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# EFFECTIVENESS AND SAFETY OF TREATMENT WITH NUCLEO(S)TIDE ANALOGUES IN PATIENTS WITH HEPATITIS B-RELATED CIRRHOSIS

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**Abstract**

Data from Bulgaria are limited on the long-term effects of nucleo(s)tide analogues (NAs) to patients with hepatitis B-related cirrhosis. The study aimed to evaluate the overall efficacy and renal safety of NAs in such cohort of patients, comparing treated with high to low-barrier NAs. We retrospectively analyzed 58 patients with HBV cirrhosis (74.1% in compensated stage) for a period of 5 years. Thirty-five patients received NAs with high-barrier of resistance: Tenofovir disoproxil fumarate and Entecavir (followed up for 51.63 ± 30.3) and 23 received NAs with low-barrier of resistance: Lamivudine and Telbivudine (followed up for 56.7 ± 48.4). After a median treatment time of 53.7 months virological response (VR) rates (HBV DNA<10 IU/ml) were 91.4% in high barrier and 87.0% in low barrier NAs groups. Undetectability of HBVDNA was influenced most by the treatments' duration. Serological response reached 57.1%, similar for the two treatment groups. One patient (1.7%) cleared HBsAg and discontinued NAs (TDF). Multidrug resistance (MDR) occurred in 15.5% of LAM recipients only. One-, 3-, 5-, 8- year MDR rates were 0.0%; 11.1%; 33.3% and 77.6%. A slight improvement of the renal function was observed in 85.7% and 69.6% of the patients treated with high and low-barrier NAs. Dose reduction for renal toxicity was required in 1.7%. Decompensated cirrhosis and

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T2DM were the main risk factors for renal function decline. Long-term therapy with high and low barrier NAs was equally effective and renally safe in patients with HBV-related cirrhosis.

**Key words:** nucleo(s)tide analogue treatment, hepatitis B-related cirrhosis, viral response, renal effects

**Introduction.** Viral suppression with oral antiviral therapy has achieved clinical benefit of decreasing necroinflammation, preventing the disease progression and reducing hepatic decompensation. Nucleo(s)tide analogues approved for the treatment of chronic hepatitis B present different profoundness of antivirological potency, barrier to resistance and renal safety profile. Data for the efficacy and renal safety of high and low barrier NAs is limited especially in a head-to-head comparisons [1].

Köklü et al. [2] reported results of a European study of 227 patients (46.0% with DC) with viral response estimated at a detection limit of 200 IU/ml. High-barrier NAs showed similar antiviral efficiency: 91.5% for TDF and 92.5% for ETV as for both higher compared to LAM: 77.0% [3, 4]. Yue-Meng et al. [5] treat patients with DC ($n = 130$) observing lower levels of VR with LAM (65.3%) than with ETV (89.1%) or LdT (83.7%) [6]. Yegin et al. [7] observe partial responders considering the relation between time and VR. For median therapeutic duration of 19.5 months the partial responders were equally distributed among treated with Lamivudine: 33.3%, Entecavir: 35.0% and Tenofovir: 32.4%. The majority of partial responders achieved and maintained virological response with prolonged monotherapy [7].

With respect to several multicentric European studies viral breakthrough in LAM treated reached as high as 32.4% but the treated were rarely tested for MD resistance, with YMDD mutations proved at less than half of the patients. The viral response achieved in the patients with changed regimen for proved MDR did not differ from those in naïve patients [3–5]. Miquel et al. [4] demonstrate results from mostly Caucasian patients receiving high barrier NAs (TDF and ETV) in Spanish cohort. For observational time of 36 m. level of VR reached 83.7%, equal for the patients with CC (82.9%) and DC (87.5%). Riveiro-Barciela et al. [3] show over 90.0% viral inhibition with high-barrier NAs, yet significantly lower for patients $>$ 65 years vs. younger. Other worse predictors of VR cited in most of the studies were high baseline HBVDNA, HBsAg levels and untreated MDR. All NAs appeared to have similar efficacy in achieving serological response increasing to 40.0% with treatment continuation. The rate of HBsAg loss in the reported studies ranged from 0.7% $\sim$ 4%, equal between different NAs [3–5, 7, 9, 10].

There is data, coming from HIV studies mostly, regarding TDF as a NA with nephrotoxic effect, while ETV, LAM и LdT are considered mainly reno-protective NAs [11–13]. Miquel et al. [4] focused on renal effects of ETV and TDF and found no difference in renal parameters between baseline and follow up as for

both NAs with, as reported in other studies, no sign of renal suppression [3,4,9]. Riveiro-Barciela et al. [3] use the same regimens in cirrhotic patients and on the 5th year of treatment demonstrate even slight improvement of eGFR (+4.2 ml/min from baseline). Dose adjustment due to nephrotoxicity was negligible (1.7–3.6%) [3,4,13,14]. Serum hypophosphatemia was also rare (0.4–2.6%), without clinically significant effects [2,13,14]. Renal toxicity in treated with NAs is most expected in simultaneous nephropathy and in co-existence of potential factors for its deterioration (T2DM, DC, diuretic use) [12,13].

The aim of the present monocentric study was to evaluate the long-term benefits and the renal safety of high and low barrier NAs in Bulgarian patients with HBV-associated cirrhosis. Analysis of predictive factors for VR achievement and occurrence of renal suppression was also proposed.

**Patients and methods.** For the period January 2015 — March 2020, 58 patients with CHB cirrhosis (84.5% men, 87.9% HBeAg negative, 79.3% with HBV DNA $>$ 2000 IU/ml) were treated with NAs. Cirrhosis was diagnosed with ultrasound, following the presence and degree of morphological changes in the liver, stage of the disease progression and complications. It was determined by patomorphological assessment and FGDS for stigmata of portal hypertension.

Portal hypertension (PH) was found in 72.4% of the patients, 31.0% of them with high graded esophageal varices (III and IV grade). The stage of cirrhosis was compensated (CC), classified as CTP A in 71.4% or decompensated (DC): as CTP class B in 20.7% and class C in 5.2%.

Co-existent diseases were found in 56.9% of the patients: 20.1% for diabetes mellitus (T2DM), 8.5% for pre-therapeutic nephropathy (3.4% CKD, 1.7% polycystic kidney disease and 3.4 % nephrolithiasis), 12.2% for cardio-vascular pathology. Current consumption of ethanol and tobacco were reported in 39.7% and 37.9%. Patients were treated with high barrier NAs: 60.3% (48.3% for TDF and 12.1% for ETV) and low barrier NAs: 44.8% (36.2% for LAM and 2.5% for LdT). The average treatment period was 53.7 months (range: 12–192), similar for high and low barrier NAs (resp.: 56.7$\pm$48.4 vs. 51.6 $\pm$30.3, $p > 0.05$). Lamivudine was changed with another NA in 15.5%. The characteristics of patients in the groups CHB Ci, treated with high and low barrier NAs are summarized in Table 1. Patients in the two groups were equivalent in terms of PH manifestation, concomitant diseases, ethylism and tobacco use ($p > 0.05$ for each of the group comparisons).

The definition of VR in our study was adopted from EASL's definition of VR: HBVDNA $<$ 10 IU/ml, by a quantitative real-time PCR assay with a maximum lower limit of detection of 10 IU/ml. VR is partial (PVR) if viremia at the last visit is reduced but still detectable ($>$ 10 IU/ml). Increase of HBV DNA $>$ 10 log 1(10-fold) from nadir was suspected for multi drug resistance (MDR) and tested for YMDD mutations. Serological parameters of HBV, clinical and laboratory tests (including serum creatinine, creatine kinase and serum phosphate)

Table 1

| Parameter | High-barrier NAs ($n = 35$) | Low barrier NAs ($n = 23$) | $p$ |
|---|---|---|---|
| Age | 56.9 ± 7.9 | 56.0 ± 10.03 | N.S. |
| Gender | | | N.S. |
| Male | 85.7% | 82.6% | |
| Female | 14.3% | 17.4% | |
| Pretreatment HBV DNA | **34 494 852 IU/ml. ± 102976948** | **12 404 499 IU/ml. ± 43 376 104** | **0.036** |
| ≤ 2000 IU/ml | 30.4% | 14.3% | N. S |
| ≥ 2000 IU/ml | 69.5% | 85.7% | |
| HBsAg qualitative | 5 815.3 IU/ml ± 3 735.4 | 3 527.6 IU/ml ± 4 162.8 | N. S |
| HBeAg (+) positive | 8.6% | 17.4% | |
| CTP (A/B/C) | 82.9%/11.4 %/5.7% | 60.9%/34.8%/4.3% | N. S. |
| MELD | 9. 84 ±3.27 | 9.23 ±3.65 | N. S. |
| T2DM | 20.0% | 21.7% | N. S |
| Pre-existing nephropathy | 5.7% | 13.1% | N. S |

were evaluated every 3 months. Renal function was assessed by measuring CrCl using BMI-compliant modified Cockcroft-Gault and Salazar-Corcoran methods. In case of reduction of CrCl < 50 ml min the dose of the respective NAs was modified according to the established European recommendations.

***Statistical analysis***. SPSS Statistics v.19.0., v.23.0 was used for statistical analysis. A cut-off of $p < 0.05$ was used to define statistical significance.

**Results.** Average treatment time is equal for all NAs: TDF (44.2 m ±23.5), ETV (57.7 m ±47.1), LAM (56.9±50.8), LdT (54.5±9.2), $p > 0.05$. Viral response in patients with CHB Ci reached 87.5%. High-barrier and low-barrier NAs demonstrated similar antiviral effectiveness: 91.4% vs. 87.0%, $p > 0.05$. The same trend was valid between the individual NAs – slightly higher rates of VR for TDF: 89.3% vs. LAM: 85.7%, $p > 0.05$. Viral response with ETV and LdT was optimal, but the small proportion of patients treated with both NAs should be noted (15.5%). The overall VR rates in CC: 93.0% and DC: 80.0% were similar, ($p > 0.05$). High to low barrier NAs achieved insignificantly higher rates of VR in patients with CC (92.9% and 93.1%, $p > 0.05$) compared to those with DC (77.8% vs. 83.3%, $p > 0.05$). Patients older than 50 years seemed to reach lower rates of VR than younger patients with either high barrier NAs (70.4% vs. 95.2%) or low barrier NAs (71.8% vs. 90.4%). The overall difference tended to approach statistical significance (70.6% vs. 91.4%, $p = 0.082$). Neither HBeAg status, nor pretreatment HBVDNA and quantitative HBsAg levels were related to VR acquirement. Finally, 12.5% of the studied subjects had partial response at the last observational visit (residual viraemia: 234 IU/ml±159.5). The only parameter by which patients with complete and partial response differed was treatment duration

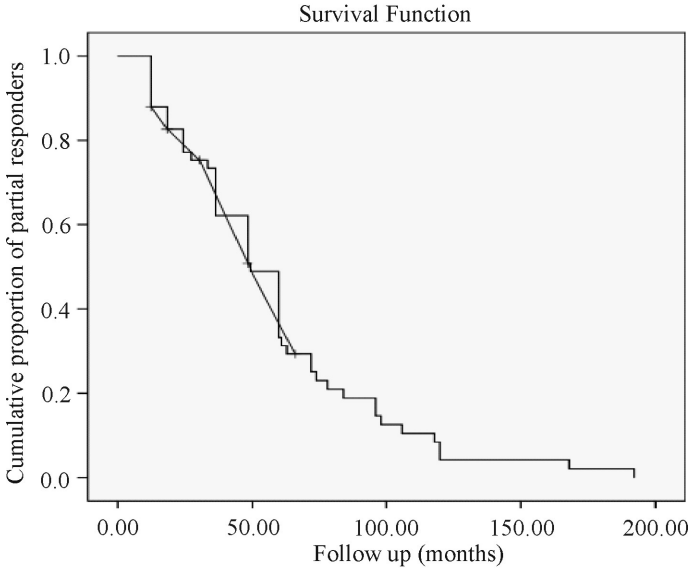


Fig. 1. Overall decline in the proportion of partial responders as treatment time progresses

(56.2 m ±39.1 vs. 32.0 m ±21.0, $p < 0.05$). Moreover, treatments' duration had a direct impact on viral response achievement. Binary logistic regression showed that the possibility of complete virological suppression was 3 times reduced in patients that had taken NAs $\leq$ 24 m (compared to those being exposed to NAs $>$ 24 m: 95% CI 1041–8646). Yet, the effect was weak: $p = 0.042$, (Table 2) because, as demonstrated with Kaplan–Meier there was a progressive decrease in partial responders' frequency in proportion to treatment duration (Fig. 1).

T a b l e 2

| Factor | | Comparator | Sig. | Odds Ratio | 95% C.I |
|---|---|---|---|---|---|
| | Treatment duration | $\leq$ 24 m vs. $\geq$24 m | 0.042 | 3.000 | 1041–8646 |

HBeAg positive patients were treated with TDF (42.8%) and LAM (57.2%). Serological response reached 66.6% and 50.0%, respectively ($p > 0.05$) with overall rates of 62.5% for both NAs. Seroconversion was 40.0%, seroreversion was not recorded until the end of follow-up. One of the subjects (1.7%) lost HbsAg at the 43th month of TDF therapy. The average level of viral breakthrough reached 15.5%, registered among LAM recipients only (42.9%). Cumulative rates at year one, 3rd, 5th, and 8th were: 0.0%; 11.1%; 33.3% and 77.6%. Viral breakthrough was not accompanied by biochemical rebound in none of the patients. All of them were tested for YMDD and proved positive for multy-drug resistance. Lamivudine was timely replaced with: TDF in 88.8% and ETV in 11.1%. Average time from

MDR detection to salvage therapy was 6–22 days (13.8±5.1). The estimated VR on the last visit did not differ between patients with and without MDR (77.8% vs. 91.8%) $p > 0.05$.

There was no difference in pre-therapeutic CrCl levels between those who started treatment with high-barrier or with low-barrier NAs: 93.0 ml / min ±17. 46 vs. 96.08 ml / min ±20.2, respectively, $p > 0.05$. An overall improvement in CrCl was observed in 79.3% of the patients during NAs treatment. It was more evident in the high barrier group than the low barrier, but the difference was n.s. (respectively, 85.7% vs. 69.6%, $p > 0.05$). The cumulative numerical increase in CrCl from pretreatment levels was 4.8 ml/min ± 12.9 ($-43 + 31$ ml/min). The increment was higher in patients treated with TDF and ETV: 5.9 ± 12.2 (93.0–98.9), still equivalent to those that received LAM and LdT: 3.1 ± 14.1 (96.1–99.2), $p < 0.05$. Transient fluctuation to sub-reference sPh values (< 2.5 mg/dL) was observed in two patients (3.4%) that received ETV and TDF – both with pre-treatment diagnosed nephrolithiasis. Dose reduction in NAs intake (TDF) was required in one (1.8%) due to a decrease in CrCl < 50 ml/min. The patient was diagnosed with a degree of stag horn calculi (requiring several ESWL interventions), and had started TDF treatment with normal serum creatinine levels (0.78 mg/dL) and CrCl (74 ml/min). At the 24th month of the treatment course an acute renal damage of postrenal type occurred (acute right-sided lithiasis, bilateral hydronephrosis with DJ stent surgical fixation). Serum creatinine levels increased by > 0.50 mg/dL (from 0.78 mg/dL to 1.35 mg/dL), sPh dropped to 1.6 mg/dL, and CrCl reduced to < 50 ml/min (from 74 ml/min to 46 ml/min.) The condition necessitated a 50.0% reduction in the TDF dose. Monitored CrCl level in thus modified regimen varied between 35–45 ml/min, not indicated for further reduction, but also not allowed for initial therapeutic dose recovery. In our study there were no renal side effects indicating discontinuation of NAs treatment. Binary one-factor logistic regression demonstrated that the risk of CrCl reduction in NAs-treated patients was nearly 5-fold higher in diabetics than in patients without T2DM (95% CI 1.608–15.243, $p = 0.005$). Table 3 shows that the odds ratio of compensated disease (CTP A) for CrCl deterioration was 2.96 times lower than in decompensated disease (CTP B + C).

T a b l e 3

| Factor | Comparator | Significance | Odds Ratio | 95% C.I. |
|---|---|---|---|---|
| CTP pretreatment | CTP B/C vs. A | 0.043 | 2.963 | 1.036–8.475 |
| T2DM | yes/no | 0.005 | 4.950 | 1.608–15.243 |

**Discussions.** The study presented 5-year monocentric experience on Bulgarian patients with HBV-related cirrhosis, treated with high and low barrier NAs. Overall, 87.5% VR rates were achieved, equal between treated with high: 91.4% and low barrier NAs: 87.0%. Asian and European studies with observation time

> 36 months report VR range between 65.3–77.0% for low barrier NAs and 83.7–92.5% for high barrier NAs. Serological response cited is as high as 40.0% with functional cure reaching 0.7–4%. In terms of VR our results are similar with even higher overall levels of serological response achieved (57.2%). Moreover, we were assessing VR, perceiving EASLs' definition (HBV DNA < 10 IU/ml), opposed to the other authors, using higher cut offs (20–2000 IU/ml). Neither pretreatment levels of HBVDNA nor these of qHBsAg turned out to impact VR in our study. These results are likely related to the rapid reduction of viral replication upon NAs. Treatment duration was the most important factor of virological response, as a proportion of partial responders declines as treatments' time progresses.

As demonstrated in numerous studies low to high barrier NAs are less effective mainly because of MDR, frequently occurring in the former. However, considering the data reported, viral breakthrough was rarely tested for YMDD mutations, and when tested – not always proved as MDR. So, there might be other reasons except MDR staying behind the viral breakthrough emergence (non-adherence?). We observed 15.3% rates of viral breakthrough, in LAM recipients only, proved as MDR and rescued in all. These facts and considering the early change of LAM with the highly potent TDF, perhaps explain the lack of statistical difference either in the antiviral effectiveness of both regimens, or in the VR between rescued and naïve patients.

In our study there was a slight improvement in renal function in 79.3% of the patents. Creatinine clearance increased equally in treated with both types nucleo(s)tide analogues. This result opposes the existing concept that the high-barrier TDF bears larger nephrotoxic potential than the other NAs. Furthermore, the numerical amelioration was more pronounced in high barrier NAs receivers (5.9 ml/min) rather than low barriers' (3.1 ml/min), yet insignificantly. Our findings agree with the reported by Riveiro-Barciela et al. [3] improved eGFR with 4.2 ml/min in treated with TDF and ETV. However, it is a fact that the only patient with known renal disease that received TDF required dose adjustment for renal toxicity.

In accordance with numerous European cohorts, we also noticed negligible renal effects (1.2% need for treatment adjustment, 2.4% levels hypophosphatemia), no indications for therapy withdrawal. Factors, per se associated with renal impairment – T2DM and decompensated cirrhosis were proved as such predictors also in patients treated with NAs. Pre-existing nephropathy was not found to negatively impact the renal function which is perhaps due to the small number of such patients in our study. The considered cohort is homogeneous, but only one patient with nephropathy falls into the group that received TDF. More data are needed for a broader assessment of the treatment effect of both types of nucleo(s)tide analogues, including from larger cohorts. Stratified analysis of individual NAs could provide even more detailed and profound assessment of their specific effects and clinical benefit which might be further compared in various clinical scenarios.

**Conclusion.** Treatment with nucleo(s)tide analogues (high and low barrier) demonstrated equal antiviral effectiveness in patients with HBV-related cirrhosis. Average follow-up time was 53.7 months (range: 12–192). Viral response rates reached 87.5%, similar for treated with high and low barrier NAs. Antiviral effectiveness was equal in CC: 93.0% and DC: 80.0%. MDR occurred in 15.5% of LAM receivers. The 1-, 3-, 5- , 8- year MDR rate were: 0.0%; 11.1%; 33.3% and 77.6%. Timely diagnosed and rescued MDR equates the antiviral potency of low barrier to high barrier NAs. Treatment duration was the most important factor influencing VR. There was also no statistical difference between the two treatment groups in terms of renal effects frequency. NAs treatment was reno-protective for 69.6% and 85.7% of low and high-barrier recipients. Independent factors for renal impairment were the decompensated stage of cirrhosis and T2DM.

## REFERENCES


[1] Dienstag J. L. (2009) Benefits and risks of nucleoside analog therapy for hepatitis B, Hepatology, **49**(suppl. 5), 112–121.

[2] Köklü S., Y. Tuna, M. T. Gülşen, M. Demir, A. Köksal et al. (2013) Long-term Efficacy and Safety of Lamivudine, Entecavir, and Tenofovir for Treatment of Hepatitis B Virus-Related Cirrhosis, Clin. Gastroenterol. Hepatol., **11**(1), 88–94.

[3] Riveiro-Barciela M., D. Tabernero, J. L. Calleja, S. Lens, M. L. Manzano et al. (2017) Effectiveness and Safety of Entecavir or Tenofovir in a Spanish Cohort of Chronic Hepatitis B Patients: Validation of the Page-B Score to Predict Hepatocellular Carcinoma, Dig. Dis. Sci., **62**(3), 784–793.

[4] Miquel M., Ó. Núñez, M. Trapero-Marugán, A. Díaz-Sánchez, M. Jiménez et al. (2013) Efficacy and safety of entecavir and/or tenofovir in hepatitis B compensated and decompensated cirrhotic patients in clinical practice, Ann. Hepatol., **12**(2), 205–212.

[5] Yue-Meng W., Y. H. Li, H. M. Wu, J. Yang, Y. Xu et al. (2017) Telbivudine versus lamivudine and entecavir for treatment-naïve decompensated hepatitis B virus-related cirrhosis, Clin. Exp. Med., **17**(2), 233–241.

[6] Kim W. R., T. Berg, R. Loomba, R. Aguilar Schall, P. Dinh et al. (2013) 43 Long Term Tenofovir Disoproxil Fumarate (Tdf) Therapy and the Risk of Hepatocellular Carcinoma, J. Hepatol., **58**1, S19.

[7] Yegin E. G., O. C. Ozdogan (2014) Partial virological response to three different nucleotide analogues in naive patients with chronic hepatitis B, Hepatobiliary Pancreat. Dis., **13**(6), 602–611.

[8] Lee K. S., Y. O. Kweon, S. H. Um, B. H. Kim, Y. S. Lim et al. (2017) Efficacy and safety of entecavir versus lamivudine over 5 years of treatment: A randomized controlled trial in Korean patients with hepatitis B e antigen-negative chronic hepatitis B, Clin. Mol. Hepatol., **23**(4), 331–339.

[9] Idilman R., F. Gunsar, M. Koruk, O. Keskin, C. E. Meral et al. (2015) Long-term entecavir or tenofovir disoproxil fumarate therapy in treatment-naïve chronic hepatitis B patients in the real-world setting, J. Viral Hepat., **22**(5), 504–510.

[10] Goyal S. K., V. K. Dixit, S. K. Shukla, J. Ghosh, M. Behera et al. (2015) Prolonged use of tenofovir and entecavir in hepatitis B virus-related cirrhosis, Indian J. Gastroenterol., **34**(4), 286–291.
[11] Fontana R. J. (2009) Side effects of long-term oral antiviral therapy for hepatitis B, Hepatology, **49**(suppl. 5), 185–195.
[12] Tsai M. C., C. H. Chen, P. L. Tseng, C. H. Hung, K. W. Chiu et al. (2016) Comparison of renal safety and efficacy of telbivudine, entecavir and tenofovir treatment in chronic hepatitis B patients: Real world experience, Clin. Microbiol. Infect., **22**(1), 95.e1–95.e7.
[13] Koklu S., M. T. Gulsen, Y. Tuna, H. Koklu, O. Yuksel et al. (2015) Differences in nephrotoxicity risk and renal effects among anti-viral therapies against hepatitis B, Aliment. Pharmacol. Ther., **41**(3), 310–319.
[14] Lampertico P., R. Soffredini, M. Viganò, C. Yurdaydin, R. Idilman et al. (2011) Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Field Practice: a Multicenter European Cohort Study of 302 NUC-Naive Patients with Chronic Hepatitis B, J. Hepatol., **54**, S293–294.

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