Systematic review and meta-analysis: Impact of antiviral therapy on portal hypertensive complications in HBV patients with advanced chronic liver disease

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Abstract

Background: The efficacy of treatment with nucleos(t)ide analogues (NAs) in non-cirrhotic chronic hepatitis B (CHB) patients is well-established. However, its impact on complications of portal hypertension in advanced chronic liver disease (ACLD) is less well-characterized.

Methods: MEDLINE/PubMed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials, and abstracts of major international hepatology meetings were searched for publications from Jan 1, 1995 to Nov 30, 2021. Randomized control trials and observational studies reporting the efficacy of NAs in ACLD patients were eligible. Pooled risk ratios (RRs) for outcomes of interest were calculated with a random-effect or fixed-effect model, as propriate.

Results: Thirty-nine studies including 14 212 ACLD patients were included. NA treatment was associated with reduced risks of overall hepatic decompensation events (RR, 0.51; 95% confidence interval [CI]: 0.37-0.71) such as variceal bleeding (RR, 0.44; 95% CI: 0.26-0.74) and also ascites (RR, 0.10; 95% CI: 0.01-1.59) on a trend-wise level. Moreover, the risks of hepatocellular carcinoma (HCC) (RR, 0.48; 95% CI: 0.30-0.75) and liver transplantation/death (RR, 0.36; 95% CI: 0.25-0.53) were also reduced by NA treatment and first-line NAs were superior to non-first-line NAs in regard to these outcomes (RR, 0.85; 95% CI: 0.75-0.97 and RR, 0.85; 95% CI: 0.73-0.99, respectively).

Conclusion: NA therapy lowers the risk of portal hypertension-related complications including variceal bleeding, as well as HCC, and liver transplantation/death.

Keywords: Advanced chronic liver disease; Antiviral therapy; Meta-analysis; Systematic review

Introduction

Chronic hepatitis B (CHB) remains a major cause of liver-related morbidity and mortality worldwide [1-3]. Patients with advanced chronic liver disease (ACLD), which is defined as advanced fibrosis or cirrhosis, are at risk of developing liver-related events (LREs) including ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma (HCC) and death [4]. Effective antiviral treatment (AVT) with nucleos(t)ide analogs (NAs) profoundly suppresses HBV-DNA, thereby improves liver biochemistry, histology, and prevents progression to ACLD [5,6]. Moreover, NA-based AVT reduces mortality, even in patients with decompensated cirrhosis [6, 7]. However, the stage-dependent impact of long-term AVT on portal hypertension-related events in patients with ACLD is less well-characterized.

To synthesize the available evidence, we conducted a systematic review and meta-analysis focusing on the impact of AVT on portal hypertension-related events and other relevant outcomes in CHB patients with ACLD. Herein, we report the major results of this collaborative study for Baveno VII consensus development.

Method

Materials and methods

We conducted this systematic review and meta-analysis in accordance with the PRISMA statement and registered it in the PROPESOL (CRD42020149282).

Search strategy

MEDLINE/PubMed, Embase, Web of Science/Web of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL), as well as abstracts of major international hepatology meetings were searched. The publications from Jan 1, 1995 (the first use of lamivudine [9] to Nov 30, 2021 were searched by two authors (TTL and LHZ) independently, using the following keywords: chronic hepatitis B, advanced chronic liver disease, cirrhosis, fibrosis, antiviral therapy, nucleotide analogs, tenofovir, entecavir, lamivudine, adefovir, and telbivudine. The full search strategy is available in the Supplementary file.

Study selection criteria

Randomized control trials (RCTs) and observational studies were eligible for inclusion, if they: (1) participants had ACLD including advanced fibrosis, compensated or decompensated cirrhosis; (2) impact of NAs on histology, variceal size or hepatic veinous pressure gradient (HVPG), occurrence of hepatic decompensation (variceal bleeding, ascites, or hepatic encephalopathy), HCC, and liver transplantation/death.

The studies were excluded, if they: (1) exclusively included non-ACLD patients; (2) used interferon (IFN)-based regimens, since IFNs are generally not recommended in patients with ACLD, especially those with portal hypertension; (3) included patients underwent liver surgery or with acute or acute on chronic liver failure.

Detailed information on study selection is shown in Figure 1.

Data extraction and quality assessment

The eligibility assessment and data extraction were performed independently by two authors (TTL and LHZ). From each eligible study the following data were extracted: (1) study characteristics: authors, year of publication, institution, country, study design (RCT or cohort), and duration of follow-up; (2) patient characteristics: number of patients, liver disease stage (advanced fibrosis, compensated or decompensated cirrhosis), antiviral agents and their comparators; (3) study outcomes: HBV suppression rate, histological regression, changes in indicators of portal hypertension severity (variceal size or HVPG), hepatic decompensation including ascites and variceal bleeding, HCC, and liver transplantation/death.

The risk of bias of individual studies was assessed by two authors with the tools of RoB 2 (for randomized trials) [10] and the ROBINS-I (for non-randomized studies) [11]. Any discrepancies were resolved by consensus or involvement of an expert hepatologist (JDJ) and a senior methodologist (YYK).

Statistical analysis

Characteristics of included studies were summarized. Risk Ratio (RR) and 95% confidence intervals (CIs) were pooled for comparison with the metafor package for R (version 3.5.3). Stratified analyses were performed to examine the effect of HBV suppression rate, clinical stage (i.e., compensated vs. decompensated), decompensation (first vs. further), and study design.

Estimates with a P value lower than 0.05 for the Cochran Q-statistic and I^2 higher than 50% for I^2 statistic were considered to have high heterogeneity. A random-effects model or a fixed-effects model was used, as appropriate. Potential publication bias was evaluated by a funnel plot analysis as well as Begg's and Egger's tests.

Results

Characteristics of the studies

The initial search identified 5053 non-duplicated publications, with 4084 articles being excluded after title and abstract review. The remaining 969 articles were full-text reviewed, and finally36 studies comprising 14 212 ACLD patients were included (Figure 1).

Among the 36 studies (8 RCT and 28 observational studies), 19 compared NA-treated vs. untreated patients, and 17 compared first line versus non-first-line NAs on interested outcomes (Table 1).

Quality of the included studies

Five of the 8 RCTs were classified as low risk, one as high risk and two as unclear risk of bias (Table 1). Eight of the 28 cohort studies (29%) were regarded as low risk. The major risks of bias were related to the "confounding" domain.

Histological improvement

Only two studies compared NA-treated with untreated patients [12,13], and one compared first-line with non-first-line treated patients [14]. NA-treated patients tended to have a higher rate of histological regression than untreated patients, but the difference did not reach statistical significance (RR, 1.38; 95% CI: 0.63-3.02; I^2=88%). Similarly, first-line NAs (entecavir and tenofovir) did not show a significantly higher rate of histological improvement than non-first-line NAs (lamivudine, adefovir and telbivudine) (RR, 1.43; 95% CI: 0.85-2.42; I^2=3%). Of note, the latter estimate was based on a single study (Figure 2).

Improvement of portal hypertension measured by HVPG

Only one small single-arm study investigated the changes of HVPG during NA therapy [15]. It demonstrated that after 12 months of lamivudine treatment, the mean HVPG decreased from 14.4 to 12.4 mmHg in 19 patients with baseline biopsy-proven cirrhosis and HVPG ≥10 mmHg, with HVPG decreased in all but one patient (who had viral breakthrough); HVPG decreased by >20% or to <12 mm Hg in 10 of the 13 patients with baseline HVPG ≥12 mm Hg.

Impact on the progression of varices

One study [16] showed that in 284 patients (81 with HBV, 197 with HCV, and 6 with HCV-HBV) with compensated cirrhosis who achieved viral suppression/eradication, progression of portal hypertension occurred only in 14 patients (4.9%), including 8 of 246 (3.3%) without esophageal varices (EV), 4 of 27 (14.8%) with grade 1 EV, and 2 of 11 (18.2%) with grade 2/3 EV at inclusion (log-rank test: $P< 0.005$).

Another study [17] demonstrated that in patients of compensated cirrhosis with no or small varices who were initially treated with lamivudine and add-on adefovir or switch-to tenofovir in emergence of resistance, the 12-year cumulative incidence of EV regression was 83% (95% CI: 52-92%), whereas the incidence of de novo F1/F2 EV development was only 10% (95% CI: 5-20%). Importantly, 6 of 7 patients with de novo varices or variceal progression had either lamivudine resistance and/or developed an HCC.

Impact on the overall rate of hepatic decompensation

Among 13 studies, seven compared NA-treated with untreated patients [18-24], and six compared first-line with non-first-line NAs [5, 25-27, 28, 29]. Overall, NA-treated patients showed a significantly lower incidence rate of hepatic decompensation (including variceal bleeding, ascites, or hepatic

encephalopathy) than that of untreated patients (RR, 0.51; 95% CI: 0.37-0.71; I^2=77%). However, the difference between the first-line and non-first-line NAs did not reach statistical significance (RR, 0.89; 95% CI: 0.64-1.25; I^2=0%) (Figure 3A).

Impact on ascites

Among five studies, three compared NA-treated with untreated patients [18, 23, 24], and two compared first-line with non-first-line NAs [5, 27]. NA-treated patients tended to have a lower rate of ascites than untreated patients (RR, 0.10; 95% CI: 0.01-1.59; I^2=96%). Similarly, there was no differences in the risk of ascites development between the first-line and non-first-line NAs (RR, 1.00; 95% CI: 0.62-1.60; I^2=0%) (Figure 3B).

Impact on variceal bleeding

Among ten studies, six compared NA-treated with untreated patients [18, 19, 21-24], and four compared first-line with non-first-line NAs [5, 25, 26, 28]. The rate of variceal bleeding was significantly lower in NA-treated than in untreated patients (RR, 0.44; 95% CI: 0.26-0.74; I^2=82%). However, there was no differences between the first-line and non-first-line NAs (RR, 0.68; 95% CI: 0.24-1.91; I^2=74%) (Figure 3C).

Impact on HCC development

Among 25 studies, 11 compared NA-treated with untreated patients [18, 22-24, 30-36], 13 compared first-line with non-first-line NAs [5, 25-29, 37-43], and one provided data on both comparisons [44]. Overall, NA-treated patients showed a significantly lower risk of HCC development than untreated

ones (RR, 0.48; 95% CI: 0.30-0.75; I^2 = 91%). Furthermore, the patients treated with first-line NAs had a significantly lower incidence rate of HCC than those treated with non-first-line NAs (RR, 0.85; 95% CI: 0.75-0.97, I^2 = 0%) (Figure 4).

Impact on liver transplantation/death

Among 21 studies, 12 compared NA-treated with untreated patients [18, 20-24, 30, 32, 33, 45-47], and 9 compared first-line with non-first-line NAs [25, 26, 28, 29, 39-41, 48, 49]. Overall, there was a significantly lower rate of liver transplantation or death in NAs treated vs. untreated patients (RR, 0.36; 95% CI: 0.25-0.53; I^2=86%). Furthermore, the patients treated with first-line NAs had a significantly lower incidence rate of liver transplantation or death than those treated with non-first-line NAs (RR, 0.85; 95% CI: 0.73-0.99; I^2 = 0%) (Figure 5).

Further subgroup analysis

Subgroup analyses by HBV suppression rate (lower than LLQ), stage of cirrhosis (i.e., compensated vs. decompensated, first vs. further decompensation) and study design showed similar results to the overall pooled RR. However, certain subgroup analyses did not reach statistical significance, probably due to limited number of studies and patients. (Supplementary Tables 1 and 2)

Publication bias

Funnel plots, Begg and Egger tests did not show evidence of publication bias (Supplementary Figures 1and 2, Supplementary Table 3).

Discussion

This systematic review and meta-analysis confirmed the observation that AVT profoundly reduces the risk of portal hypertension-related complications, i.e., hepatic decompensation including variceal bleeding. Moreover, it also reduces the risk of HCC and liver transplantation/death in ACLD patients.

AVT has dramatically changed the clinical course of CHB owing to the effective HBV suppression. However, our results contrast an earlier meta-analysis reporting that AVT has no effect on liver-related mortality [50]. This discrepancy may be due to profound differences in study selection. Furthermore, we found that compared with non-first-line NAs, the first-line NAs further ameliorated the risks of HCC and liver transplantation/death. This is not surprising, since the higher drug resistance rate of non-first-line NAs would jeopardize their long-term benefits despite they had a similar 1-year efficacy to the first-line NAs [51]. This finding is also in line with the studies of NAs on the HVPG and varices, which reported a link between virological breakthrough and adverse outcomes [16, 17].

One important observation of this study is that AVT decreases the portal hypertension and related complications. One uncontrolled study measured the HVPG reported that 76% of 19 patients had an HVPG response after one year lamivudine therapy [15]. This result is in line with reports on patients with HCV-induced ACLD who achieve sustained virologic response to interferon-free therapies [52]. Besides the uncontrolled study design, the interpretation of the data on changes in HVPG in NA-treated patients is complicated by the uncertainty regarding the meaningful decrease in HVPG in the context of the removal of the primary etiology, as indicated by Baveno VII [4]. Two studies used endoscopic finding as a surrogate for changes in portal hypertension [16, 17]. Both of the studies demonstrated that AVT could reduce the progression of gastroesophageal varices. Additional support to this notion is a recent publication showing that nearly 80% (271/341) of NA-treated patients with compensated cirrhosis do

not have high-risk varices, thereby providing indirect evidence that NAs prevents the progression /promotes the regression of high-risk varices [53]. However, these studies did not have comparative groups (NA-treated vs. untreated, first-line NAs vs. non-first-line NAs) probably due to the ethical consideration and practical issues.

Our meta-analysis observed a trend towards higher rates of histological regression in patients on AVT. The failure to reach statistical significance is probably due to the low number of studies and patients included. One important large uncontrolled study [54] reported that in patients receiving one year of adefovir/tenofovir therapy followed by 4 years of tenofovir therapy, 87% (304/348) of those with follow-up liver biopsy showed a fibrosis improvement; furthermore, 74% (71/96) of those with cirrhosis at baseline achieved cirrhosis resolution. In addition, our long-term follow-up study also confirmed the histological benefit of entecavir-based AVT in CHB patients with advanced fibrosis or early cirrhosis [6].

Although our meta-analysis indicates a substantial decrease in risk of hepatic decompensation and mortality, it is also evident that a relevant proportion still develop adverse outcomes, despite virological suppression. Although there is evidence for the use of the Baveno VI criteria for ruling-out high-risk varices [53, 55], data on non-invasive criteria to re-stratify the risk of decompensation in patients with ACLD who achieve viral suppression are limited [56].

We acknowledge some limitations of our study. (i) The number of studies on portal hypertension-related events, especially the changes in variceal size and HVPG, was limited. (ii) Only a few studies explicitly described outcomes of ACLD patients. Some studies included patients with different stages of liver disease; therefore, the heterogeneity of the patients brings difficulties to the interpretation. (iii) The overall quality of the included studies is not high. However, the current study systematically reviewed

all eligible studies and synthesized the available evidence regarding the effect of NA-based AVT on complications of portal hypertension and other LREs in ACLD, thereby extending the knowledge that can be derived from individual studies.

In conclusion, this systematic review and meta-analysis demonstrated that NAs, especially first-lines NAs, lowers the risk of portal hypertension-related complications including variceal bleeding, HCC, and liver transplantation/death. These findings prompted the Baveno VII faculty to include HBV suppression (in addition to HCV cure and alcohol abstinence) into the definition of "removal of the primary etiological factor".

Author contributions

SSK, MM, and JJD contributed to the study concept and design. TTL and LHZ performed the data extraction. ML, TTM, SSW, WW, QZ, and SC assessed the quality of involved studies. YYK, ML, and TTM performed the analyses and drafted the manuscript. YYK, SSK, MM, and JJD made critical revisions to the manuscript. All authors revised and approved the final manuscript.

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Declarations

Conflict of interest All authors declare no conflict of interest with respect to this manuscript.

Statement of ethics Institutional Review Board approval was not required due to this article does not contain any studies with human participants or animals performed by any of the authors.

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Figure Legends:

Figure 1. Flowchart of study selection for meta-analysis

Figure 2. Risk ratio of histological improvement for NA-treated vs. untreated patients.

Figure 3. Risk ratio of hepatic decompensations for NA-treated vs. untreated patients. (A) for overall decompensation events, (B) for ascites, and (C) for variceal bleeding.

Figure 4. Risk ratio of HCC development. (A) for NA-treated vs. untreated patients, (B) for patients received first-line NAs vs. non-first-line NAs.

Figure 5. Risk ratio of liver transplantation/death. (A) for NA-treated vs. untreated patients, (B) for patients received first-line NAs vs. non-first-line NAs.

Supplemental Figure 1. Funnel plots for comparison of NA-treated vs. untreated patients. (A) for histological improvement, (B) for decompensation, (C) for ascites, (D) for variceal bleeding, (E) for HCC, and (F) for liver transplantation/death.

Supplemental Figure 2. Funnel plots for comparison of first-line NAs vs. non-first line NAs. (A) for decompensation, (B) for ascites, (C) for variceal bleeding, (D) for HCC, and (E) for liver transplantation/death.