in clinical practice is consistent with those of Phase III studies, in that no major safety issues or serious side effects have been reported to date^[21-25,29-40,44]. As a controlled trial, patients have been carefully selected in order to be able to be included. Excluded patients usually have advanced liver diseases or comorbidities. The latter commonly require administration of concomitant medications. The addition of different medications may have an important impact upon study drug pharmacokinetics, efficacy and safety. The strict inclusion criteria of these studies did not allow testing unexpected adverse events due to drug to drug interactions, nor potential toxicity in patients with advanced liver disease. For this reason, studies reporting results in “real life” are necessary to add information to controlled clinical trials reports^[44].

There are some safety concerns when using the newer

NUCs in CHB cirrhotic patients. Lactic acidosis (LA) with ETV was first reported in 2009. Five of 16 HBV cirrhotic patients treated with ETV developed lactic acidosis. One of the patients died, and the other 4 recovered after treatment discontinuation. A significant correlation between the MELD score and the development of lactic acidosis was observed ($P = 0.002$). The single components of the MELD score - bilirubin, INR, and creatinine - also correlated with the development of lactic acidosis ($P = 0.003$, $P = 0.003$, and $P = 0.008$, respectively). LA developed in patients with more severe liver dysfunction (MELD score > 20)^[45]. There were no cases of LA reported in the ETV 901 study or in the clinical practice studies, considering that 8% to 49% of patients included were cirrhotics^[22,26,30-41]. A recent study using ETV and/or TDF in compensated or decompensated HBV cirrhotic patients in real-life clinical practice demonstrated that both drugs can be safely used in this subgroup of high risk patients^[46]. Safety of ETV in decompensated HBV cirrhotic patients was confirmed in an open label study^[47]. This data suggested that ETV can be used, but should be applied cautiously, in patients with severe decompensated liver disease. As per reported NUCs preclinical data, a usual concern with the long term administration is their potential carcinogenicity. After a 5 year period of ETV administration, only 3 cases of the novo non liver neoplasms were identified: two gastric and one pancreatic adenocarcinoma^[13,44]. However, to date, there is no evidence for the occurrence of cancers as a result of ETV treatment in patients. A global phase IV study (the REALM study), preliminary results of which were discussed above^[35], is continuing to address this safety concern in patients treated with ETV during a 10-year follow-up period.

Tenofovir

In phase III trials the overall incidence of AEs was comparable in patients receiving TDF *vs* ADV^[14]. The most common AEs in both studies included headache, nasopharyngitis, back pain, nausea, and fatigue. Nephrotoxicity may be a potential concern with TDF, based on evidence from post-marketing surveillance of patients receiving TDF for HIV infection, but so far the problem appears to be less evident in patients with HBV infection^[22,43]. Results from the long term follow up of phase III studies have been recently presented^[20]. At year 6, less than 2% of patients discontinued TDF due to an adverse event, and less than 1.5% experienced a confirmed renal event (≥ 0.5 mg/dL increase in serum creatinine from baseline, phosphorus < 2 mg/dL, or CrCL < 50 mL/min)^[21]. The use of tenofovir has been associated with greater loss of bone mineral density during the early months of therapy in HIV monoinfected patients, although no HBV monoinfected patient experienced bone fractures in these studies^[16-20]. Bone mineral density (BMD) remained stable from year 4 through year 6, for both hip and lumbar spine^[20]. Recent data suggests that in HBV monoinfected patients, bone mineral loss

might be related to vitamin D deficiency and not to TDF treatment^[48]. Nevertheless, BMD should be periodically evaluated in HBV patients taking TDF^[44]. Safety data collected from the European cohort study concerning TDF were generally consistent with the long term clinical study safety data^[42].

Median serum creatinine, eGFR and phosphorus blood levels remained unchanged over time. Approximately 2% of the patients showed > 0.5 mg/dL increase of serum creatinine or < 2 mg/dL phosphorus or proteinuria. The proportion of patients with eGFR < 50 mL/min by MDRD increased from 3% at baseline to 6% at the end of the study. TmPO₄/GFR ratio, a marker of urinary phosphate reabsorption, was reduced in nearly 20% of the patients at baseline and in nearly 30% during follow-up. TDF doses were reduced to 300 mg/48 h in 10 patients (3%, decline of eGFR in all) and discontinued in an additional 9 patients (3%, renal-related events in 2 cases). Overall, 5% stopped TDF (HBsAg loss in 5, adverse events in the remaining 11)^[42]. In the GEMINIS study serum creatinine clearance and phosphorous levels remained stable. No frequent AEs were reported. Four renal events were detected, all in NUC-experienced patients (prior long-term LAM +/- ADV therapy) with comorbidities: diabetes (2 patients), renal insufficiency (2 patients), and cirrhosis (1 patient)^[43].

A French multicentre prospective cohort (Vireal study) evaluated the tolerance of TDF treatment in a real life cohort, including elderly patients with comorbidities^[49]. Unfortunately, 58% of the 441 HBV patients treated were NUC-experienced or resistant and were not included in the review of the virological response discussed above. The 2-year data reported no major safety issues. Forty-eight elderly patients were subsequently analyzed: mean age 71 ± 6 years, 73% male, 87% HBeAg-negative, 58% advanced fibrosis and 79% treatment experienced. Although 82% of elderly had prior GFR < 90 mL/min (estimated by CKD-EPI formula), GFR remained stable or improved in 91%. The mean GFR was 73, 69 and 70 mL/min at baseline, 1 and 2 years. This study showed that TDF safety and tolerance were similar in elderly and younger patients^[49]. Also, TDF can be safely used in patients with mild renal impairment. A prospective, randomized, double-blind trial of TDF *vs* emtricitabine (FTC)/TDF combination in LAM-resistant patients compared mild renal impairment (MRI; CrCL 50 ≤ 80 mL/min by Cockcroft-Gault) patients (74/280; 26%) and normal renal function (NRF; CrCL ≥ 80 mL/min) patients (206/280; 74%)^[50]. No patients had a confirmed increase in serum creatinine of ≥ 0.5 mg/dL, and 1% (2-NRF) had transient phosphorus < 2 mg/dL. Nine MRI patients had CrCL < 50 mL/min (pre-treatment range: 49-61 mL/min) that stabilized with dose adjustment. No differences were observed in percentage change in spine or hip BMD over 96 wk, and no clinically relevant bone loss was noted in either group. The safety of patients with MRI receiving TDF was similar to NRF patients; in MRI patients there was

no evidence of increased risk for renal- or bone-related complications^[50]. In TDF treated patients serum chemistries, including creatinine and phosphorus, should be monitored every 6 mo. Monitoring may be more frequent in patients with impaired baseline renal function or other medical conditions that increase the risk of renal failure^[51].

TDF was also used in HBV patients with decompensated liver disease in a phase II double-blind randomized study^[52]. TDF, alone or in combination with FTC, was demonstrated to be safe in this population. As previously mentioned, TDF was safe when used in this group of patients in real-life clinical practice^[46].

PREDICTORS OF RESPONSE IN CLINICAL PRACTICE

The factors that determine the likelihood of achieving a virological and/or serological response are called predictors of response. They can be classified as viral or host related, or as baseline or on-treatment depending on the time point of evaluation. Many viral and host factors affect treatment response, and not achieving the desired response might be related to a combination of them. Before initiating treatment, it is useful for patients and physicians to know the likelihood of achieving a response, so that they can decide whether treatment benefits outweigh its costs and its risks. Also, predictors may be helpful to guide the continuation of antiviral therapy^[4].

In CHB therapy, some baseline and on-treatment predictors of subsequent response have been identified. These factors are stronger predictors of treatment outcomes and are more useful for IFN/PegIFN based than for NUCs based therapies^[4]. Predictors of response for the existing NUCs at various time points vary for different agents. In HBeAg positive patients, baseline factors predictive of antiHBe seroconversion are low viral load (HBV DNA below 2 × 10⁸ IU/mL), high serum ALT levels, and high activity scores on liver biopsy^[4]. HBV genotype does not influence the virological response to any of the available NUCs^[4,53]. Virological response (undetectable HBV DNA) at 24 wk during treatment with LAM or LdT and at 48 wk during treatment with ADV is associated with a lower incidence of resistance, *i.e.* an improved chance of maintained virological response in both HBeAg positive and HBeAg negative patients and with a higher chance of antiHBe seroconversion in HBeAg positive patients^[4]. A decline of HBsAg, HBeAg and HBV DNA levels during NUC treatment in HBeAg positive patients may identify cases with subsequent HBeAg or HBsAg loss^[4,54-56].

Evaluation of predictors of response tends to be difficult in real world studies since patients' characteristics are heterogeneous and treatment duration and parameters evaluated may vary between studies. But there are some data reported with ETV treatment in the studies cited above, and unfortunately none of the TDF studies reported predictors of response. In the

ORIENTE study, virological response in the HBeAg positive patients at week 12 correlated significantly with antiHBe seroconversion rate at week 48: odds ratio for this correlation at week 12 was 8 (95%CI: 1.17-54.5, $P < 0.05$). This correlation was also observed at weeks 24, 36 and 48 ($P = 0.003$, 0.002 and 0.017, respectively)^[22]. In the single centre study from Italy, the presence of cirrhosis (OR = 1.730, 95%CI: 1.082-2.766, $P = 0.022$) and absence of HBeAg at baseline (OR = 0.479, 95%CI: 0.273-0.842, $P = 0.011$) were independent predictors of earlier clearance of serum HBV DNA^[26].

In our study from Argentina, baseline HBV DNA $\geq 7 \log_{10}$ IU/mL (HR = 9.40, 95%CI: 3.46-25.54, $P < 0.001$) and Metavir A score ≥ 2 (HR = 2.48, 95%CI: 1.39-4.40, $P = 0.002$) predicted HBeAg clearance in ETV treated patients^[29]. Being HBeAg positive at baseline (HR = 11.1, 95%CI: 0.96-128, $P = 0.053$) and HBV DNA clearance before week 48 (HR = 7.76, 95%CI: 0.96-62.4, $P = 0.054$) tended to predict HBsAg seroclearance, but they were not statistically significant^[29]. In the Hong Kong cohort baseline HBV DNA levels $\geq 8 \log_{10}$ copies/mL and undetectable HBV DNA levels at week 24 were associated the higher possibilities of achieving undetectable HBV DNA at year 3 of ETV treatment^[31]. In the Japan cohort, HBV DNA levels $< 7.6 \log_{10}$ copies/ml (OR = 15.8, 95%CI: 43.1-79.9, $P = 0.001$) predicted HBV DNA undetectable levels after 3 years of ETV treatment^[33]. Serum albumin < 3.5 g/dL (RR = 2.0, 95%CI: 1.1-3.6, $P = 0.019$) was the only significant determinant of HBeAg seroconversion^[33]. In the Chinese study, high baseline HBV DNA levels (OR = 0.532, 95%CI: 0.315-0.896, $P = 0.018$) and virological non-response at week 24 (OR = 6.093, 95%CI: 2.099-17.685, $P = 0.001$) to ETV monotherapy were the independent risk factors for a partial virologic response at 1 year^[34]. In the TREATMENT CHB study from Taiwan, baseline ALT > 5 -times ULN (HR = 1.810, 95%CI: 1.062-3.085, $P = 0.001$) and baseline HBV-DNA level (HR = 0.812, 95%CI: 0.700-0.942, $P = 0.014$) were independent factors associated with HBeAg loss in ETV treated patients^[37]. In the Australian cohort, patients with baseline DNA levels $< 10^8 \log_{10}$ IU/mL vs $> 10^8 \log_{10}$ IU/mL ($P = 0.001$) and HBeAg negative patients ($P = 0.001$) achieved more rapidly complete virological suppression^[40].

In summary, baseline HBV DNA levels and HBeAg status appeared to predict HBV DNA clearance and HBeAg clearance/seroconversion in clinical practice. There is little information about predictors of HBsAg clearance/seroconversion. There is no information about how HBsAg and/or HBeAg baseline and on-treatment levels impact on treatment response in real life.

CONCLUSION

Is ETV or TDF treatment effective in clinical practice? Can the results observed in CT be extrapolated to clinical practice? Efficacy is the ability of a drug or intervention to produce an effect under optimal conditions, whereas

effectiveness is its usefulness in routine practice^[57]. Clinical trials differ in many ways from clinical practice, and many patients treated in clinical practice would have been excluded from these trials. This is the main reason why studies performed in routine clinical practice provide useful information for the treating physician. This review shows that ETV and TDF used in clinical practice have similar response rates when compared with CT, with low rates of resistance and favorable safety profiles.

Studies performed in clinical practice have some limitations when compared with CT. They are, in most cases, retrospective; the treatment protocol is not standardized; adverse events may be under-reported since there is no strict register of safety parameters; and they include a variable number of patients. These treatments were conducted at referral centres by highly trained specialists with experience in the field who have participated in CT. This ensures treatment effectiveness, but tends to exclude less experienced investigation centres. Another concern is that patient compliance to these long term treatment regimens may be poorer and less controlled than compliance to short term strictly monitored treatments in CT. Most of the studies reviewed show a low rate of patients lost to follow up and a low rate of non-adherence^[58]. Even if adherence is not strictly evaluated in these types of studies, it can be assumed that if there is a low rate of virological breakthroughs and resistance, adherence has to be good to maintain treatment responses.

Despite the pros and cons, studies performed in real life conditions represent everyday practice and add important information about long term treatment effectiveness and safety in this clinical setting. This review shows that patients treated with first line NUCs at referral centres, with good clinical follow-up and adherence to international guidelines, can achieve high treatment response rates with a very low rate of adverse events.

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