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Relationship between nephrotoxicity and long-term adefovir dipivoxil therapy for chronic hepatitis B

A meta-analysis

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Abstract

Background: To assess the relationship between adefovir dipivoxil and renal function after anti-hepatitis B virus therapy and elucidate the risk factors involved.

Methods: Based on the requirements of the Cochrane systematic review methodology, 21 observational articles on adefovir dipivoxil-associated renal dysfunction were obtained by searching various databases, between January 1, 1995 and July 1, 2016. The Newcastle Ottawa Scale was used to evaluate risk bias. Parameters for 4276 chronic hepatitis B patients were analyzed by Review Manager and R software, and glomerular filtration rate, creatinine clearance, and serum creatinine values were extracted to evaluate renal function.

Results: Renal dysfunction was more likely to occur in patients receiving the adefovir dipivoxil therapy (odds ratio [OR] 1.98, 95% confidence interval [CI] 1.40–2.80) than the none-adefovir dipivoxil group. Subgroup analysis showed that renal function predictive value is higher for glomerular filtration rate (OR 2.42, 95% CI 1.34–3.14), compared with serum creatinine levels (OR 1.51, 95% CI 0.75–3.04). The rate of adefovir dipivoxil-associated renal dysfunction was 12% (95% CI 0.08–0.16). Older patients and patients with renal insufficiency, hypertension, and diabetes mellitus were more prone to developing adefovir dipivoxil-associated renal dysfunction; however, integrated raw data were insufficient for further detailed analysis.

Conclusion: Long-term adefovir dipivoxil therapy is connected to renal dysfunction in chronic hepatitis B, necessitating the monitoring of kidney function.

Abbreviations: ADARD = adefovir dipivoxil-associated renal dysfunction, ADV = adefovir dipivoxil, CCT = controlled clinical trial, CI = confidence interval, HBV = hepatitis B virus, IFN = interferon, mtDNA = mitochondrial DNA, NOS = Newcastle Ottawa Scale, OR = odds ratio, RCT = randomized controlled trial.

Keywords: adefovir dipivoxil, chronic hepatitis B therapy, meta-analysis, renal function, risk factors

1. Introduction

Today, antiviral therapies for hepatitis B virus (HBV) infection include interferon (IFN) and orally administered nucleotide analogs, of which adefovir dipivoxil (ADV) is 1 of the most commonly used drug. However, risks of renal dysfunction related to ADV use have been recognized.[1] Adverse effects of long-term ADV therapy in chronic hepatitis B patients include an increase and decrease in serum creatinine levels and glomerular filtration rate (GFR), respectively, osteomalacia, decreased serum phosphorus

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levels, and Fanconi syndrome.[2–10] ADV-related nephrotoxicity was defined as a serum phosphorus value of <0.48 mmol/L or an increase in serum creatinine of ≥44.2 μmol/L from baseline on 2 consecutive occasions by a randomized controlled trial (RCT),[11] and dose-dependent renal tubule damage.[12] ADV treatment for HBV infection potentially poses a high risk for renal dysfunction, which needs to be addressed. We performed this study with the purpose of estimating the effect of ADV therapy for HBV infection on renal function over time and assess the risk factors involved.

2. Methods

2.1. Data sources and literature searches

PubMed, Embase, Wanfang, Chinese Science and Technology Periodicals Database (VIP), and Chinese National Knowledge Infrastructure (CNKI) were searched for the purposes of this study between January 1, 1995 and July 1, 2016. Additional searches were performed on article collections found on Google Scholar, Web of Science, Wiley, and The Cochrane Library. The search keywords were "adefovir dipivoxil", "nephrotoxicity", "renal (kidney) functions", "blood urea nitrogen", "glomerular filtration rate", "creatinine clearance", "serum creatinine", "serum phosphorus", and their synonyms and related terms. In addition, we manually searched *Chinese Journal of Hepatology* and *Chinese Journal of Experimental and Clinical Virology* to identify pertinent literature. We also expanded our search to include the references cited in the selected publications.

2.2. Criteria for inclusion and exclusion

Studies with chronic hepatitis B patients using ADV in antiviral therapy at a daily dose of 10 mg (randomized controlled trials [RCTs], cohort studies, controlled clinical trials [CCTs], and self-controlled studies) were included. This study is a secondary analysis; therefore, ethical approval is not necessary. For a study to qualify, strict selection criteria regarding patients had to be met, with disclosed relevant information covering race, age, sex, and underlying diseases, including diabetes mellitus, hypertension, drug-induced renal damage, and chronic kidney disease. The data, with a follow-up period of at least 2 years, had to be published in full text. A decrease of GFR, levels of creatinine clearance (Ccr), and levels of serum creatinine were chosen as follow-up biochemical outcomes.[13]

We excluded repeated studies, reviews, case reports, and trials which were published as abstracts or interim reports.

2.3. Data extraction and quality assessment

The studies were selected by 2 reviewers (QL and YD) independently, and subsequently, data were extracted on the basis of the inclusion and exclusion criteria. If the 2 reviewers had different opinions, a third reviewer (WZ) would examine the data and convene with the 2 initial reviewers to discuss the choices. Only upon reaching a consensus among the 3 reviewers were the data incorporated. As the data included in the study are based on cohort studies, case-control studies, and self-controlled studies, which were carried out as observational studies, the standard Newcastle Ottawa Scale (NOS) was chosen to evaluate the risk of bias.

2.4. Statistical analysis

Odds ratio (OR) with 95% confidence interval (CI) was used to describe the results for each included study. Depending on the absence or presence of significant heterogeneity, the fixed-effect or random-effect method was used in this meta-analysis. Chi-square and I^2 tests were used to assess heterogeneity, with the statistical significance cut-off $P < 0.05$. The OR with 95% CI was used to assess the risk of kidney damage of ADV long-term treatment against HBV. The publication bias was measured by funnel plots, whereas funnel plot asymmetry was evaluated by Egger and Begg tests. Analysis of cohort and case-control studies were performed with the Review Manager 5.3 (RevMan, Cochrane Collaboration, Oxford, England, UK), and the rates were used to evaluate the proportion of ADV-associated renal dysfunction events in self-controlled studies with R 3.2.2 (www.r-project.org).

3. Results

3.1. Description of trials included in the meta-analysis

Our electronic search detected 1006 studies. Endnote X7 was used to remove the 571 duplicate articles. Following a review of the titles and abstracts, and based on selection criteria mentioned in the methods section, an additional 367 articles were excluded, leaving 68 articles. Based on the full-text context of the remaining articles, 21 studies were finally selected with 4276 patients with HBV infection. Of these studies, 4 were cohort studies,[14–17] 5 were case-control studies,[18–22] and the rest were self-controlled studies[23–34] (Fig. 1). Among the included studies, 5 were published in Chinese, whereas the rest were published in English. Study populations of cohorts and case-control studies had comparable baseline characteristics between ADV group and control group. Detailed information is summarized in Table 1.

3.2. Risk of bias in included studies

As the 21 studies included in this meta-analysis were observational studies (cohort studies, case-control studies, and self-controlled studies), the NOS was used to assess the risk of bias. After quality evaluation, only 3 studies[14,16,18] obtained the highest score for the selection of study groups. The rest had lower scores. Nine studies [14–18,20–22,27] got full marks for comparability of cases and controls. The marks for the rest were low, almost at the level of self-control studies. As the kidney-related

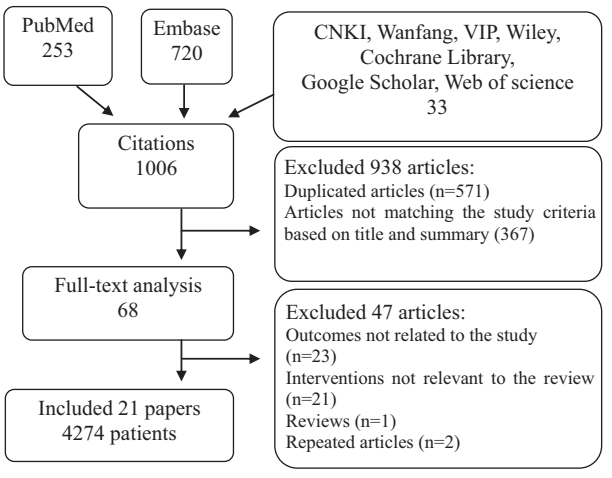

Figure 1. Flowchart showing the process of abstracts screening and studies selection.

Table 1

Characteristics of studies included in this meta-analysis.

Reference	Study design	Region	Sex (M/F)	Mean age, y		Sample size		Intervention		Follow-up, mos	Definition of renal dysfunction
				ADV	Control	ADV	Control	ADV	Control		
Ha et al, 2009[18]	C-C	USA	222/68	46.7±11.8	46.2±11.6	145	145	ADV 10 mg	ETV 0.5 (1) mg	ADV 48/ ETV 41	Decrease of eGFR from base line >10%
Hadziyannis et al, 2006[23]	S-C (RCT)	Multicenter	103/22	47±10	/	125	/	ADV 10 mg	/	80	Scr >0.5 mg/mL
Jia et al, 2015[19]	C-C	China	235/95	46.2±9.2	48.6±8.7	165	165	ADV 10 mg (+LAM)	ETV 0.5 mg	60	Scr $>10^4$ μmol/L
Marcellin et al, 2008[15]	Cohort (RCT)	Multicenter	103/27	34±11.2	36±11.3	65	65	ADV 10 mg	Informal treatment	60	Increase of Scr from base line
Mauss et al, 2011[21]	C-C	Germany	44/20	38 (18–63)	43 (20–73)	32	32	ADV 10 mg	ETV 0.5 mg	24	Decrease of eGFR from base line >20 mL/min
Qi et al, 2015[16]	Cohort	China	95/26	49 (24–70)	42 (19–64)	60	61	ADV 10 mg	ETV 0.5 mg	23	Decrease of eGFR from base line >20%
Tian et al, 2013[33]	S-C	China	177/66	15–75	/	243	/	ADV 10 mg (+ETV or LAM or LDT)	/	24–108	Scr >106 μmol/L $P<0.8$ mmol/L (>2 times, interval time >3 mos)
Kim et al, 2012[25]	S-C	Korea	511/176	49 (17–77)	/	687	/	ADV 10 mg (+LAM)	/	27	Decrease of eGFR from base line >20%
Minde et al, 2012[27]	S-C (RCT)	China	397/83	32±10	/	480	/	ADV 10 mg	/	60	Increase of Scr from base line > 0.5 mg/mL
Zhu et al, 2012[34]	S-C	China	12/19	72±5	/	31	/	ADV 10 mg	/	36	Increase of Scr, BUN, and UA
Mao et al, 2009[31]	S-C (RCT)	China	115/39	46.1±10.1	/	154	/	ADV 10 mg	/	60	Increase of Scr from base line >0.5 mg/dL (2 successive)
Ning et al, 2015[32]	S-C	China	50/25	18–69	/	75	/	ADV 10 mg (+LAM)	/	24	$P<0.96$ mmol/L
Hartono et al, 2013[24]	S-C	Singapore	200/71	47.03±1.65	/	271	/	ADV 10 mg alone or combined treatment	/	28.98 (95%CI 26.46–31.50)	Scr >0.5 mg/dL, eGFR <60 mL/min/1.73 m^2
Kim et al, 2011[20]	C-C	Korea	NA	NA	NA	64	97	ADV 10 mg	ETV 3 mg	ADV 29/ETV 23	Decrease of *P*, eGFR <30 mL/min/1.73 m^2
Manolakopoulos et al, 2011[14]	Cohort	Greece	61/29	53±13	50±12	46	44	ADV 10 mg (+LAM)	Placebo	37±21	Decrease of Ccr from baseline >30%
Jia et al, 2011[22]	C-C	China	56/29	53.1±8.8	53.3±7.4	45	40	ADV 10 mg (+LAM)	LAM 100 mg	24	Increase of Scr >2 times level of base line
Gu et al, 2010[17]	Cohort	China	370/109	35.5±11.6	40.5±15.3	203	276	ADV 10 mg	Placebo	48	Scr >124 μmol/L
Tamori et al, 2010[28]	S-C	Japan	25/12	55 (33–69)	/	37	/	ADV 10 mg (+LAM)	/	38	Increase of Scr >1.3 times the level of baseline
Lampertico et al, 2007[26]	S-C	Italy	122/23	56 (19–77)	/	135	/	ADV 10 mg (+LAM)	/	36	Decrease of Ccr from baseline >0.5 mg/dL (2 different monitoring points)
Vassiliadis et al, 2010[30]	S-C	Greece	54/6	56 (22–74)	/	60	/	ADV 10 mg (+LAM)	/	48	Increase of Scr >UNL
Tanaka et al, 2014[29]	S-C	Japan	228/64	47 (25–75)	/	292	/	ADV 10 mg (+LAM)	/	60	eGFR <50 mL/min/1.73 m^2

For data extraction, randomized controlled trials were regarded as cohort studies or self-control studies.

Doses in combination therapy: LAM 100 mg + ETV 0.5 mg, LDT 600 mg.

The symbol / indicates that the self-control study has no control group.

ADV = adefovir dipivoxil, C-C = case-control study, Ccr = creatinine clearance, Cohort = cohort study, eGFR = estimated glomerular filtration rate, ETV = entecavir, LAM = lamivudine, LDT = telbivudine, NA = not available, P = serum phosphorus levels, RCT = randomized controlled trial, S-C = self-control study, Scr = serum creatinine, UAL = upper normal limit.

Table 2

Risk of bias of studies included in this meta-analysis.

Study	Selection (≤4*)	Comparability (≤2*)	Exposure/outcome (≤3*)
Ha et al, 2009[18]	****	**	***
Hadziyannis, S.J. 2006[23]	***	*	**
Jia et al, 2015[19]	**	*	**
Marcellin et al, 2008[15]	***	**	**
Mauss et al, 2011[21]	***	**	**
Qi et al, 2015[16]	****	**	**
Tian et al, 2013[33]	***	*	**
Kim et al, 2012[25]	***	*	**
Minde et al, 2012[27]	***	**	**
Zhu et al, 2012[34]	***	*	**
Mao et al, 2009[31]	***	*	**
Ning et al, 2015[32]	***	*	**
Hartono et al, 2013[24]	***	*	**
Kim et al, 2011[20]	***	**	**
Manolakopoulos et al, 2011[14]	****	**	**
Jia et al, 2011[22]	***	**	**
Gu et al, 2010[17]	***	**	**
Tamori et al, 2010[28]	***	*	**
Lampertico et al, 2007[26]	***	*	**
Vassiliadis et al, 2010[30]	***	*	**
Tanaka et al, 2014[29]	***	*	**

A study can be awarded a maximum of 4 stars (****) within the "Selection," and 3 stars within the "Exposure" or "Outcome" categories.
A maximum of 2 stars (**) can be given for "Comparability."

biochemical indicators were not the primary outcome indicators in the selected studies, only 1 study [18] in outcome measurement obtained the highest marks. Most included studies lack control points, resulting in low NOS scores. With scores of 5 stars or more, all included studies had acceptable overall quality (Table 2). Sensitivity analyses indicated that no study significantly affected the results of this meta-analysis (details in Supplementary Material 1, http://links.lww.com/MD/B468).

3.3. Meta-analysis result of cohort and case-control studies

The total number of patients in cohort and case-control studies was 1750, and heterogeneity was not significant according to the chi-square test and I^2 measurement ($P=0.46$, $I^2=0\%$). After applying the fixed-effect model, significant nephrotoxicity after long-term ADV treatment was indicated (OR 1.98, 95% CI 1.40–2.80; Fig. 2). To determine whether a different biochemical outcome may influence the results, a subgroup analysis was conducted using the levels of serum creatinine and GFR (4 and 3 studies, respectively). In both cases, the chi-square test and I^2 measurements showed no significant heterogeneity ($P=0.42$, $I^2=0\%$ for serum creatinine levels studies; and $P=0.24$, $I^2=30\%$ for GFR studies). The fixed-effect model was therefore used for studies with both outcomes. After long-term ADV treatment, both a significant increase of serum creatinine levels (OR 1.51, 95% CI 0.75–3.04; Fig. 3) and a significant decrease of GFR (OR 2.42, 95% CI 1.34–3.14; Fig. 4) were indicated. Our analysis showed that GFR is a more sensitive indicator than serum creatinine levels in ADV-related renal function damage, which

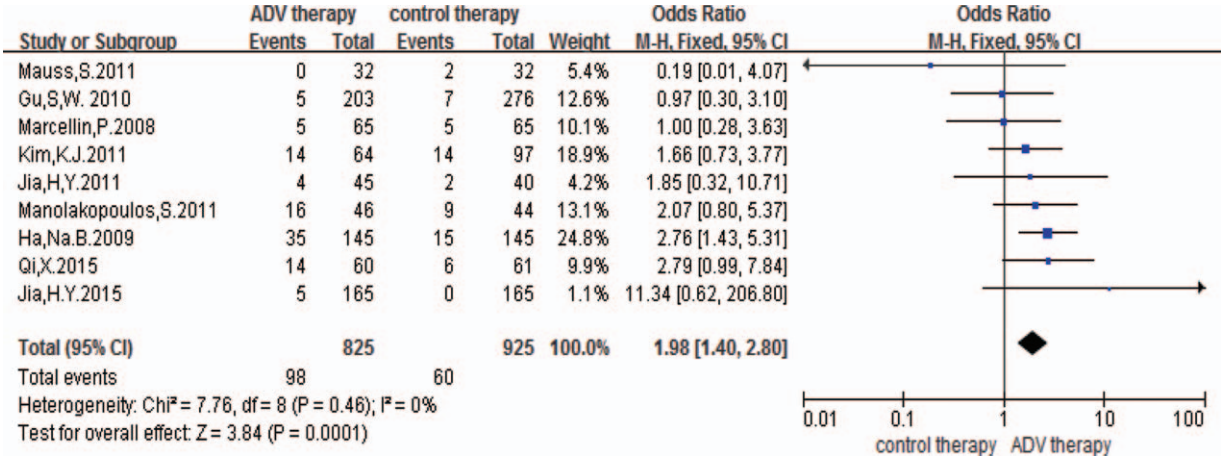

Figure 2. Nephrotoxicity risk between adefovir and control therapy in cohort and case-controlled studies.

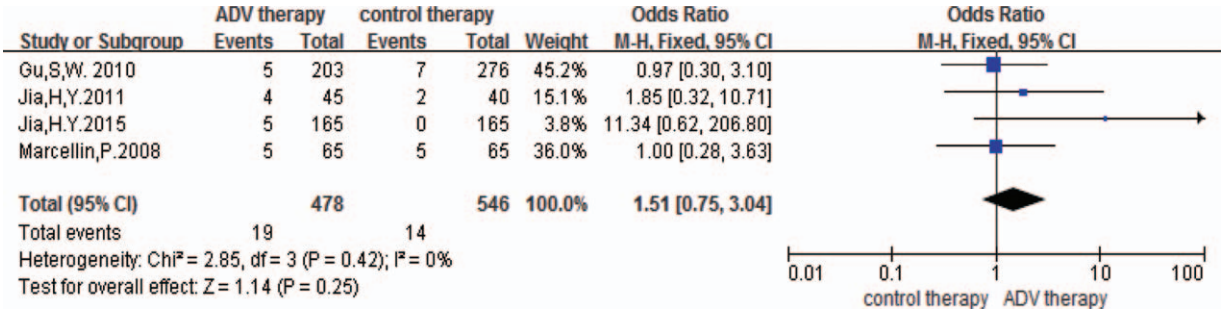

Figure 3. Serum creatinine increase between adefovir and control therapy in cohort and case-control studies.

may help us to identify potential renal impairment earlier in clinic practice.

3.4. Meta-analysis result of self-controlled studies

The total number of included patients was 2579, from 12 self-controlled studies, and the heterogeneity was significant (I^2 measurement, $P<0.05$, $I^2=97.3\%$). According to the random-effect model, the rate of renal dysfunction in long-term adefovir treatment was 12% (95% CI 0.08–0.16; Fig. 5). As the results could be influenced by various factors, we performed subgroup analysis on the time of publication, the length of follow-up, the detection method of renal dysfunction, the number of patients, and the geographical areas of studies, but high heterogeneity between studies was observed ($I^2>75\%$). The origin of heterogeneity was not discovered. Interestingly, the heterogeneity of the studies from China and Japan decreased markedly ($I^2=44.5\%$), and the result suggested that ADV would lead to high incidence of renal dysfunction in the random-effect model, with rate of 34% (95% CI 0.08–0.16; Fig. 6).

3.5. Analysis of risk factors

Age, sex, and underlying illness were analyzed as independent risk factors for renal damage. In 5 of the 21 studies included in the analysis, researchers observed that older patients receiving long-term ADV treatment were more likely to suffer renal impairment.[3,12,14,23,35] In total, there were 3123 men and 1009 women in all analyzed studies, but none of the selected researchers noted any correlation between renal impairment and sex. Na et al concluded that sex had no obvious effect in long-term ADV treatment ($P>0.005$, both in univariate and multivariate analysis). In contrast, hypertension, diabetes, renal insufficiency, liver or kidney transplantation, and diuretics were all found to be risk factors of ADV-related renal damage.[18,19,25,36]

3.6. Publication bias

Funnel plots of analysis results regarding precision are shown with 95% CIs in Fig. 7. There was no distinct publication bias in the analysis of cohort and case-control studies. Egger and Begg tests indicated that no statistically significant publication bias was found ($P>0.1$). However, statistically significant bias of publication was found between self-controlled studies ($P<0.05$) according to Begg and Egger tests.

4. Discussion

Adefovir dipivoxil is a HBV nucleotide analog that can inhibit HBV polymerase activity and decrease the level of serum HBV DNA, thus controlling virus replication. The drug reduces the level of mitochondrial DNA (mtDNA) in cells by inhibiting human mtDNA polymerase-γ, disrupting the oxidative phosphorylation processes, thus leading to cell damage. ADV's potential toxicity against mitochondria could form the basis for renal dysfunction associated with this drug.[5] ADV is not recommended as a first-line antiviral agent, but its activity in patients with lamivudine resistance is undisputed, especially in economically underdeveloped areas and countries.

All included studies received NOS scores of 5 stars or more. This meta-analysis of acceptable quality showed that long-term use of ADV against HBV could lead to kidney damage, especially in the group of cohort and case-control studies (OR 1.98, 95% CI 1.98–2.80), and the causality is apparent. Excluding articles written in Chinese did not affect this finding (details in Supplementary Material 2, http://links.lww.com/MD/B468). In

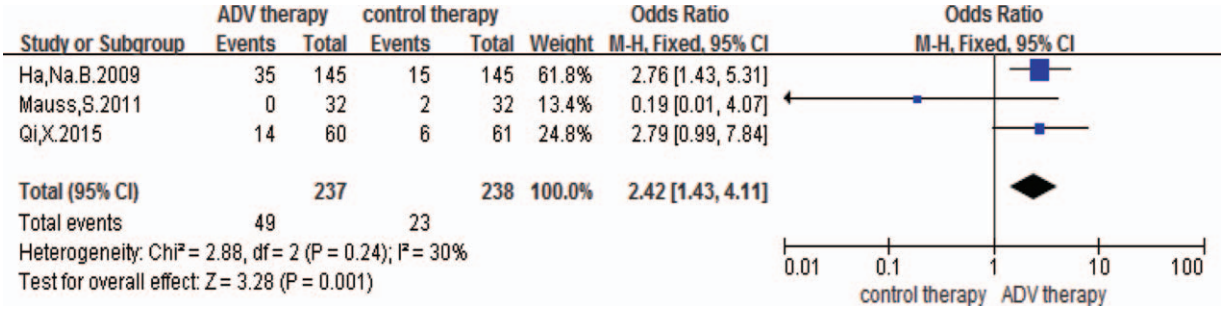

Figure 4. Glomerular filtration rate (GFR) decrease between adefovir and control therapy in cohort and case-controlled studies.

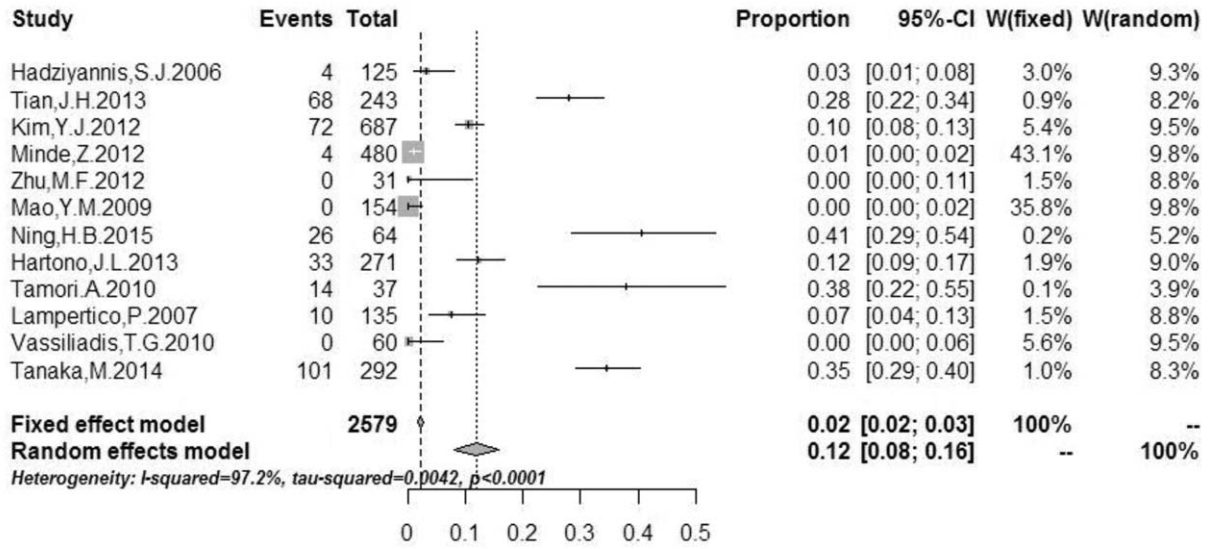

Figure 5. Rate of adefovir dipivoxil associated nephrotoxicity in self-controlled studies.

the past, many short-term clinical studies shaped the belief that ADV is relatively safe for renal function,[5,9,11,19] but Tanaka et al[29] proposed that using ADV for more than 2 years is more likely to result in renal damage than short-term treatment. When ADV is used for long-term treatment, the patients should be closely monitored. Therefore, our study selected the studies that followed up on their patients for more than 2 years.

Yang et al[35] also discussed the relationship between ADV treatment and renal insufficiency in their recent meta-analysis, and found that the risk of renal dysfunction was related to treatment duration. Yang et al pointed out that long-term ADV therapy is a high risk factor of kidney damage (Peto OR 2.68, 95% CI 1.47–1.47), consistent with the results of this study (Peto OR 1.97, 95% CI 1.4–2.77). However, the method of extraction and number of studies examined was different with the above study. The focus of our study is long-term ADV therapy (follow-up time >2 years) approximating clinical treatment, whereas target patients in this analysis received treatment for significantly longer periods.

As the adverse effects of ADV therapy are cumulative, requiring a certain time to manifest, the related short-term high-quality RCT studies could not be utilized and the latter follow-up studies of these RCTs were only regarded as self-control. The results point to ADV as a risk factor for renal impairment, and to GFR as a more sensitive outcome indicator than serum creatinine for patients' monitoring, especially in long-term patients, older patients, and patients suffering from renal insufficiency, hypertension, or diabetes. More attention should be paid to monitoring patients' GFR, to avoid missing early signs of renal insufficiency. The incidence of renal damage is as high as 34% in the analysis of self-controlled studies in China and Japan, possibly due to high infection rate, frequent utilization of ADV, long-term treatment, and analyzed studies incorporating patients with cirrhosis and primary carcinoma of the liver.

This study is not without limitations. We cannot ignore the fact that no RCT was analyzed in the study, and that the quality of studies included was suboptimal. In addition, positive studies were more likely to be published compared with negative ones, which influenced the meta-analysis and caused major publication bias. Restrictions imposed by included studies, such as the difference in patients' inclusion criteria, assessment of renal function, and definition of ADV-associated renal dysfunction, affected the results. An insufficient number of studies were selected, with the majority of them being self-controlled studies. As a result, we could not perform an in-depth analysis. The risk factors of ADV-associated renal dysfunction were not quantitatively analyzed because the data could not be extracted, which affected the accuracy of the analysis.

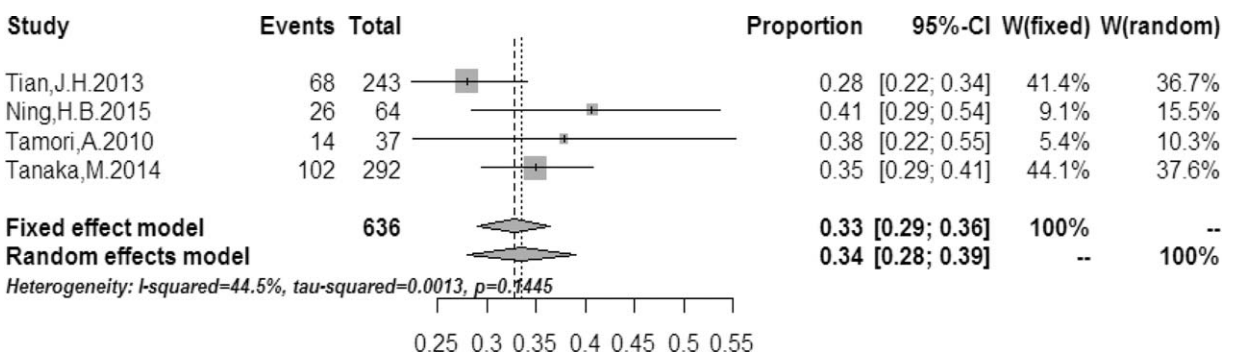

Figure 6. Rate of adefovir dipivoxil associated nephrotoxicity in self-controlled studies in the region of China and Japan.

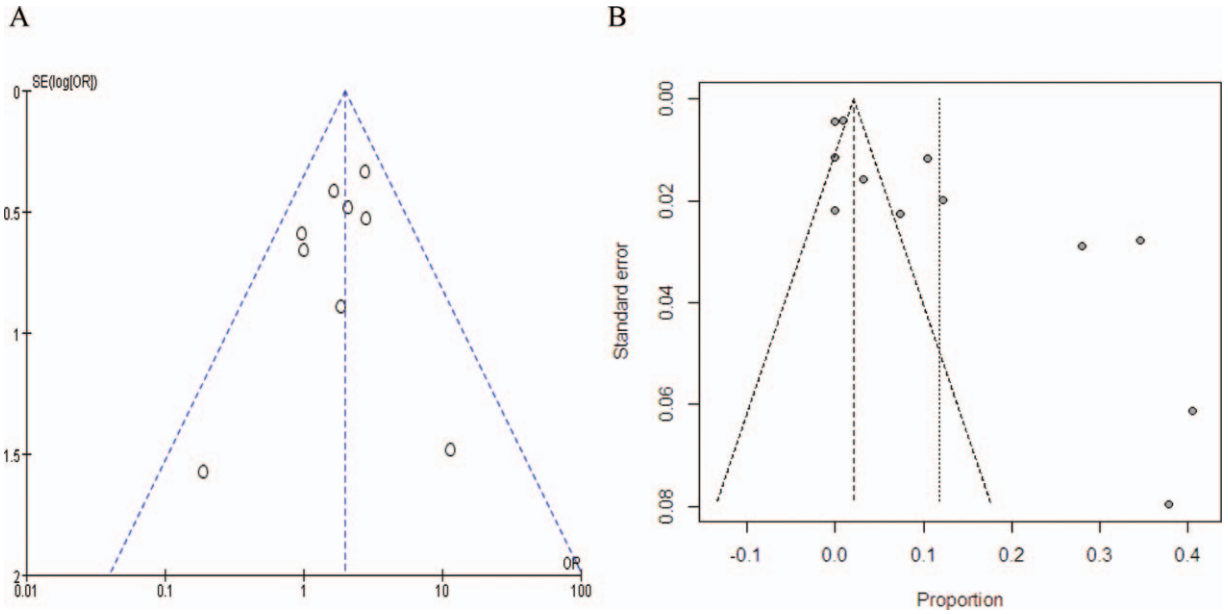

Figure 7. Analysis of publication bias. A, Funnel plots of ADV-related nephrotoxicity in cohort studies and case-control studies. B, Funnel plots of ADV-related nephrotoxicity in self-control studies. ADV = adefovir dipivoxil.

5. Conclusions

In conclusion, long-term ADV therapy of HBV infection can cause renal dysfunction. GFR is a better outcome indicator than serum creatinine levels. It is necessary to pay attention to monitoring patients in later stages of the therapy, especially for treatments longer than 2 years or involving older patients, patients with hypertension, renal insufficiency, or diabetes. Although ADV is not a first-line treatment in present clinical practice and additional high-quality studies are required to validate these observations, a large number of patients are treated with ADV. Promoting the conclusions of this study to patients infected with HBV and receiving adefovir therapy is advisable and would be helpful in making clinical decisions.

6. Declarations

6.1. Availability of data and materials

Since self-controlled studies had no control groups, we used R (www.r-project.org) to analyze this data. The metaprop command of R package meta was used to merge rate values (detailed information is presented in Supplementary Material 3, http://links.lww.com/MD/B468).

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