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Effect of entecavir and tenofovir disoproxil fumarate on hepatocellular carcinoma in subjects with chronic hepatitis B: a meta-analysis

Sara M. Tony[1], Mohamed E. A. Shaaban[2], Ahmed I. M. Mohamed[2] and Mohamed E. A. Abdelrahim[3*]

Abstract

Background: A meta-analysis was made to assess the impact of entecavir comparison with tenofovir disoproxil fumarate as nucleos(t)ide analogue on hepatic cellular carcinoma (HCC). The study had subjects with chronic hepatitis B virus (HBV). Systemic research was done for all studies concerned with our topic till the date (March 2022). We included 19 studies in which 27,618 subjects participated. All subjects included were diagnosed with chronic HBV at the beginning of the study. A total of 15,734 subjects from the overall 27,618 were medicated with entecavir; however, 11,884 subjects were on tenofovir disoproxil fumarate. We calculated the odds ratio (OR) with confidence intervals (CIs) of 95% to evaluate the impact of entecavir and tenofovir disoproxil fumarate on HCC in subjects with chronic HBV by applying a dichotomous approach with a random or fixed-effect model.

Results: Chronic HBV subjects treated with entecavir showed a higher significant biochemical response than those treated with tenofovir disoproxil fumarate (OR 1.39; 95% CI 1.21–1.60, at $p < 0.001$). Also, no significant difference was detected with entecavir compared to tenofovir disoproxil fumarate concerning the occurrence of hepatic cells cancer (OR 1.26; 95% CI 0.96–1.67, $p = 0.10$), virological response (OR 0.89; 95% CI 0.63–1.25, $p = 0.49$), and seroconversion (OR 1.27; 95% CI 0.76–2.14, $p = 0.37$).

Conclusions: The use of entecavir resulted in a significantly higher biochemical response; nevertheless, it did not show any significant variation concerning the occurrence of hepatic cancer, virological response, or serological conversion compared to tenofovir disoproxil fumarate in chronic HBV subjects. So, results interpretation needs to be carried out carefully owing to the limited number of studies included in specific comparisons, e.g., serological conversion.

Keywords: Chronic hepatitis B virus, Entecavir, Tenofovir disoproxil fumarate, Virological response, Serological conversion, Hepatocellular carcinoma, Biochemical response

1 Background

Hepatic cancer is considered the third predominant reason for death cases related to cancer disease worldwide [1]. It also represents the second main reason for deaths resulting from cancer disease worldwide [2]. Hepatic cellular carcinoma (HCC) is considered the most prevalent hepatic cancer, representing approximately 90% of primary hepatic cancers [2]. Infection with chronic

*Correspondence: mohamedemam9@yahoo.com

[3] Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
Full list of author information is available at the end of the article

hepatitis B virus (HBV) represents the main risk factor for HCC [3]. The occurrence of HCC is the highest in regions where HBV infection is widespread. [4]. In current years, the increased accessibility to antiviral therapy and hepatitis B virus vaccines caused a decrease in the frequency of HBV infection throughout different areas [5], though in 2012, almost 300 million subjects were infected with chronic HBV [6]. Also, the percentages of immunized people against the hepatitis B virus in widespread regions did not elevate significantly from this year, except in South Asia [7]. Therefore, HCC caused by HCV remains a danger to public health in the world. Most chronic hepatitis B subjects are managed by using interferon of α type and/or a nucleotide, or nucleotide analogue [8]. Interferon stimulates the synthesis of hundred genes, enhancing the natural responsiveness of subject immunity against hepatic cells infected with HBV [9]. However, nowadays, analogues of nucleotides occur and proceed to inhibit the replication of HBV directly by stopping the process of reverse transcription of the virus [10]. Interferon implication in practical clinical aspects is not allowed till now, as it can cause serious adverse events that comprise hypolymphemia, leukopenia, thrombopenia, depression, and sleeplessness [11]. Undesired adverse events that result from applying analogues of nucleotide (nucleoside) are usually mild and rare [11]. Currently, nucleotide and nucleoside analogues approved for managing chronic HBV in the world include entecavir, tenofovir alafenamide, lamivudine, tenofovir disoproxil fumarate (adefovir dipivoxil), and (telbivudine). Both entecavir ($C_{12}H_{15}N_5O_3$) and tenofovir disoproxil fumarate ($C_{23}H_{34}N_5O_{14}P$) are selected from those previous drugs to be used as a first-line treatment due to limited detected hepatic cell resistance compared with the other analogues [11]. Continuous management with (nucleoside) and (nucleotide) analogues can postpone the clinical development of chronic HBV in subjects who developed cirrhosis and those who did not [12]. Though nucleos(t)ide analogues stop viral replication, they do not entirely eradicate the hepatitis B virus in numerous subjects [13]. Consequently, numerous chronic HBV subjects need prolonged antiviral management [11]. Clinical studies have reported that nucleos(t)ide analogue management also decreases the risk of HCC in chronic HBV subjects to different degrees [11, 14], though several studies have not shown significant differences among various nucleos(t)ide analogues about decreases in HCC frequency [15–18], excluding subjects who developed cirrhosis previously [15–18]. Comparing different studies concerning various nucleos(t)ide analogues is confusing, their management protocols, varieties in the study design, periods of investigation, and selection techniques [15]. Comparatively limited numbers of studies on a broad scale were done. Those studies assessed efficiencies of various nucleos(t)ide analogues for decreasing HCC risk, most of which were retrospective analyses with an essentially higher risk of selection bias than a prospective study or randomized control trial [19–23]. Also, several studies comparing the effectiveness of various nucleos(t)ide analogues for decreasing hepatocellular carcinoma frequency, comprising one randomized control trial [24], interpreted information gathered from comparatively limited samples [15–33]. The small sample size may affect the statistical strength of the results. As prolonged management is recommended for numerous chronic HBV subjects, the selection of which nucleos(t)ide analogue to be used in such circumstances must include serological conversion, the therapeutic response of subjects for treatment of viruses, responding of viruses, renal toxicity, and nucleos(t)ide analogue resistance, features which have been extensively studied, though the comparative efficiencies of nucleos(t)ide analogues for a long-term decrease in hepatocellular carcinoma risk and the influence of cirrhosis on hepatocellular carcinoma outcomes concerning nucleos(t)ide analogue-treated chronic hepatitis B subjects are topics that have not been assessed carefully. To ease the evidence-based selection of nucleos(t)ide analogues for long-term antiviral management in chronic HBV subjects, we completed this meta-analysis to compare the efficacies of nucleos(t)ide analogues in chronic hepatitis B subjects. Consequently, we lead this meta-analysis study on the impact of entecavir compared with tenofovir disoproxil fumarate as nucleos(t)ide analogue on HCC in subjects with chronic HBV and studying their influence on different outcomes.

2 Method

2.1 Study design

The current meta-analysis included research regarding the declaration of epidemiology with a pre-established study protocol [34]. Numerous search engines were used to collect and analyze data, including OVID, Embase, PubMed, and Google Scholar databases.

2.2 Data pooling

Data were collected from randomized controlled trials, observational studies, and retrospective studies investigating the impact of entecavir compared with tenofovir disoproxil fumarate as nucleos(t)ide analogue on HCC in subjects with chronic HBV and studying their influence on different outcomes. Research studies carried out on humans in any language were only incorporated. Inclusion criteria were not affected by the sample size. Excluded research represented commentaries, review articles, and research that did not introduce association determination. The study procedure is represented

clearly in Fig. 1. The studies were incorporated into this study of meta-analysis only if the inclusion criteria listed below were matched:

1. Study is either prospective, observational, randomized controlled, or retrospective.
2. Population concerned was subjects suffering from chronic HBV.
3. Protocol of intervention based on entecavir and tenofovir disoproxil fumarate.
4. The study included entecavir compared with tenofovir disoproxil fumarate

The exclusion criteria were as follows:

1. Studies that lack clarification for influences of entecavir compared with tenofovir (disoproxil fumarate) on HCC in chronic HBV subjects
2. Studies with subjects treated with medication other than entecavir and tenofovir disoproxil fumarate as nucleos(t)ide analogue
3. Studies lack concentration on the effect of comparative results.

2.3 Identification

The system of search approaches were designed based on the PICOS concept [35]; it can be defined as P (population): chronic HBV subjects; I (intervention): entecavir; C (comparison): entecavir compared with tenofovir disoproxil; O (outcome): therapeutic effect, the occurrence of hepatocellular carcinoma, virological response, and transformation of serology; and S (design of the study): no limitation [36].

Initially, a systemic search was done in the following databases: OVID, PubMed, the library of Cochrane, Embase, and Google Scholar until March 2022. We searched by using keywords and similar words, including chronic HBV, entecavir, tenofovir disoproxil fumarate, virological response, serological conversion, hepatocellular carcinoma, and biochemical response as shown in Table 1. All included studies were gathered and put into

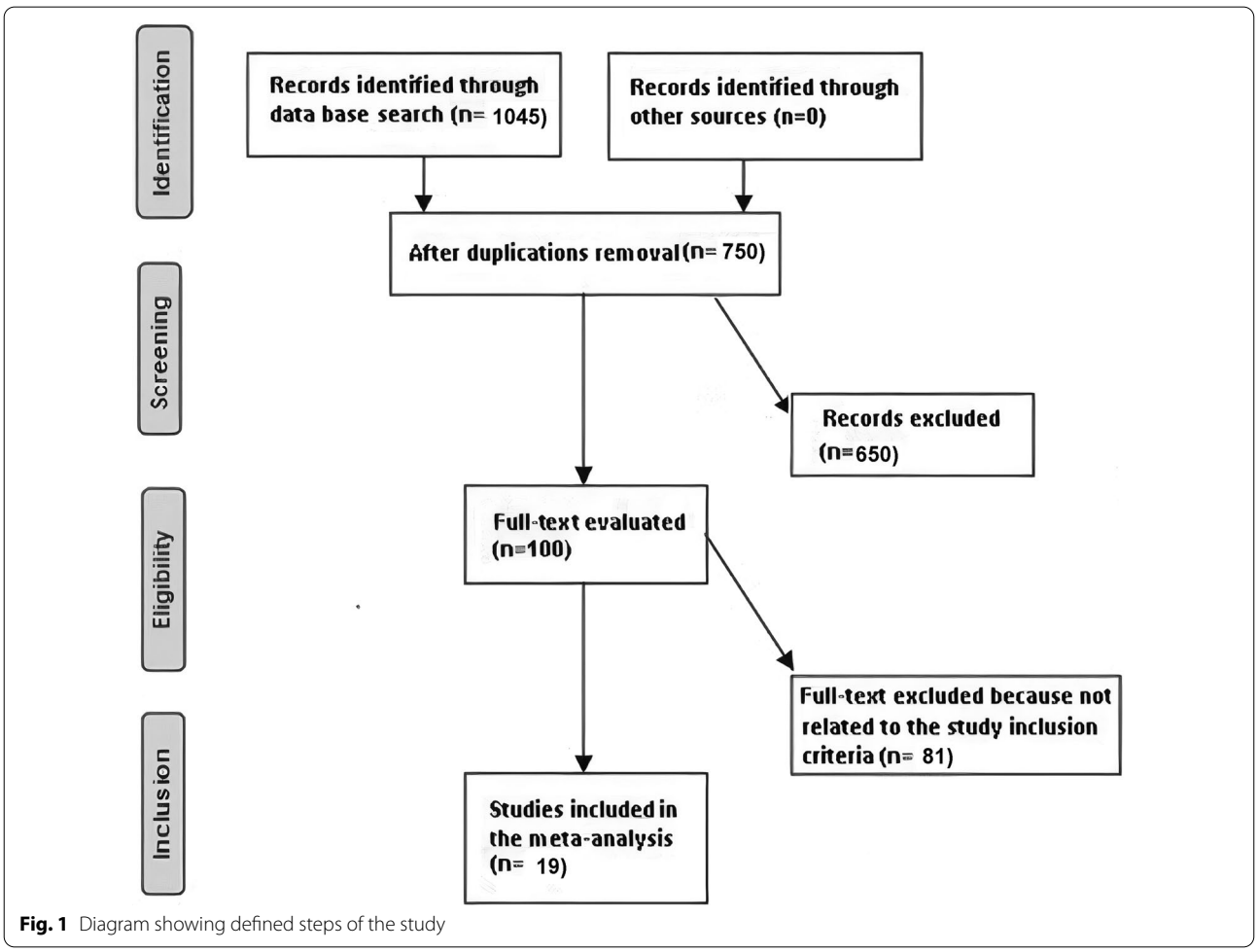

Fig. 1 Diagram showing defined steps of the study

Table 1 Search strategy for each database

Database	Search strategy
PubMed	#1 "chronic hepatitis B"[MeSH Terms] OR "entecavir"[All Fields] OR "hepatocellular carcinoma"[All Fields] OR " serological conversion "[All Fields] #2 "tenofovir disoproxil fumarate"[MeSH Terms] OR "chronic hepatitis B"[All Fields] OR "biochemical response"[All Fields] OR "virological response"[All Fields] #3 #1 AND #2
Embase	'chronic hepatitis B'/exp OR 'entecavir'/exp OR 'hepatocellular carcinoma'/exp OR 'serological conversion' #2 'tenofovir disoproxil fumarate'/exp OR 'biochemical response'/exp OR 'virological response' #3 #1 AND #2
Cochrane library	(chronic hepatitis B):ti,ab,kw (entecavir):ti,ab,kw OR (hepatocellular carcinoma):ti,ab,kw (Word variations have been searched) #2 (serological conversion):ti,ab,kw OR (tenofovir disoproxil fumarate):ti,ab,kw OR (biochemical response):ti,ab,kw OR (virological response):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

a file of the EndNote program. Then, all duplications were excluded. Also, research abstracts and titles were reviewed to exclude studies that did not concentrate on the linkage between entecavir and tenofovir disoproxil fumarate in treating chronic HBV.

2.4 Screening

Data have been curtailed based on the following criteria: properties concerning studies and subjects in a structured way; last name of the principal author, duration of research, year of publishing, country, area of research, and design of the study; type of population, subjects overall number, population information, medication properties, classifications, the qualitative and quantitative approach of assessment, source of information, and interpretation of results [37]. The data were retrieved from a single study when differences were found in the impact of entecavir compared to tenofovir disoproxil fumarate on HCC in HBV subjects. The possibility of bias occurrence in these studies was analyzed by employing two authors who separately evaluated the quality of methods used in the studies included. The tool (bias risk) from the Cochrane Guidebook concerned with intervention Systematic Reviews of Version (5.1.0) was utilized to evaluate the research methods' quality [38]. In terms of the assessment criteria, each study was rated and assigned to one of the following three risks of bias: low: if all quality criteria were met, the study was considered to have a low risk of bias; unclear: if one or more of the quality criteria were partially met or unclear, the study was considered to have a moderate risk of bias; or high: if one or more of the criteria were not met, or not included, the study was considered to have a high risk of bias. A reevaluation of the original article addressed any inconsistencies.

2.5 Eligibility

Principal results concentrated on evaluating the impact of entecavir in comparison with tenofovir disoproxil fumarate on HCC in chronic HBV subjects and interpreting entecavir in comparison with tenofovir disoproxil fumarate were isolated, to form a summary.

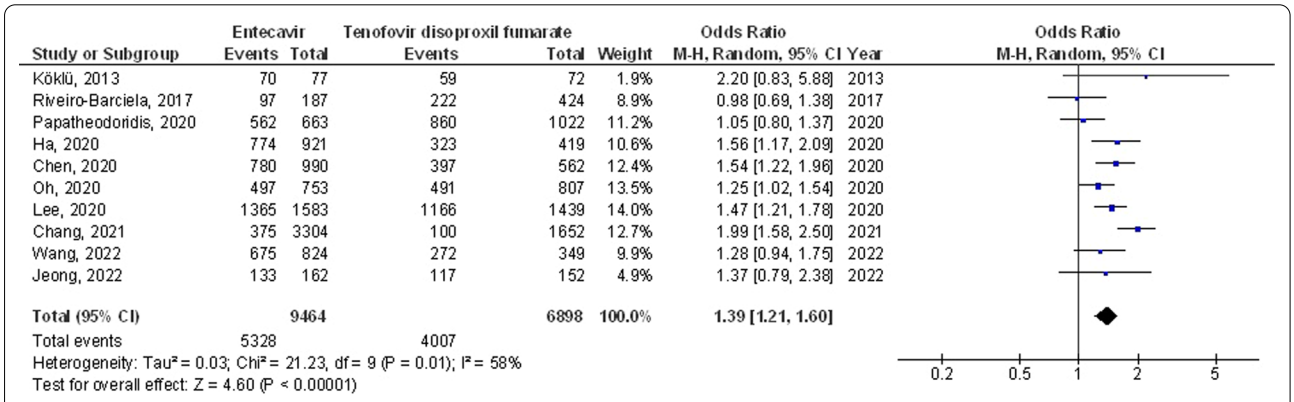

Fig. 2 Difference between the impact of entecavir and tenofovir disoproxil concerning results of biochemical response in chronic HBV subjects

Table 2 Characteristics of the selected studies for the meta-analysis

Study	Country	Total	Entecavir	Tenofovir disoproxil fumarate
Köklü [15]	Turkey	149	77	72
Tsai [16]	Taiwan	183	97	86
Coffin [17]	Canada	259	127	132
Idilman [18]	Turkey	355	183	172
Riveiro-Barciela [25]	Spain	611	187	424
Kim [26]	Korea	1325	721	604
Choi [27]	Korea	1738	869	869
Oh [28]	Korea	1560	753	807
Papatheodoridis [24]	Europe	1935	772	1163
Lee [29]	Korea	3022	1583	1439
Chen [30]	Taiwan	1552	990	562
Ha [31]	Korea	1340	921	419
Chang [32]	Taiwan	4956	3304	1652
Lee [33]	Korea	726	405	321
Su [19]	USA	3287	2193	1094
Shin [20]	Korea	1794	894	900
Na [21]	Korea	1336	671	665
Wang [22]	China	1173	824	349
Jeong [23]	Korea	317	163	154
	Total	27,618	15,734	11,884

2.6 Inclusion

Only the publications comparing the effects of entecavir versus tenofovir disoproxil fumarate were considered for sensitivity analysis. Entecavir and tenofovir disoproxil fumarate were compared as nucleos(t)ide analogues in subclass and sensitivity analyses.

2.7 Statistical analysis

The odds ratio (OR) and 95% CI were calculated using the dichotomous technique with a random or fixed-effect model in this meta-analysis. I2 index ranged from 0 to 100% was measured. Values of 0%, 25%, 50%, and 75% indicated no, low, moderate, and high heterogeneity, respectively [39]. When I2 was greater than 50%, the random-effect model was used; when it was below 50%, the fixed-effect model was used. As previously explained, a subgroup analysis was accomplished by stratifying the initial evaluation for result categories. For the present analysis, a p value of 0.05 was found to be statistically significant concerning variations among subgroups. Egger regression test was used to assess bias in selection objectively (publication bias was deemed existent if $p \geq 0.05$) and subjectively by looking at funnel graphs of the logs of ORs vs their standard errors (SE) [35]. The two-tailed test was used to calculate overall p values. Reviewer Manager version 5.3 was used to provide the statistical findings and graphs (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

3 Results

In total, 1045 relevant papers were screened. Only 19 studies in the period between the year 2013 and the year 2022 were included in this meta-analysis [15–33]. Data obtained from these studies are shown in Table 2.

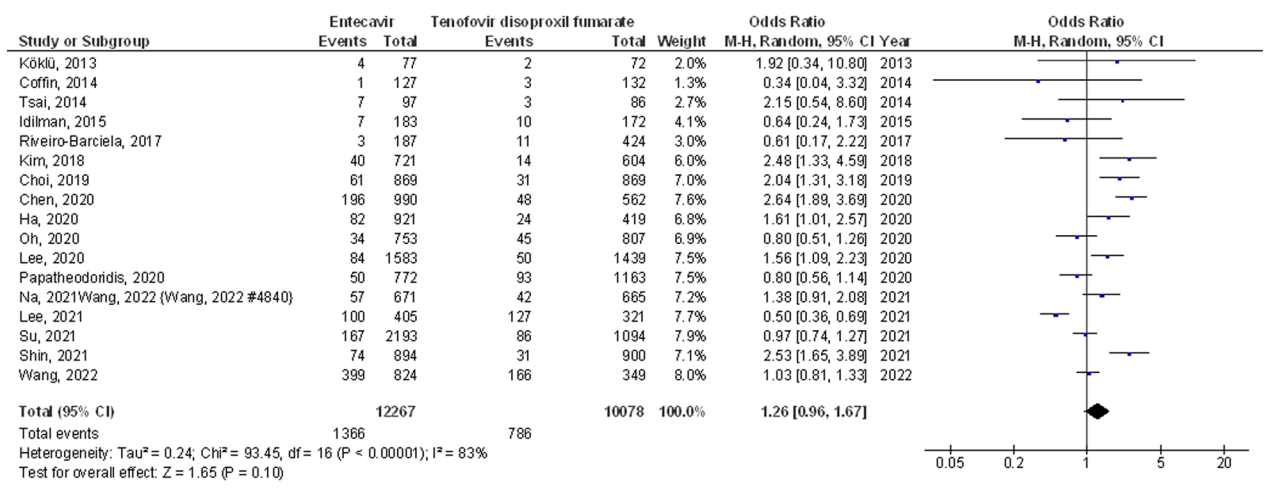

Fig. 3 Difference between the impact of entecavir and tenofovir disoproxil concerning HCC occurrence in chronic HBV subjects

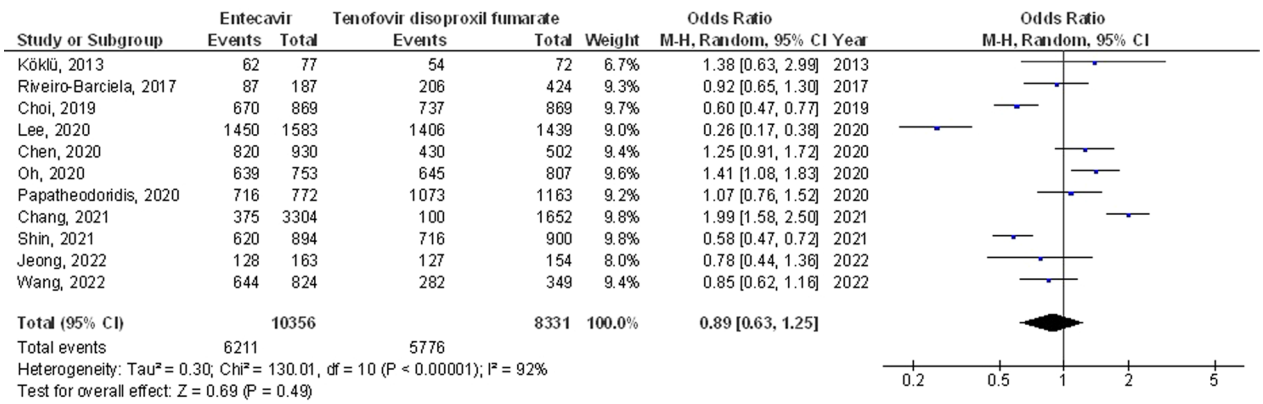

Fig. 4 Difference between the impact of entecavir and tenofovir disoproxil concerning the results of virological responses in chronic HBV subjects

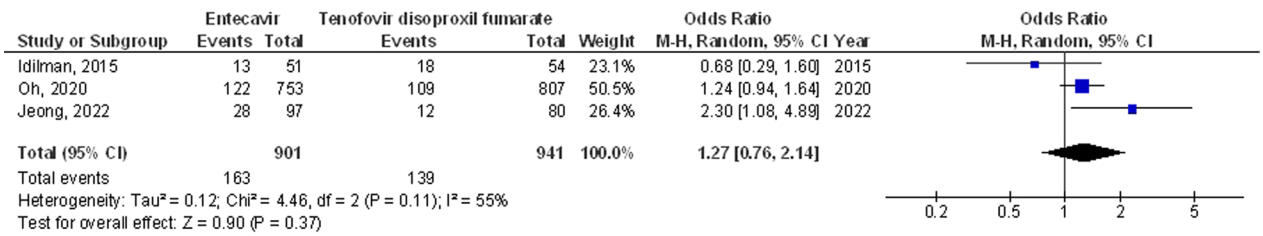

Fig. 5 Difference between the impact of entecavir and tenofovir disoproxil concerning results of seroconversion in chronic HBV subjects

The selected studies included 27,618 subjects with HBV at the baseline of the studies; 15,734 were medicated with entecavir, and 11,884 used tenofovir disoproxil fumarate.

The number of participants was between 149 and 4956 subjects at the study's beginning. Ten studies revealed data concerning the biochemical response, 17 studies revealed results concerning the occurrence of hepatocellular carcinoma, 11 studies revealed results concerning virological response, and 3 studies revealed data concerning serological conversion.

The use of entecavir resulted in a significantly higher biochemical response in subjects with chronic HBV compared with tenofovir disoproxil fumarate (OR 1.39; 95% CI 1.21–1.60, $p<0.001$) with moderate heterogeneity (I2 = 58%) as illustrated in Fig. 2. No significant difference was shown by entecavir concerning occurrence of HCC (OR 1.26; 95% CI 0.96–1.67, $p=0.10$) with high heterogeneity (I2 = 83%), virological response (OR 0.89; 95% CI 0.63–1.25, $p=0.49$) with high heterogeneity (I2 = 92%), and serologic transformation (OR 1.27; 95% CI 0.76–2.14, $p=0.37$) with moderate heterogeneity (I2 = 55%) when compared to tenofovir disoproxil fumarate in subjects suffering chronic HBV as shown in Figs. 3, 4, and 5.

Individualized variables such as age, race, and sex were not adjusted into stratified models to explore their effect on comparison outcomes because no data were available on these variables. Furthermore, a visual check of the distribution curve and quantitative variables using Egger regression analysis revealed no proof of selection bias ($p=0.87$). Nevertheless, most of the papers used in the study had poor method quality, slight selective publication bias, insufficient results, and biased reporting.

4 Discussion

The current meta-analysis involved 19 studies recruiting 27,618 subjects suffering from chronic HBV at the baseline of studies; 15,734 were medicated using entecavir. Also, 11,884 used tenofovir disoproxil fumarate [15–33]. The use of entecavir resulted in a significantly higher biochemical response in subjects having chronic HBV compared to tenofovir disoproxil fumarate. However, entecavir did not show any significant variation in HCC, virological response, and serological conversion occurrence compared with tenofovir disoproxil fumarate in subjects with chronic HBV. This insignificance difference suggests further additional research to assess these results. However, high p values in virological response and serological conversion revealed that more studies would not affect the detected nonsignificant difference. So, interpretation of resulted data should be made

carefully owing to the limited number of studies available, e.g., serological conversion.

All nucleos(t)ide analogues used for treating chronic HBV bind to the enzyme DNA polymerase of HBV competitively. This holds the reversed transcription process of the virus and hinders the reproduction (replication) process of the virus, though nucleos(t)ide analogues do not affect HBV circular DNA bonds. As a result, viral DNA conserves its stability and remains stable inside hepatic cell nuclei for prolonged periods [40]. HBV levels are elevated significantly if nucleos(t)ide analogue medication is ceased before DNA polymerase of the virus is inhibited or destroyed by revenue of cellular protein because the single-stranded circular DNA is being used as a pattern to generate viral transcripts, which then function as templates for the initial reverse transcription process. [41] Consequently, reaching targeted chronic hepatitis B, clinical result demands HBV replication inhibition for long periods. Stopping the development of hepatic cirrhosis and hepatocellular carcinoma is an essential therapeutic objective, which are essentially connected to inhibiting the virus. Though various nucleos(t)ide analogues have similar effects on hepatocellular carcinoma, progress is not clear, and cirrhosis effect on the protective nucleos(t)ide analogues medications has not been sufficiently considered. Present guidelines for chronic HBV management suggest entecavir and tenofovir disoproxil fumarate as first-line therapy [42]. The rate of medication tolerance found for different nucleos(t)ide derivatives drives these recommendations. The decline of hepatitis B virus suppression and development of resistance to such nucleos(t)ide analogues necessitate a rescue medication that includes either entecavir or tenofovir disoproxil fumarate [42]. Despite entecavir tolerance being uncommon, some viral modifications that give lamivudine or telbivudine tolerance may also elevate the probability of entecavir tolerance [43]. Concerning selecting the best nucleos(t)ide analogue for decreasing the risk of HCC, no significant difference was found between entecavir and tenofovir disoproxil fumarate monotherapy. Resistance prevention is required to achieve prolonged inhibition of HBV replication. The research concluded that tenofovir disoproxil fumarate alone was cheaper than other nucleos(t)ide analogues for treating chronic HBV based on average yearly and entire life illness expenses for each subject, lifelong expenses and life expectancy, and quality-adjusted life year [44]. However, further study revealed that lamivudine + adefovir dipivoxil was nearly equivalent to tenofovir disoproxil [45]. Except for rescuing medication following the start of medication tolerance, no guidelines or recommendations concerning using a mix of various nucleos(t)ide analogues are currently present [11]. Nucleos(t)ide analogue treatment against the virus is found to be the cause of reducing the hazard of HCC indirectly by reducing DNA load of HBV and enhancing hepatic inflammatory response, and also throughout stimulating HBeAg seroconversion. Earlier studies show that nucleos(t)ide analogues can stop cirrhosis deterioration histologically and reduce the ratio of HCC by stopping virus replication. Many studies reported that hepatocellular carcinoma could progress into chronic hepatitis B subjects even with effective hepatitis B virus suppression [45–47]. Our results show that the decrease in risk of HCC was found to be statistically equivalent when the comparison is held between entecavir and tenofovir disoproxil fumarate ($p > 0.05$). Entecavir might be favored over tenofovir disoproxil fumarate because of the greater possibilities of tenofovir disoproxil fumarate for undesired side effects, and perhaps because physicians obtained a more significant experience concerning using entecavir because it was approved for chronic hepatitis B management in 2005, whereas tenofovir disoproxil fumarate use started in 2008.

This meta-analysis showed the influence of entecavir compared with tenofovir disoproxil fumarate on HCC in the case of chronic HBV subjects. Additional research is required to illustrate these correlations and compare the impact of entecavir and tenofovir disoproxil fumarate on the variables studied. Larger, more consistent samples are required for more significant results. This was also revealed in a prior meta-analysis study that found entecavir to have comparable encouraging results in treating HCC [48–56]. Because current meta-analysis cannot explain if various ages, races, and sex are linked with the findings, well-conducted randomized clinical trials are needed to investigate these parameters and the combination of various ages, ethnicity, and other variables of individuals.

In summary, the findings showed that entecavir produced a much stronger biochemical response in chronic HBV subjects than tenofovir disoproxil fumarate. In participants with chronic HBV, however, there was no significant difference in the prevalence of virological response, HCC, or serological transformation when entecavir was tested against tenofovir disoproxil fumarate.

4.1 Limitations

Bias may have occurred in the selection process of this review study as a high number of studies were not included in this meta-analysis study. In addition, a high number of ignored studies failed to fulfill the criteria of inclusion previously mentioned. Additionally, this review did not determine if there was a linkage between our results and the subjects' age, race, and sex. The study was designed to evaluate the impact of entecavir compared to tenofovir disoproxil fumarate on HCC in chronic HBV subjects. Also, it

relied on results collected from studies carried out previously. This can result in bias caused by insufficient detailed information. Factors probably resulted in bias incorporated variables like age, gender, and subjects' status of nutrition.

5 Conclusions

The use of entecavir resulted in a significantly higher biochemical response; nevertheless, it did not show any significant variation concerning the occurrence of hepatic cancer, virological response, or serological conversion compared to tenofovir disoproxil fumarate in chronic HBV subjects, though results interpretation needs to be carried out carefully owing to the limited number of studies included in specific comparisons, e.g., serological conversion. This insignificance difference suggests further additional research to assess these results. Well-conducted randomized clinical trials are also needed to investigate these parameters and the combination of various ages, ethnicity, and other variables of individuals.

Abbreviations

OR: Odd ratio; CIs: Confidence intervals; HCC: Hepatic cellular carcinoma; HBV: Chronic hepatitis B virus.

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Author contributions

Conception and design: MA. Administrative support: ST, ME, AM and MA. Provision of study materials: ST, ME, AM and MA. Collection and assembly of data: ME. Data analysis and interpretation: MA. Manuscript writing: MA. Final approval of manuscript: ST, ME, AM and MA. All authors read and approved the manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Beni-Suef Specialized Hospital, Beni-Suef, Egypt. [2]Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt. [3]Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt.

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