DOI:
10.1093/rheumatology/kead243

Document Version
Peer reviewed version

OXFORD UNIVERSITY PRESS | Rheumatology

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Journal:	*Rheumatology*
Manuscript ID	RHE-23-0462.R1
Manuscript Type:	Systematic Review and Meta Analysis
Date Submitted by the Author:	08-Apr-2023
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Keywords Please select a minimum FIVE keywords from the list provided. These keywords will be used to select reviewers for this manuscript. The keywords in the main text of your paper do not need to match these words.:	Rheumatoid arthritis < RHEUMATIC DISEASES, Infections and arthritis < RHEUMATIC DISEASES, Hepatic < TISSUES, Viruses < INFECTION, Biological therapies < THERAPIES

HBV reactivation in patients with rheumatoid arthritis treated with anti-interleukin-6: a systematic review and meta-analysis.

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Abstract

Objectives

To assess the possibility of hepatitis B virus reactivation (HBVr) in patients with rheumatoid arthritis (RA) under anti-interleukin(IL)-6 treatment.

Methods

We performed a systematic literature search for articles regarding HBVr in RA patients under anti-IL-6 treatment using PubMed, Scopus and Embase. The search was performed with no date limits and lastly updated on 28th January 2023. Results from all databases were combined and duplicates were excluded, as were non-english articles, case reports, position-articles, comments and pediatirc studies.

Results

Our initial search led to 427 articles; 28 were duplicates, 46 non-English, 169 reviews, 31 books/ letters, 25 case-reports, 88 were irrelevant with meta-analysis aim and 21 were excluded due to inadequate information, leaving 19 articles for further analysis, with a sum of 372 patients with chronic (CHB) or resolved HBV infection. The overall risk for HBVr in patients with CHB was 6.7% increasing to 37% when only patients with CHB and no antiviral prophylaxis were included. On the contrary, HBVr was close to 0% in patients with resolved HBV infection, irrespective of antiviral prophylaxis. All patients experiencing HBVr in these studies were successfully managed with antiviral treatment and/or drug withdrawal.

Conclusion

Overall, anti-IL-6 treatment comes with a significant risk of HBVr in patients with chronic HBV infection; risk is diminished when antiviral prophylaxis is used. In contrast, in patients with resolved HBV infection, the risk of HBVr seems to be extremely low. Large, well-designed studies (either controlled trials or multicentre/international observational studies) are warranted to further validate these results.

Keywords: Tocilizumab; HBV; HBV reactivation; anti-IL-6; rheumatoid arthritis

Key messages

- HBV reactivation risk in rheumatoid arthritis patients with chronic hepatitis B was 37%
- HBV reactivation risk was almost 0% in patients with resolved HBV infection
- No patients under antiviral prophylaxis suffered HBV reactivation

1. Introduction

Hepatitis B reactivation (HBVr) is a well-recognized problem in everyday practice in patients receiving immunosuppressive/immunomodulatory treatment, like those living with autoimmune inflammatory rheumatic diseases (AIIRD) (1).

The definition of HBVr differs among various guidelines, however it could be summarized as HBV DNA rise >10-100 fold in patients with detectable HBV DNA at baseline or as HBV DNA and/or HBsAg appearance in patients who are HBV DNA- or HBsAg-negative at baseline respectively (2, 3). The clinical course of HBVr varies from a simple HBV DNA rise and HBsAg seropositivity without hepatitis, to mild reactivation with clinical hepatitis, or even fulminant liver failure with transaminasemia, encephalopathy and coagulopathy, depending on pre-treatment HBV status, liver fibrosis and patient co-morbidities (2-4).

Various factors are associated with HBVr including those related to HBV, to host and to immunosuppressive/immunomodulatory treatment, broadly classifying HBVr risk as high (>10%), moderate (1-10%), or low (<1%) (5). This risk seems to be higher among patients with chronic hepatitis B (CHB), defined as HBV surface antigen (HBsAg) and/or detectable HBV DNA, than those with resolved HBV infection, defined as HBV core antibody (HBcAb) seropositivity with negative serum HBsAg and HBV DNA (5-7) (8, 9).

For patients living with AIIRD, HBVr risk seems higher in patients receiving B-cell depleting therapies like rituximab, even though this risk is probably lower when compared with patients with lymphoma (1, 3, 10-12). The use of tumor necrosis factor inhibitors (TNFi) also poses a considerable risk, as does the prolonged use of corticosteroids, especially in high doses (1, 5, 13-15), while HBVr risk seems to be low in patients under conventional disease-modifying antirheumatic drugs (1, 5). Data regarding HBVr in patients under anti-interleukin (IL)-6 treatment, one of the major bDMARDs used in RA are scarce (16, 17). Notably, IL-6 is a cytokine that controls a number of pathways, promoting also liver regeneration hence playing a crucial role potentially in protecting against HBV infection (18, 19).

The aim of this systematic literature review and meta-analysis is to analyze the risk of HBVr in patients with rheumatoid arthritis (RA) under anti-IL-6 treatment.

2. Materials and methods

2.1 Method

The meta-analysis was conducted following the recommended items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines (20) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (21). The

Newcastle-Ottawa scale (score 0 to 9) was used to assess the quality for non-randomized controlled trials (RCTs) (22). Quality of the studies was assessed by two investigators (SK, TA) and in case of disagreement, consensus was reached upon discussion with a third assessor (GEF). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

2.2 Study identification

We performed a systematic literature search for relevant articles using PubMed, Scopus and Embase. The search was performed with no date limits and lastly updated on 28th January 2023. The search strategy focused on the following search terms: ("tocilizumab"[All Fields] OR “sarilumab” [All Fields] ("immunosuppression therapy"[MeSH Terms] OR "immunosuppressive therapy"[All Fields])) AND ("HBV"[All Fields] OR ("hepatitis b"[MeSH Terms] OR "hepatitis b"[All Fields])) AND ("arthritis, rheumatoid"[MeSH Terms] OR "rheumatoid arthritis"[All Fields] OR ("autoimmune diseases"[MeSH Terms] OR "autoimmune diseases"[All Fields]) OR ("rheumatic diseases"[MeSH Terms] OR "rheumatic diseases"[All Fields])). Reference lists of relevant articles were also reviewed.

The search results were screened by two independent reviewers (SK, TA) using the titles and abstracts, and all articles considered relevant were evaluated in full-text. In case of disagreement, consensus was reached after discussion with a third reviewer (GEF). Results from all databases were combined and duplicates were excluded, as were non-english articles, case reports, position-articles, comments and studies with pediatric population.

2.3 Statistical analysis

Meta-analysis was performed using both the fixed and random effects method. Since it was not feasible to collect detailed information for each individual patient, the analysis was performed on the aggregated data; such data were extracted from the reported results of the studies after determination of their significance. The meta-analysis was conducted using the R statistical computing language (edition 4.2.2) (23), within the Windows (Microsoft) environment and using the specialized package meta for the R language (24, 25). In the studies that the mean value and standard deviation (SD) were not reported, the median and 1st and 3rd quartiles were used to estimate the mean value and SD, as proposed by Hozo et.al. (26). An improved method suggested by Bland was also used in cases where the maximum and minimum values were reported (27). For such estimations of the mean value and standard deviation, the software Deep Meta Tool, Version 1 was used (28). If only the minimum and maximum values were reported then the range rule was applied to estimate the SD, and the mean value was considered equal to the median. Finally, for studies based on case series with detailed information for each patient, mean value and SD were calculated. In studies reporting on multiple groups treated with different agents, these groups were included separately in the meta-analysis. Assessment for risk of bias at individual study level was not performed; however, risk of bias was evaluated cumulatively by the relevant funnel plots.

3. Results

3.1 Search results

Our initial search led to 427 articles; 28 of them were excluded as duplicates. From the remaining 399 manuscripts, 46 were non-English, 169 were reviews, 31 books and letters, 25 case reports, while 88 were deemed to be irrelevant with the aim of the meta-analysis. Of the remaining 40 articles, 21 were excluded due to the lack of adequate information regarding treatment and disease, leaving 19 articles for further analysis (Table 1 and Figure 1). In screening assessment agreement between researchers was 100%, while regarding quality assessment, agreement between researchers reached 98%; all studies were of medium-high quality.

3.2. Meta-analysis

3.2.1 Patients included in the meta-analysis

A total of 372 patients with CHB or resolved HBV infection were included in the meta-analysis with a median age of 64 years (range 18-91 years); data on gender were largely lacking; out of the 74 patients where gender was reported, 25 were male (33.8%). Forty-one patients had CHB and 279 resolved HBV infection, with only 19 patients receiving antiviral prophylaxis upon anti-IL6 initiation (Table 2). Fourteen patients experienced HBVr with a median time between anti-IL6 initiation and HBVr 5.5 months (range 1-86 months). Of note, all patients experiencing HBVr were not under antiviral treatment (Table 2). A total of 5 patients initiated antiviral treatment after HBVr, all with entecavir. No deaths after HBVr were reported.

3.2.2 HBVr rates based on HBV status

In order to calculate HBVr risk based on patients' HBV status, we divided our patients in 2 groups where group 1 were patients with CHB and group 2 patients with resolved HBV infection.

For both groups, the forest plot (Figure 2) showed acceptable heterogeneity (I2=51%) for patients for CHB and excellent heterogeneity (I^2=0) for those with resolved HBV; publication bias was minimal for both groups. The aggregated percentage of HBVr for patients with CHB was 6.7% (95% CI: 0-31.1%) (and 5.4 for the fixed effects model), and almost zero percent for patients with resolved HBV (actually from the 718 patients in this group, 3 experienced HBVr, however according to both random and common effects models the overall reactivation proportion was 0% (95% CI: 0-0.9%). The comparison of aggregated reactivation percentages indicated that there is a statistically significant difference with patients with CHB showing higher reactivation rates than patients with resolved HBV infection ($p<0.04$, for the fixed effects models).

3.2.3. HBVr in patients without antiviral prophylaxis

Figure 3 depicts the findings based on excluded patients who received antiviral prophylaxis. There was poor heterogeneity among patients with CHB (83%) and excellent homogeneity among patients with resolved HBV infection (0%); publication bias was minimal. The aggregated percentage of HBVr for patients with CHB was 31% (95%CI: 0-99%) (and 14.75 for the fixed effects model), while for patients with resolved HBV infection, the aggregated percentage of recurrence was almost zero percent (actually from the 172 patients in this group, 3 experienced recurrence resulting in a percentage of 1.7%, 95% CI: 0-3.7%), however according to both common and random effects models the overall reactivation proportion for the meta-analysis approach was 0% with 95% CI: 0%. The comparison of aggregated reactivation percentages indicated that there is a statistically significant difference with patients with CHB having higher reactivation rate than patients with resolved HBV infection ($p<0.01$, for the common effects model).

4. Discussion

In this SLR and meta-analysis we found that HBVr was about 7% in patients with CHB but negligible in patients with resolved HBV infection. In the former group, HBVr risk rose up to 33% without anti-viral treatment administration. In contrast, HBVr remained trivial for RA individuals with resolved HBV infection who did not receive anti-viral treatment.

IL-6 is a pleiotropic cytokine exerting its functions through a 130 kD signal-transducing β-receptor (gp130), linked with either its membrane receptor (IL-6R) or the soluble one (sIL-6R) (29). Apart from being a main mediator of inflammatory processes, IL-6 is also involved in the homeostatic liver mechanisms. In fact, it promotes liver regeneration and protects liver cells from injuries caused by immune responses, alcohol and viral infections (30, 31). Moreover, IL-6 seems to play a crucial role in protecting against HBV infection. Firstly, it seems to exert a dose-dependent inhibition in HBV entry in the hepatocyte by down-regulating sodium taurocholate co-transporting polypeptide (NTCP), most likely by inhibiting hepatocyte nuclear factor-4-alpha (HNF4a) expression (32, 33). Secondly, it also seems to inhibit covalently closed circular DNA (cccDNA) formation in HBV infected cells and control HBx expressions and HBV replication (19, 33). Finally, IL-6 may also prevent cccDNA accumulation, making its role crucial for host defence against HBV infection (31). Given the beneficial role of IL-6 in controlling HBV infection, the use of anti-IL-6 drugs could come with a certain risk of HBVr; however, data regarding this issue are scarce, limited mainly to case reports and small studies.

As mentioned earlier, the hepatitis B status (chronic vs resolved) of the patient is one of the most critical factors affecting the risk for HBVr. Towards this direction, recent EULAR recommendations for the screening and prophylaxis of AIIRD patients for chronic and opportunistic infections, suggests that all patients who are starting treatment with immunosuppressants/immunomodulators, should be screened for hepatitis B status, examining in the first instance

HBsAg, anti-HBcore and anti-HBs (34). The same is also suggested by the recent EULAR recommendations for the use of IL-6 blockers in inflammatory conditions (35). It is established that the risk for HBVr in individuals who have chronic HBV and are starting treatment with bDMARDs is considerably high and referral to hepatologist for administration of anti-viral treatment is imperative (34). A recent meta-analysis has shown that this holds true for patients with inflammatory arthritis treated with TNF-inhibitors (36). However, data for other bDMARDs are limited. In this SLR and meta-analysis, we demonstrate that this is the case for RA patients treated with tocilizumab as well.

Regarding patients with resolved HBV infection, risk for HBVr appears to be much lower and monitoring with LFTs and HBV-DNA is suggested over universal prophylaxis, in the recent EULAR recommendations (34). However, meta-analyses or large studies in these patients for anti-IL-6 drugs are lacking. Our data, offer additional evidence that prophylaxis does not seem to be necessary for these patients, since HBVr seems to be a rather rare event, with a rate close to 0%. Even though these drugs are relatively safe and given once daily, anti-viral prophylaxis in these patients is most probably not cost-effective; instead, close monitoring with HBV-DNA and/or LFTs would be a reasonable approach (37). Although data are still limited, this seems to be the case for other b-ts-DMARDs used for inflammatory arthritis, with the exception of rituximab, for which the risk for reactivation appears to be considerably higher (12, 36, 38, 39).

Our study has important strengths, as well as limitations. To the best of our knowledge, we present the first meta-analysis of HBVr in patients with RA under anti-IL-6 treatment. On the other hand, the number of studies included in our meta-analysis is not high. However, heterogeneity of these studies is found to be high enough in our analysis and results seem to be adequate, in our opinion, to draw some initial conclusions. Additionally, our meta-analysis is based on observational studies only, as there are no randomized controlled trials examining this issue. Of note all studies included, were of acceptable quality, as assessed by the Newcastle-Ottawa scale. The latter, although has its drawbacks, it has been widely used from EULAR and other organizations in the development of recommendations (40-42).

In conclusion, our SLR and meta-analysis, provide evidence that in RA patients with CHB treated with anti-IL6 drugs, prophylaxis and referral to hepatologist should be made, while for patients with resolved hepatitis, anti-viral prophylaxis does not seem to confer additional benefit and close monitoring is most probably a more beneficial approach. More evidence is needed to reach robust conclusions not just for IL-6i but also for drug categories such as the JAK-inhibitors to enable more informed and targeted clinical decisions. Towards this direction, randomized controlled trials enrolling RA patients treated with specific class of bDMARDs with chronic or resolved hepatitis, receiving or not anti-viral prophylaxis would be desirable. Other type of studies, however, could be also helpful. For example, relevant data derived from big registries or multicentre (and preferably international) observational studies designed for this purpose (i.e HBVr after exposure to specific bDMARDs) would give some answers.

Author Contributions: Conceptualization, G.F., E.N., F.A., T.A.; Data collection, S.K., T.A.; Statistical analysis, A.P.; Writing—original draft preparation, S.K., G.F., A.D.B., A.P., E.N., F.A., T.A.; Writing—review and editing .K., G.F., A.D.B., A.P., E.N., F.A., T.A. All authors have read and agreed to the published version of the manuscript.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Data Availability Statement: Not applicable

Conflicts of Interest: S.K., T.A., A.P., F.A. and A.D.B. have no conflict of interest. G.F has received honoraria/speaker fees: Abbvie, Pfizer, UCB, Novartis, AEnorasis, Janssen, Genesis. E.N. has received speaker honoraria/participated in advisory boards for Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, Lilly, Fresenius and holds research grants from Pfizer and Lilly.

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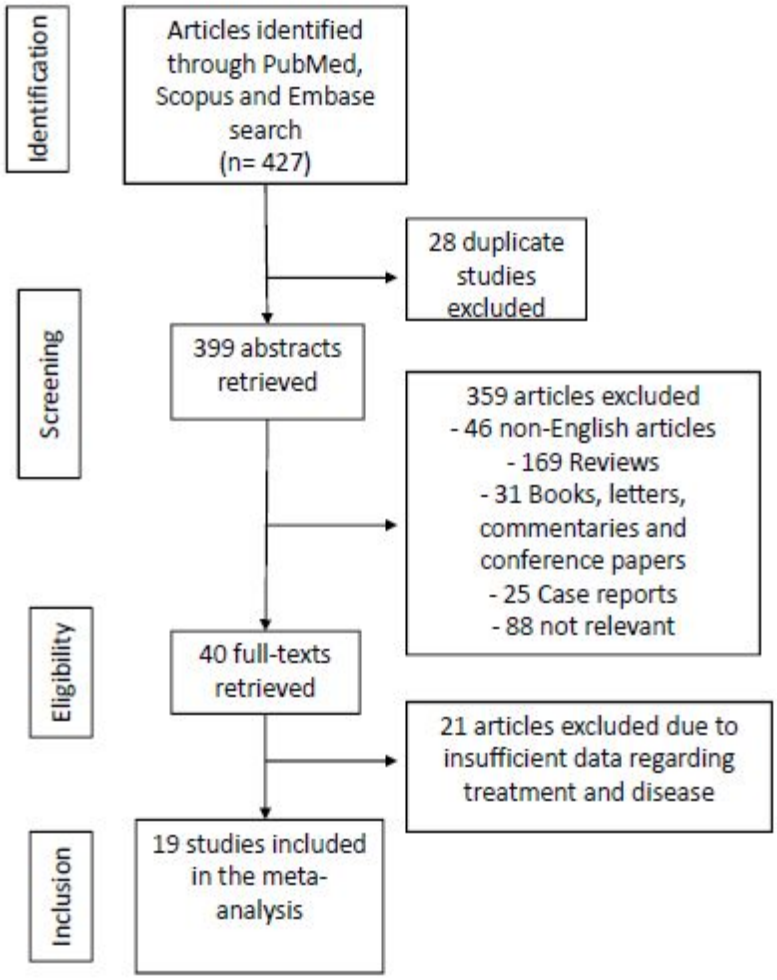
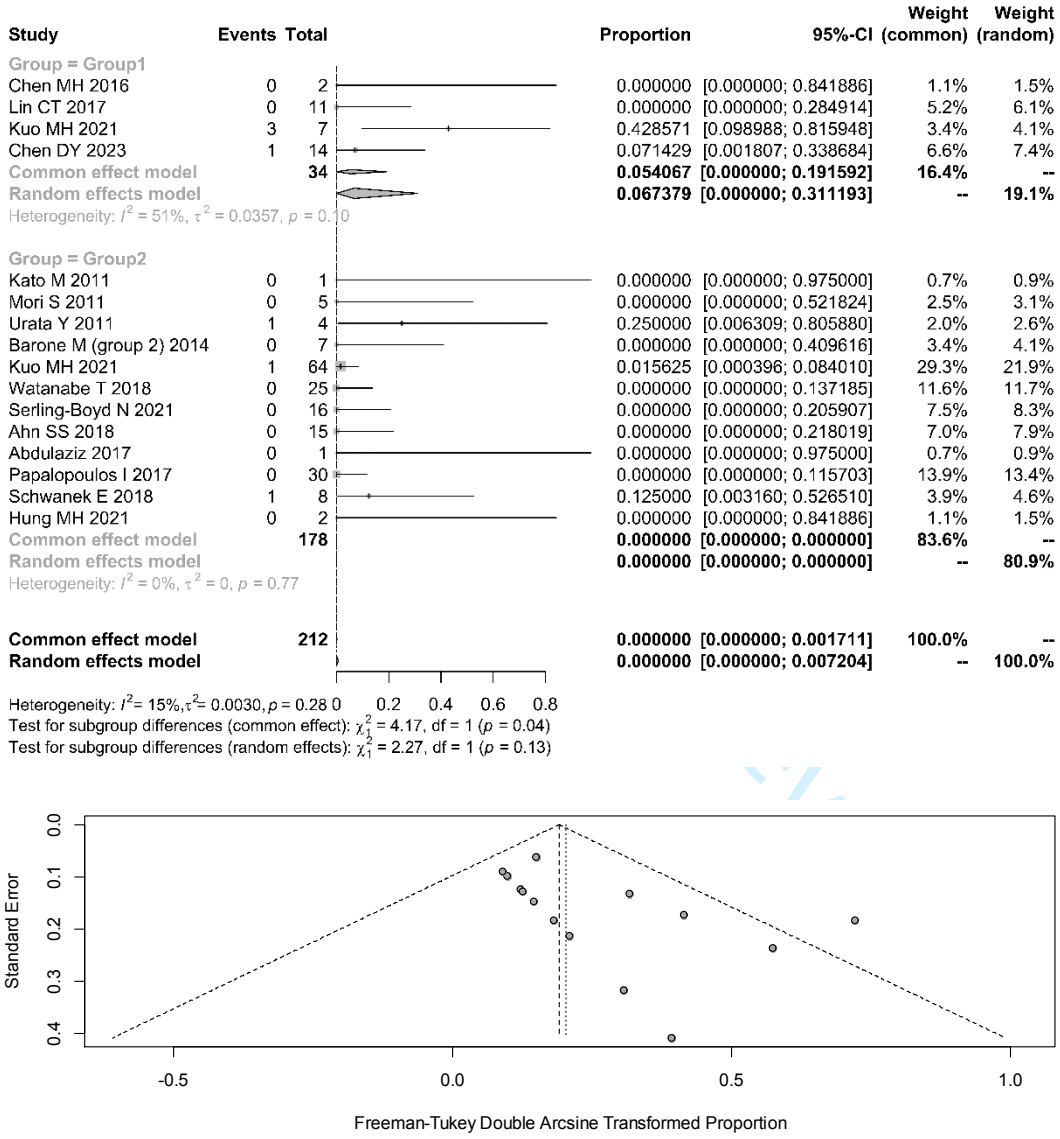
FIGURES

Figure 1. Flowchart of articles selection



Abbreviations: n=number

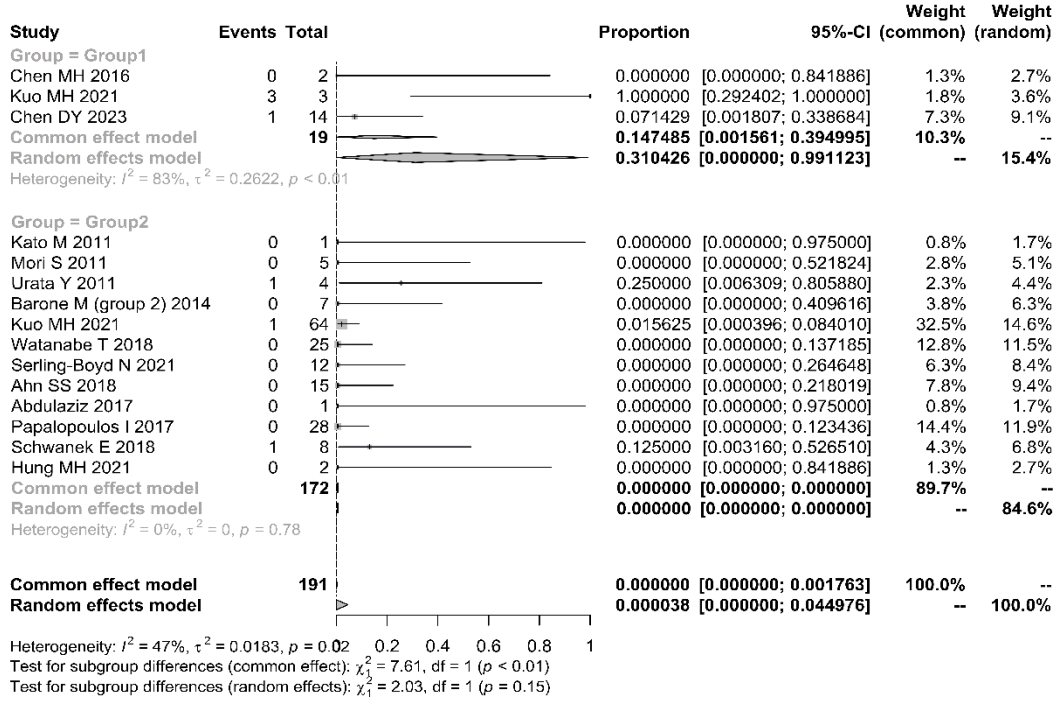
Figure 2. HBV reactivation rates in patients with CHB (group 1) and resolved HBV infection (group 2) and responding funnel plot.

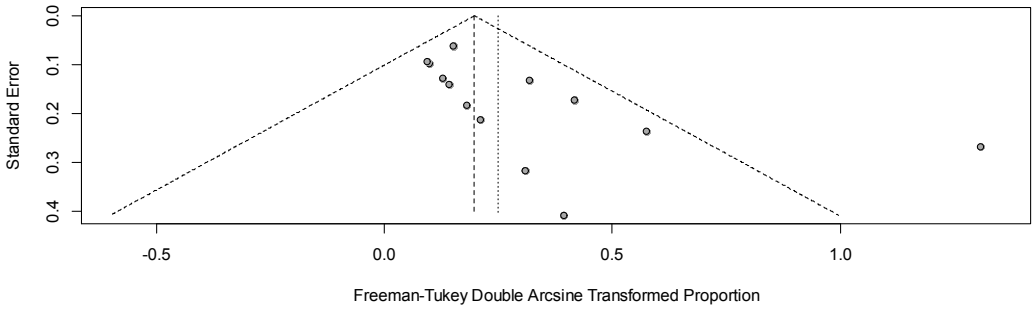


Events column indicates reactivation events while the Total column indicates the total number of patients. Proportion corresponds to the relevant proportion of the events in the total population

Abbreviations: HBV: Hepatitis B virus; CHB: Chronic hepatitis B

Figure 3. HBV reactivation rates in patients with CHB (group 1) and resolved HBV infection (group 2) with no antiviral prophylaxis and responding funnel plot





Events column indicates reactivation events while the Total column indicates the total number of patients. Proportion corresponds to the relevant proportion of the events in the total population

Abbreviations: HBV: Hepatitis B virus; CHB: Chronic hepatitis B

TABLES

Table 1. Studies included in the meta-analysis.

Author, Year	*Design of study*	*Patients ! (total n)*	*HBV status before treatment*	*Prophylaxis (n)*	*HBV Reactivation*	*Concomitant DMARD/GC Treatment in HBVr patients*
Mori et al., 2011(43)	Prospective	5	Resolved	No	No	-
Kato et al., 2011 (44)	Prospective	1	Resolved	No	No	-
Urata et al., 2011 (45)	Prospective	4	Resolved	No	1	MTX
Koike et al., 2014 (46)	Prospective	52	Chronic or Resolved	NS*	No	-
Barone et al., 2015(47)	Prospective	7	Resolved	No	No	-
Nakamura et al., 2016 (48)	Retrospective	18	Resolved	No	2	Prednisolone (1), MTX (2)
Fukuda et al., 2017 (49)	Prospective	48	Resolved	No	1	MTX
Chen et al., 2017 (50)	Retrospective	2	Chronic	No	No	-
Chen et al., 2017 (51)	Prospective	48	Chronic or Resolved	2 with CHB (ADV, ETV)	3 with CHB	MTX (2), HCQ (3), SSZ (2)
Abdulaziz et al., 2017 (52)	Retrospective	1	Resolved	No	No	-
Papalopoulos et al., 2018 (53)	Retrospective	30	Resolved	2 (ETV, LMV)	No	-
Ahn et al., 2018 (54)	Retrospective	15	Resolved	No	No	-
Schwaneck et al., 2018 (55)	Retrospective	8	Resolved	No	1	MTX, Prednisone

Watanabe et al., 2019 (56)	Retrospective	25	Resolved	No	1	GCs, MTX
Lin et al., 2019 (57)	Retrospective	11	Chronic	ETV or LMV	No	-
Serling-Boyd et al., 2021 (58)	Retrospective	10	Resolved	NS	No	-
Kuo et al, 2021 (59)	Retrospective	71	Chronic or Resolved	3 with CHB**	4 (3 CHB, 1 Prior,)	MTX (3), Prednisolone (4), SSZ (3)
Hung et al., 2021 (60)	Prospective	2	Resolved	NS	No	-
Chen et al., 2023 (61)	Retrospective	14	Chronic	NS	1	NS

a. ! Patients with rheumatoid arthritis treated with anti-IL-6

b. *NS: Not Specified

c. **The antiviral drug isn't specified

d. ADV: adefovir, DMARD: Disease modifying antirheumatic drugs; ETV: entecavir, LMV: lamivudine, CHB: Chronic HBV infection, MTX: Methotrexate, HCQ: Hydroxychloroquine, SSZ: Sulfasalazine, GCs: Glucocorticoids

Table 2. Characteristics of patients included in meta-analysis.

Characteristics	n=372
Demographics	
Male gender, n/N* (%)	25/74 (33.8)
Age (years), median (range)	64 (18-91)
HBV status	
CHB, n/N* (%)	41/320 (12.8)
Resolved HBV infection, n/N* (%)	279/320 (87.2)
Antiviral prophylaxis, n/N* (%)	19/294 (6.5)
Patients with HBVr, n/N (%)	14/372 (3.8)
Concomitant treatment of patients with HBVr	
Methotrexate, n/N† (%)	10/14 (71.4)
Prednisone-equivalent, n/N† (%)	8/14 (57.1)
Sulfasalazine, n/N† (%)	5/14 (35.7)
Hydroxychloroquine, n/N† (%)	2/14 (14.3)
Antiviral prophylaxis, n/N† (%)	0/14 (0)
Time duration from anti-IL-6 treatment initiation and HBVr (months), median (range)	5.5 (1-86)
Post-HBVr antiviral treatment, n/N† (%)	5/14 (35.7)
Entecavir, n/N! (%)	5/5 (100)
Outcome	
Resolution, n/N† (%)	14/14 (100%)

a. *Total of patients that this information was available
b. † Total of reactivation cases
c. ! Total of patients that received antiviral treatment
Abbreviations: CHB: Chronic hepatitis B; HBV: Hepatitis B virus; HBVr: Hepatitis B virus reactivation; IL-6: Interleukin-6