SAFETY AND EFFICACY OF TENOFOVIR AS COMPARED TO OTHER NUCLEOT(S)IDE ANALOGUES IN THE TREATMENT OF CHRONIC HEPATITIS B – A SYSTEMATIC REVIEW WITH MIXED-TREATMENT COMPARISON

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Introduction

- NAs serve as a safe and effective option in the treatment of people with HBV. Their use is however often limited due to capacity of virus to develop drug resistance.
- TDF is a promising alternative to other NAs because it shows high efficacy and does not induce drug-resistance even after long-term treatment.
- The aim of our study was to compare safety and efficacy of TDF with other NAs, i.e.: ADV, ETV and LAM, which are frequently used in the treatment of HBV.

Methods

Inclusion criteria:

- Population: adult patients (>18 years) with HBV.
- Interventions: trials comparing TDF, ADV, ETV, LAM and combination thereof with each other or PLC.
- Suitable clinical trials with or without double-blinding:
  - Randomised controlled trials (RCTs)
  - Endpoints (at least 1 included in the study): undetectable HBV DNA, HBeAg seroconversion HBsAg loss, ALT normalization, ALT breakthrough, histological improvement, withdrawals due to adverse events (AE)
  - Adverse events: general AE, serious/severe AE.
- Studies in English, Polish, French and German were included.

Exclusion criteria covered the following:

- Patients after organ transplantation receiving immunosuppressive therapy,
- Patients receiving chemotherapy,
- HIV and/or HDV coinfected,
- Treatment period shorter than 12 weeks,
- Application of so called “standard” therapy without definition in control group.

Databases and sources searched:

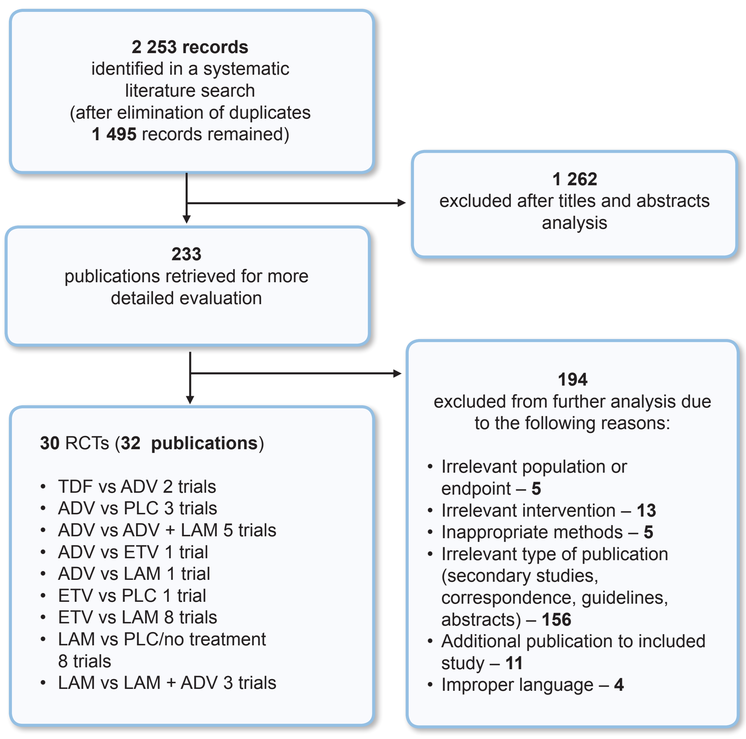
- MEDLINE (via PubMed), EMBASE, CENTRAL.
- Clinical trials registries (www.clinicaltrials.gov),
- webpages of associations dealing with societies of liver diseases (AGA, ILTS, AASLD, APASL, BSG, EASL, IASL, UEGF).

The search was performed up to June 2010. Two authors independently reviewed the articles at each stage of the selection.

Statistical analyses

- Mixed treatment comparison (MTC) was performed with WinBugs software
- Fixed-effect or random-effect model was used on the basis of the results of Deviance Information Criterion (DIC). The model for which value of DIC was lower was considered appropriate.
- Results for each comparison were expressed as relative risk (OR) with 95% confidence intervals (CI).

Figure 1. Systematic literature search according to QUOROM



Results

Study flow

We identified 2 253 records as a result of a systematic search of which 1 495 records remained after removal of duplicates. After further elimination of irrelevant abstracts 233 records were subjected for detailed evaluation of which 48 publications describing 30 relevant RCTs were included (Figure 1).

Study characteristics

Twenty eight of included trials were two-armed comparisons of different interventions with placebo or active control. One study compared two different doses of LAM with placebo and the other one was a three-armed study comparing LAM with ADV, both in monotherapy with combined treatment of these drugs. Available comparisons with the number of corresponding trials were depicted in Figure 1. In most trials increased ALT level and/or HBV DNA were utilized as diagnostic criteria for HBV, however some trials applied also biopsy for this purpose. Diagnostic criteria for HBV were not described in one RCT (Vassiliadis 2009). Six trials included patients without proved drug resistance, while nine other trials enrolled only those with treatment-resistant infections (eight with LAM resistance and one with IFN resistance). Resistance status was not described in the remaining 15 publications. Fourteen trials enrolled only HBeAg(+) patients, seven included HBeAg(-) individuals, while in remaining nine trials both HBeAg(+) and HBeAg(-) were recruited. In most trials follow-up did not exceed 52 weeks, however in seven trial it was longer and lasted up to 230 weeks. Studies’ credibility ranged from low (1 out of 5 points in Jadad scale) to very high (5 out of 5 points in Jadad scale) (Table 1).

HBeAg seroconversion

Fourteen trials were eligible for network analysis which allowed to assess the rate of HBeAg seroconversion in general HBeAg(+) population and in the subset of patients without resistance to LAM.

There were no statistically significant differences between TDF and remaining comparators with respect to HBeAg seroconversion (Table 2).

Undetectable HBV DNA

Twenty two trials were eligible for network analysis which allowed to assess the rate of HBV DNA decrease under the level of detection in general population, subpopulation of HBeAg(+) patients and subsets of patients without resistance to LAM.

TDF in general population of HBV patient was more effective than ADV (OR = 13,16 [3,21; 54,20]), LAM (OR = 61,09 [11,10; 503,78]) and ETV (OR = 9,55 [1,53; 76,98]) with respect to decrease of HBV DNA below detection limit. Superiority of TDF over ADV (OR = 21,60 [1,67; 285,40]) and LAM (OR = 82,24 [4,34; 2492,52]) was also shown in the subgroup of patients with HBeAg(+), however comparison with ETV revealed no significant differences (OR = 11,24 [0,53; 324,57]). Similar results were obtained for subsets of patients without LAM resistance within both general and HBeAg(+) populations. After 12 weeks of treatment TDF revealed higher efficacy as compared to ADV in general population and was superior to all comparators in the population of HBeAg(+) patients (Table 3).

Alanine aminotransferase normalization

Nineteen trials were eligible for network analysis which allowed to assess the rate of ALT normalization in general population, subpopulation of HBeAg(+) patients and their subsets of patients without resistance to LAM.

No statistically significant differences between TDF and comparators with respect to ALT normalization were observed in either population. TDF, however, showed superiority to ADV in the subset of patients without LAM resistance within HBeAg(+) population (OR = 1,78 [1,05; 3,02]) (Table 4).

Histological improvement

Ten trials were eligible for network analysis which allowed to assess the rate of histological improvement in general population, subpopulation of HBeAg(+) patients and its subset of patients without resistance to LAM.

There were no statistically significant differences between TDF and remaining comparators with respect to histological improvement (Table 5).

Adverse events

Ten trials were eligible for network analysis which allowed to assess the rate of general AE in general population and its subset of patients without resistance to LAM.

There were no statistically significant differences between TDF and remaining comparators with respect to rate of general AE (Table 6).

Serious adverse events

Eleven trials were eligible for network analysis which allowed to assess the rate of serious AE in general population and its subset of patients without resistance to LAM.

There were no statistically significant differences between TDF and remaining comparators with respect to rate of general AE (Table 7).

Withdrawals due to AE

Thirteen trials were eligible for network analysis which allowed to assess the rate of withdrawals due to AE in general population and its subset of patients without resistance to LAM.

There were no statistically significant differences between TDF and remaining comparators with respect to rate of general AE (Table 8).

Table 1. Characteristics of RCTs included in the analysis

Trial	Resistance	HBeAg	No. of patients (dose)	Follow-up [weeks]	JS
ADV-437 [1]	nd	+	ADV: 171 (10 mg) PLC: 167	48	5/5
ADV-438 [2]	nd	-	ADV: 123 (10 mg) PLC: 61	48	4/5
Akyildiz 2007 [3]	+ (LAM)	+ OR -	ADV:25 (10 mg) A+L: 29 (10 + 100 mg)	12	1/5
CALM [4]	nd	+ OR -	LAM: 436 (100 mg) PLC: 215	139[a]	3/5
Chan 2007 [5]	nd	-	LAM: 84 (100 mg) PLC: 83	102	4/5
Dienstag 1999 [6]	-	+	LAM: 66 (100 mg) PLC: 71	52	3/5
EARLY [7]	-	+	ADV: 34 (10 mg) ETV: 35 (0,5 mg)	52	2/5
ETV-014 [8]	+ (LAM)	+ OR -	ETV: 47 (0,5 mg) ETV: 42 (1 mg) LAM: 45 (10 mg)	52	4/5
ETV-022 [9]	nd	+	ETV: 357 (0,5 mg) LAM: 358 (100 mg)	52	4/5
ETV-023 [10,11]	nd	+ OR -	ETV: 261 (0,5 mg) LAM: 264 (100 mg)	52	3/5
ETV-026 [12]	+ (LAM)	+	ETV: 147 (1 mg) LAM: 146 (100 mg)	52	5/5
ETV-027 [13]	nd	-	ETV: 3361 (0,5 mg) LAM: 317 (100 mg)	52	2/5
ETV-047 [14]	-	+ OR -	ETV: 34 (0,5 mg) LAM: 34 (100 mg)	24	4/5
ETV-056 [15]	+ (LAM)	+ OR -	ETV: 116 (1 mg) PLC: 29	12	3/5
Ijaz 2008 [16]	nd	+ OR -	ADV: 4 (10 mg) A+L: 4 (10 + 100 mg)	ADV: 79 A+L: 71	1/5
Kim 2006 [17]	+ (LAM)	+ OR -	LAM: 37 (100 mg) LAM discontinuation: 37	96	3/5
Lai 1998 [18]	nd	+	LAM: 142 (25 mg) LAM: 143 (100 mg) PLC: 72	52	3/5
Lai 2002 [19]	nd	+ OR -	ETV: 46 (0,5 mg) LAM: 41 (100 mg)	24	3/5
Perrillo 2004 [20]	+ (LAM)	+	LAM: 49 (100 mg) A + L gr 1: 46 (100 +10 mg)	52	4/5
Peters 2004 [21]	+ (LAM)	+	ADV: 20 (10 mg) LAM: 19 (100 mg) A+L: 20 (10 + 100 mg)	48	5/5
Rapti 2007 [22]	+ (LAM)	-	ADV:14 (10 mg) A+L: 28 (10 + 100mg	ADV: 128[a] A+L: 171[a]	1/5
Ren 2007 [23]	-	+	ETV: 21 (0,5 mg) LAM: 21 (100 mg)	48	2/5
Schiff 2003 [24,25]	+ (IFN)	+	LAM: 119 (100 mg) PLC: 56	52	3/5
Sung 2008 [26]	-	+	LAM: 57 (100 mg) A+L: 58 (100 + 10 mg)	52-104	4/5
Tassopoulos 1999 [27]	nd	-	LAM: 60 (100 mg) PLC: 65	24	5/5
TDF-102 [28]	nd	-	TDF: 250 (300 mg) ADV: 125 (10 mg)	48	4/5
TDF-103 [28]	nd	+	TDF: 176 (300 mg) ADV: 90 (10 mg)	48	4/5
Vassiliadis 2009 [29]	-	-	ADV: 15 (10 mg) A+L: 45 (10 + 100 mg)	230[a]	1/5
Yao 2009a [30]	nd	+	LAM: 329 (100 mg) PLC: 110	12	2/5
Zeng 2006 [31,32]	nd	+	ADV: 360 (10 mg) PLC: 120	12	4/5

Abbreviations: A+L = ADV + LAM; JS = Jadad scale; a) mediane

Table 2. HBeAg seroconversion after 48–52 weeks of treatment

Status HBeAg	LAM resistance	TDV vs ADV OR [95% CI]	TDV vs ETV OR [95% CI]	TDV vs LAM OR [95% CI]
HBeAg(+)	Mixed population	1,26 [0,64; 2,61]	1,80 [0,62; 5,29]	1,96 [0,68; 5,71]
	Non resistant	1,26 [0,64; 2,61]	1,68 [0,55; 5,17]	1,72 [0,56; 5,26]

Table 3. HBV DNA loss after 48–52 weeks of treatment

Status HBeAg	LAM resistance	TDV vs ADV OR [95% CI]	TDV vs ETV OR [95% CI]	TDV vs LAM OR [95% CI]
48–52 weeks of treatment				
General population	Mixed population	13,16 [3,21; 54,2]	9,55 [1,53; 76,98]	61,09 [11,10; 503,78]
	Non resistant	13,00 [3,42; 51,94]	8,73 [1,22; 83,96]	41,88 [6,41; 478,24]
HBeAg(+)	Mixed population	21,60 [1,67; 285,40]	11,24 [0,53; 324,57]	82,24 [4,34; 2492,52]
	Non resistant	21,53 [2,82; 168,5]	9,22 [0,68; 164,64]	45,41 [3,65; 1039,61]
12 weeks of treatment				
General population	Mixed population	5,25 [1,30; 53,94]	4,08 [0,28; 140,96]	5,08 [0,24; 314,07]
	Non resistant	5,66 [1,14; 68,47]	4,36 [0,17; 213,13]	6,04 [0,09; 759,30]
HBeAg(+)	Mixed population	117,30 [5,94; >105]	88,89 [2,54; >105]	114,16 [2,38; >105]
	Non resistant	126,00 [6,03; >105]	96,34 [2,44; 843170,32]	136,46 [2,27; >105]

Table 4. ALT normalization after 48–52 weeks of treatment

Status HBeAg	LAM resistance	TDV vs ADV OR [95% CI]	TDV vs ETV OR [95% CI]	TDV vs LAM OR [95% CI]
General population	Mixed population	1,30 [0,28; 6,19]	0,63 [0,08; 5,27]	2,15 [0,32; 17,15]
	Non resistant	1,30 [0,89; 1,88]	0,65 [0,33; 1,29]	1,05 [0,53; 2,05]
HBeAg(+)	Mixed population	1,79 [0,15; 20,27]	1,10 [0,06; 23,30]	3,22 [0,18; 64,72]
	Non resistant	1,78 [1,05; 3,02]	0,83 [0,37; 1,90]	1,36 [0,61; 3,05]

Table 5. Histological improvement after 48–52 weeks of treatment

Status HBeAg	LAM resistance	TDV vs ADV OR [95% CI]	TDV vs ETV OR [95% CI]	TDV vs LAM OR [95% CI]
General population	Mixed population	1,27 [0,88; 1,81]	0,66 [0,33; 1,32]	1,17 [0,60; 2,25]
	Non resistant	1,27 [0,88; 1,81]	0,75 [0,37; 1,51]	1,17 [0,60; 2,26]
HBeAg(+)	Mixed population	1,39 [0,35; 5,50]	0,60 [0,06; 5,73]	1,26 [0,15; 10,39]
	Non resistant	1,38 [0,79; 2,40]	0,80 [0,32; 1,96]	1,25 [0,54; 2,86]

Table 6. General AE after 48–52 weeks of treatment

Status HBeAg	LAM resistance	TDV vs ADV OR [95% CI]	TDV vs ETV OR [95% CI]	TDV vs LAM OR [95% CI]
General population	Mixed population	1,05 [0,72; 1,52]	1,07 [0,46; 2,44]	1,15 [0,50; 2,63]
	Non resistant	1,05 [0,72; 1,52]	1,11 [0,47; 2,61]	1,17 [0,50; 2,73]

Table 7. Serious AE after 48–52 weeks of treatment

Status HBeAg	LAM resistance	TDV vs ADV OR [95% CI]	TDV vs ETV OR [95% CI]	TDV vs LAM OR [95% CI]
General population	Mixed population	0,98 [0,51; 1,97]	2,52 [0,57; 12,76]	2,37 [0,54; 11,90]
	Non resistant	0,98 [0,51; 1,99]	1,65 [0,23; 13,10]	1,36 [0,19; 10,98]

Table 8. Withdrawal due to AE after 48–52 weeks of treatment

Status HBeAg	LAM resistance	TDV vs ADV OR [95% CI]	TDV vs ETV OR [95% CI]	TDV vs LAM OR [95% CI]
General population	Mixed population	0,88 [0,20; 4,57]	10,91 [0,88; 189,39]	3,99 [0,33; 65,02]
	Non resistant	0,88 [0,06; 14,66]	30,34 [0,35; 3723,01]	10,82 [0,12; 1167,41]

Conclusions

TDF demonstrated the highest efficacy with respect to reduction of viral load in patients with chronic HBV In general population. TDF demonstrated superiority as compare to all investigated therapeutic options after one year of treatment. In HBeAg(+) population TDF showed higher rate of viremia clearance as compared to ADV and LAM.

TDF maintained a very good safety profile. The risk of general and serious adverse events was not increased.

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Abbreviations

ADV	Adefovir
ALT	Alanine Aminotransferase
ETV	Entecavir
HBV	Chronic Hepatitis B viral Infection
HBeAg	Hepatitis B Virus Antigen e
HBV DNA	Hepatitis B Virus DNA
LAM	Lamivudine
NA	Nucleotide/nucleoside Analog
OR	Odds Ratio
PLC	Placebo
RCT	Randomized Clinical Trial
TDF	Tenofovir