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Risk of Hepatitis B Reactivation in Inflammatory Arthritis Patients Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs): a Systematic Review and Meta-analysis

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Abstract

Objectives—To assess hepatitis B (HBV) reactivation rates in patients with resolved or chronic HBV infection, receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs) and with or without antiviral prophylaxis.

Methods—We conducted a systematic review and meta-analysis. Electronic searches were conducted in Pubmed, Medline and EMBASE using OVID through 12/31/2015. A search strategy was developed for each database using the following inclusion criteria: participants (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, resolved, or chronic HBV infection), interventions (TNF inhibitors, non-TNF biologic or non-biologic DMARDs), and outcomes (hepatitis B reactivation). Four reviewers independently extracted study data and assessed study quality with the Newcastle-Ottawa scales. To determine the pooled hepatitis B reactivation rate, the variances of the raw proportions were stabilized using a Freeman-Tukey-type arcsine square root transformation, using a random-effects model.

Results—Twenty-five studies met the inclusion criteria. The overall pooled rate of hepatitis B reactivation was 1.6% (95% CI, 0.8–2.6%) in patients with resolved hepatitis B. Similar rates were observed in resolved patients on TNF inhibitors (1.4%, 95% CI, 0.5–2.6%), non-TNF biologics (6.1%, 95% CI, 0.0–16.6%) and non-biologic DMARDs (1.7%, 95% CI, 0.2–4.2%). We also

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found the reactivation rate was lower in chronic HBV infection patients who received antiviral prophylaxis (9.0%, 95% CI, 4.1–15.5%), than those who did not (14.6%, 95% CI, 4.3–29.0%).

Conclusion—We found the hepatitis B reactivation rate in inflammatory arthritis patients receiving DMARDs was low in resolved patients and moderate in chronic HBV infection patients. Further, lower rates were observed in chronic HBV infection patients using antiviral prophylaxis.

Keywords

Hepatitis B; Disease Modifying Anti-Rheumatic Drugs; Reactivation; Rheumatoid Arthritis

INTRODUCTION

Hepatitis B reactivation is characterized by an abrupt increase or reappearance of hepatitis B virus (HBV) DNA in patients with inactive chronic or resolved HBV infection (1), resulting in a wide range of clinical consequences from asymptomatic increase in liver enzymes to potentially life-threatening fulminant liver failure. Generally, patients with chronic HBV (defined by HBsAg-positive) have five to eight-fold higher risk for hepatitis B reactivation than patients with resolved HBV (defined by HBsAg-negative and HBcAb positive) (2). Hepatitis B reactivation was first reported in cancer and transplant patients who frequently received chemotherapy or immunomodulatorys (3, 4). A possible etiology is the disruption of the ability of the host immune system to control HBV replication (5). With the development of biological immunomodulators in the past two decades, evidences suggests that hepatitis B reactivation was associated with use of tumor necrosis factor (TNF) inhibitors in inflammatory arthritis, such as rheumatoid arthritis, and psoriatic arthritis (5–16). There were also reports in patients receiving non-TNF biologic DMARDs like abatacept and tocilizumab (7, 17, 18). Hepatitis B reactivation can be largely prevented by HBV screening in all patients before the start of immunomodulators and by initiating antiviral prophylaxis in patients with chronic HBV infection (19).

Data on hepatitis B reactivation rates in rheumatology patients are limited to case series and small observational studies. The largest systematic review found that among 468 resolved rheumatoid arthritis (RA) patients, the crude hepatitis B reactivation rate was about 1.7% (20). The other review found a 12.3% rate in 122 chronic HBV infection RA patients receiving TNF inhibitors (21). A recent meta-analysis found the overall pooled hepatitis B reactivation rate was 3.0% in resolved and 15.4% in chronic HBV infection inflammatory arthritis patients (22). In 2015, the American Gastroenterological Association published their technical review on hepatitis B reactivation during immunosuppressive drug therapy. Inflammatory arthritis patients received biologic DMARDs monotherapy are regarded to have moderate risk (1–10%) for hepatitis B reactivation (19). The risk of hepatitis B reactivation in inflammatory arthritis patients using non-biologic DMARDs is regarded to be generally low (<1%) (19).

The hepatitis B reactivation risk has been described mainly in resolved or chronic HBV infected patients receiving TNF inhibitors. Identifying HBV reactivation rates associated with different DMARD regimens, and with the addition of anti-viral prophylaxis, is critical for counseling patients on their individualized risks. Cases reported in previous systematic

reviews (20–22) were frequently treated with combination DMARD regimens, with or without concurrent glucocorticoids or antivirals. These analyses were often under-powered, limiting the precision of pooled risk estimates for individual drugs (19). Since the last published meta-analysis in 2014 (22), several large observational studies have been published, allowing us to examine the hepatitis B reactivation rates under different treatment scenarios. The aims of the current systematic review and meta-analysis were: 1) to examine the hepatitis B reactivation rates in inflammatory arthritis patients with resolved or chronic HBV infection and did not receive antiviral prophylaxis, including subgroup analyses by DMARD type; 2) to examine the hepatitis B reactivation rate in inflammatory arthritis patients with chronic HBV who received antiviral prophylaxis.

METHODS

Study identification

We considered the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (23) as the standard for protocol development. Considering hepatitis B reactivation as an adverse event, we also referenced the guidance specifically designed for systematic review of adverse effects published by the Cochrane Adverse Effects Methods Group (24) and Centre for Reviews and Dissemination (25). The electronic search was conducted in Pubmed, MEDLINE (1990–December 2015) and EMBASE (1990–December 2015) using OVID. A search strategy was developed for each database by combining the medical subject headings and/or text terms into PICO categories: participants (‘rheumatoid arthritis’ or ‘psoriatic arthritis’ or ‘ankylosing spondylitis’ or ‘inflammatory arthritis’), interventions (‘methotrexate’ or ‘leflunomide’ or ‘tumor necrosis factor or anti tumor necrosis factor alpha’ or ‘TNF’ or ‘etanercept’ or ‘infliximab’ or ‘adalimumab’ or ‘golimumab’ or ‘certolizumab’ or ‘abatacept’ or ‘rituximab’ or ‘tocilizumab’ or ‘tofacitinib’), and outcomes (‘hepatitis B’ or ‘HBV’ or ‘hepatitis B reactivation’ or ‘reactivation’ or ‘liver failure’). The results from three databases were combined and duplicates were excluded. We also manually searched the reference lists of key published articles.

Study selection

The search results were screened by four independent reviewers (TL, KY, ST, MMA) using the titles and abstracts, and all articles considered relevant were evaluated in full-text. We included case series, retrospective and prospective observational studies to fulfill the study objectives. Figure 1 presents the study inclusion flow chart (23).

Data collection

We developed a data extraction form based on the Cochrane Consumers and Communication Review Group’s data extraction template, pilot-tested it on 10 randomly-selected included studies, and refined it accordingly. Data collected included study characteristics, such as published year, settings, country, patient population, patient numbers for resolved and chronic HBV, ever use of antivirals, length of follow-up, and percentage of baseline glucocorticoids used. We also extracted the total number of patients at risk, the baseline DMARDs exposures and the number of HBV reactivation cases in total and in DMARD

subgroups. HBV status was defined as: resolved if HBsAg (–) and HBcAb (+); or chronic HBV infection if HBsAg (+), with or without HBcAb, regardless of detectable HBV DNA (26). We categorized DMARD exposures into TNF inhibitors, non-TNF biologic DMARDs and non-biologic DMARDs groups based on the DMARDs patients received at baseline. For the TNF inhibitors and non-TNF biologic DMARDs groups, we included patients who had combined non-biologic DMARDs (e.g., adalimumab plus methotrexate). Patients in non-biologic DMARDs group could only receive non-biologic DMARDs. Since there are few validated quality assessment scales for non-randomized studies, we adopted the Newcastle-Ottawa Scale to evaluate the quality of included studies, using the Agency for Health Research and Quality threshold (poor, fair or good quality; see Appendix for the detailed scoring). Studies with poor quality were excluded from the analysis. Four investigators extracted the data from individual studies (TL, KY, ST, MMA); data extraction was then confirmed by a second investigator. Disagreements were resolved by consensus, and when consensus could not be reached, by the senior author (DHS).

Study outcome

The primary study outcome was hepatitis B reactivation after DMARD initiation, defined by: 1) seroconversion from HBsAg (–) at baseline to HBsAg (+) during follow-up; or 2) undetectable HBV DNA at baseline with detected HBV DNA during follow-up; or 3) detectable HBV DNA at baseline and >1 log increase in HBV DNA during follow-up based on American Gastroenterological Association guideline (19). We applied these criteria and re-categorized some reactivation cases into non-cases based on the above definition. For example, some studies defined HBV reactivation solely based on an increase of liver enzymes only. By applying our outcome definition, we reclassified these cases as non-reactivation cases.

Data synthesis

Pooled rates of HBV reactivation were calculated using random-effects models, and the variances of the pooled rates were stabilized by the double arcsine transformation. This method was found to produce less bias and mean squared error than the traditional log transformation (27). We presented the HBV reactivation rates by HBV status (resolved or chronic HBV), receipt of antiviral prophylaxis at baseline, and DMARDs use at baseline (TNF inhibitors, non-TNF biologics, and non-biologic DMARDs). We assessed heterogeneity among studies using the Cochran Q test and quantified inconsistencies across studies and their impact on the analysis by using the I^2 statistic (28). All analyses were done by MetaXL 1.4 (<http://www.epigear.com>).

In sensitivity analyses, we excluded studies with small sample size in the subgroups, pre-defined as <10 patients. We also performed a subgroup analysis in chronic HBV infection patients receiving antivirals throughout follow-up in the non-biologic DMARDs group.

RESULTS

Characteristics of included studies

We identified 318 studies from the Pubmed, MEDLINE and EMBASE databases after removing duplications (Figure 1). Abstract review led to excluding 61 systematic reviews, 41 qualitative reviews and 7 case reports and 138 other studies did not meet the PICO inclusion. From the remaining 71 studies, we further excluded 46 studies which received a poor Newcastle-Ottawa Scale quality score (N=3), were not published as full papers (N=39) or were not clear in exposures or outcomes (N=4). Twenty-five studies were included in the analysis (Figure 1).

The characteristics of the included studies (5–18, 29–39) are presented in Table 1. The study design for most of the included studies was retrospective or prospective observational (N=23), and 21 conducted in a single-center setting. Fifteen studies (60%) reported antiviral prophylaxis used at DMARD initiation in inflammatory arthritis patients (5, 6, 8–10, 12, 13, 17, 30, 33–37, 39). No studies included patients using antiviral prophylaxis with resolved hepatitis B. We identified a total of 1,032 patients with resolved and 259 with chronic HBV infection patients for meta-analysis.

HBV reactivation rates

Twenty-four studies reported the HBV reactivation rates in inflammatory arthritis patients with resolved hepatitis B (5–18, 29–38). The pooled estimate for HBV reactivation was 1.6% (95% CI 0.8–2.6; I^2 15.1%, see Table S1) overall, 1.4% (95% CI 0.5–2.6; I^2 17.3%, see Table S2) in patients received TNF inhibitors, 6.1% (95% CI 0.0–16.6; I^2 52.1%, see Table S3) in non-TNF biologic DMARDs users and 1.7% (95% CI, 0.2–4.2; I^2 29.0%, see Table S4) in non-biologic DMARDs users (Table 2). There was no statistically significant heterogeneity found overall and neither across the DMARDs subgroups.

Seven studies reported HBV reactivation rate in chronic HBV infection patients without antiviral prophylaxis (6, 17, 29–31, 35, 36) and seven with (5, 6, 13, 17, 30, 36, 39) antiviral prophylaxis. Table 3 shows that the pooled reactivation rates in chronic HBV infection patients with antiviral prophylaxis were lower than those without antiviral prophylaxis in overall (9.0% vs. 14.6%, see Table S5 and S8), and in patients receiving TNF inhibitors subgroup (4.4% vs. 15.6%, see Table S6 and S9), but not in the non-biologic DMARDs (27.1%, 95% CI 12.4–44.8 vs. 22.4%, 95% CI 8.1–40.8, see Table S7 and S10) subgroup. Significant heterogeneity was found in the overall pooled estimates of the DMARDs with antiviral prophylaxis (p for heterogeneity: 0.02) and without antiviral prophylaxis groups (p for heterogeneity < 0.001).

In sensitivity analysis, we excluded studies with a sample size <10 in DMARD subgroups. This excluded three studies in resolved hepatitis B patients receiving non-TNF biologics (7, 12, 38) and one study in non-biologic DMARDs (10). The pooled reactivation rate was 1.0% (95% CI 0.0%–4.6%) in non-TNF biologics and 1.4% (95% CI 0.4%–3.0%) in non-biologic DMARDs group. In the subgroup analysis of chronic HBV infection patients consistently receiving antivirals after non-biologic DMARDs initiation, the pooled rate was 14.8% (95% CI 2.6–32.9; p for heterogeneity 0.58).

DISCUSSIONS

In this systematic review and meta-analysis, we found that among all inflammatory arthritis patients with resolved hepatitis B receiving DMARDs of any type without antiviral prophylaxis, the HBV reactivation rate was low (1.6%). Reactivation rates were similar across patients receiving TNF inhibitors, non-TNF biologics and non-biologic DMARDs. The reactivation rate was substantially higher (14.6%) in chronic HBV infection patients without antiviral prophylaxis. Among all chronic HBV infection patients, including those receiving TNF inhibitors, reactivation rates were lower among those receiving antiviral prophylaxis.

Although relied on small observational studies, the risk of hepatitis B reactivation was consistently reported 0–5% in resolved hepatitis B patients receiving TNF inhibitors (5–7, 10–14, 16, 18, 31–34, 38, 40). In 2014, Cantini et al conducted a meta-analysis for the prevalence of hepatitis B reactivation in 10 studies which included 536 rheumatic and dermatologic patients using DMARDs. They found the overall reactivation rate was 3.0% (p for heterogeneity <0.01) in resolved hepatitis B patients and 2.6% (p for heterogeneity 0.04) in TNF inhibitors users (22). The present meta-analysis added 15 studies and estimated hepatitis B reactivation rates in 1,032 inflammatory arthritis patients with resolved hepatitis B and found an overall rate of 1.6% (p for heterogeneity 0.27) and 1.4% (p for heterogeneity 0.26) in patients receiving TNF inhibitors. We found a similar rate in patients receiving non-biologic DMARDs only (pooled rate: 1.7%) compared with those receiving TNF inhibitors. Expert opinion has suggested that in patients with resolved hepatitis B, non-biologic DMARDs monotherapy is associated with lower relative risk (<1%) for reactivation than biologic DMARD use (19). In studies included in present meta-analysis for non-biologic DMARDs (12, 29, 35, 38), combination treatments (eg, methotrexate plus hydroxychloroquine or sulfasalazine) and low dose glucocorticoids (5–10 mg prednisone per day) were frequently observed. Although American Gastroenterological Association 2015 guidelines stated that the reactivation risk is less than 1% in resolved patients using either non-biologic DMARDs or low dose glucocorticoids alone (19), we estimated a risk of 1.6% after combining non-biologic DMARDs and glucocorticoids.

Previous systematic reviews and meta-analyses did not have adequate sample size to examine the reactivation rates in chronic HBV infection patients with or without antiviral prophylaxis (21, 22). We found the overall reactivation rate was lower in chronic HBV infection patients receiving antiviral prophylaxis (9.0%) than those without prophylaxis (14.6%), and a lower risk for antiviral prophylaxis was also observed in the TNF inhibitor subgroup: 4.4% with prophylaxis vs. 15.6% without. However, we observed higher point estimates (22–27%) in non-biologic DMARDs users without or with antiviral prophylaxis. We compared the characteristics of included studies in both groups and found most of them came from high HBV prevalence countries (e.g., China, Turkey) (29, 30, 39) and 70–80% of patients received DMARDs in combination with glucocorticoids. Further, the prescribing of antivirals may have been targeted to high risk patients. In other words, the use of antivirals seemed to be confounded by indication, i.e., chronic HBV infection status. In the group without antiviral prophylaxis, the prevalence of active chronic HBV infection (HBsAg-positive, HBV DNA >20,000 IU) ranged from 12–30% (29, 30, 35), whereas a rate of 50%

was found in a large study in China among those using prophylaxis (30). Finally, 39% (7 of 18) of patients in this study discontinued antivirals during follow-up and 71% of them developed reactivation (30). These issues all likely may contribute to the higher rates observed in non-biologic DMARDs users than overall estimates, and also contribute to the overall heterogeneity of pooled analyses. Therefore, we performed a sensitivity analysis in a subgroup of patients who consistently received antivirals during follow-up and found a much lower reactivation rate than primary analysis in non-biologic DMARDs users (pooled estimate: 14.8%; 95% CI, 2.6–32.9; p for heterogeneity 0.58) and lower than patients not receiving antivirals. While the absolute reactivation rate remained high (9%) despite the use of antivirals, 5 out of 7 antiviral prophylaxis studies (5, 6, 30, 36, 39) used lamivudine only for HBV reactivation prevention. Drug resistance is common with lamivudine, but much less common with entecavir (41). The American Gastroenterology Association 2015 recommends using antiviral agents with higher barrier to resistance (entecavir, tenofovir or adenovir) for HBV reactivation prevention (19).

Our study included up-to-date studies and a large sample size, capable of providing precise reactivation rates in resolved or chronic HBV infection patients receiving biologic or non-biologic DMARDs and with or without antiviral prophylaxis. However, there were limitations. First, all included studies were observational, non-controlled studies. It is possible that the estimated prevalence of HBV reactivation represents an upper bound as some cases may have been clinically quiescent HBV reactivation, as well most studies come from academic medical center. We only provided the crude reactivation rates which may be confounded by hepatitis B status (eg, HBV DNA or liver enzyme levels) and DMARDs regimens. Analyses were generally homogenous in resolved hepatitis B groups whereas significant heterogeneity was seen in the overall estimates of chronic HBV infection groups. This may reflect the complexity of treatment choices of DMARDs and antivirals in chronic HBV infection patients. Some patients indicated for antivirals cannot receive them due to the economic burden (30). Second, although we initially intended to examine the reactivation rates both in inactive and active chronic HBV infection patients, it was hard to categorize few cases who had HBsAg (+) and HBV DNA >2,000 but less than 20,000 IU without HBeAg data, which was infrequently reported in included studies. Therefore, we think it is more appropriate to report rates in “chronic HBV infection” group by combining active and inactive cases to avoid misclassification bias. Third, we categorized DMARDs exposures based on the baseline information only, which was similar to an intent-to-treat scenario. Misclassification bias may occur especially in non-biologic DMARD group, as patients may switch to biologic DMARDs due to lack of efficacy during follow-up. Details regarding DMARD exposures during follow-up were lacking in the studies examined. Finally, there is a lack of standard quality assessment scores for observational studies included for meta-analysis. Although we adopted the Newcastle-Ottawa Scale to evaluate the quality of included studies, it may not differentiate the quality of included studies, as 22 of 25 studies were regarded as fair quality using the Agency for Health Research and Quality threshold.

In conclusion, our meta-analysis found the hepatitis B reactivation rate was low in inflammatory arthritis patients with resolved hepatitis B and in all subgroups defined by specific DMARDs. The reactivation rates were lower in chronic HBV infection patients receiving antiviral prophylaxis. However, reactivation rates in resolved patients receiving

non-biologic DMARDs exceeded expert opinion estimate of <1%. In the real-world practice, combination of non-biologic DMARDs and glucocorticoids is a common choice for RA patients with moderate to high disease activity (41, 42). Our findings of similar risk between combination of non-biologic DMARDs and glucocorticoids and TNF inhibitors urge the awareness from physicians.

Future larger prospective studies with detailed antivirals exposure record and adjustment for hepatitis B severity are needed to define the effectiveness of antivirals in rheumatology patients. The prevention of hepatitis B reactivation relies on the hepatitis B screening to define the baseline status (no hepatitis B, resolved or chronic) before the start of immunosuppressive agents (26, 43, 44). Our previous work found the hepatitis B testing rate was only 20–25% in the U.S. and Taiwanese RA populations (45). Together with the current findings, it is crucial to improve the physician's awareness for this adverse event and the follow-up risk management plan for high-risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovations

- Our study included up-to-date studies and a large sample size, capable of providing precise reactivation rates in resolved or chronic HBV infection patients receiving biologic or non-biologic DMARDs and with or without antiviral prophylaxis.
- We found that among all inflammatory arthritis patients with resolved hepatitis B receiving DMARDs of any type without antiviral prophylaxis, the HBV reactivation rate was low (1.6%) and remained low in DMARD subgroups.
- Combination of non-biologic DMARDs and glucocorticoids was common in included studies. We found a similar reactivation risk between combination of non-biologic DMARDs and glucocorticoids (1.7%) and TNF inhibitors (1.4%). This finding is higher than expected (~1%) from the American Gastroenterological Association 2015 guideline and urges the awareness from physicians, as combination of non-biologic DMARDs and glucocorticoids is a common choice for RA patients with moderate to high disease activity.
- Among all chronic HBV infection patients, including those receiving TNF inhibitors, reactivation rates were lower among those with antiviral prophylaxis than those without.

Figure 1.
Study inclusion flow chart

Included study characteristics

Table 1

Study	Year	Design	Settings	Country	Disease composition	Screened (N)	HBV prevalence (%)	Lab evidence [†]	Antivirals Prophylaxis	Antivirals	Baseline Glucocorticoids, %	Quality
Xu 2015 (29)	2015	POS	Single center	China	RA	115	46.1%	NO	NO	---	NA	FAIR
Padovan 2015 (17)	2015	ROS	11 centers	Italy	RA	NA	NA	YES	YES	LAM/TEN/ADE	97.20%	GOOD
Mo 2015 (30)	2015	POS	Single center	China	RA	496	7.3%	NO	YES	LAM	81.00%	FAIR
Jin 2015 (31)	2015	ROS	Single center	Italy	PsA, RA, AS	1218	18.1%	YES	NO	---	50.00%	FAIR
Barone 2015 (18)	2015	POS	Single, china	China	RA, PsA	162	19.8%	YES	NO	---	NA	FAIR
Ye 2014 (6)	2014	POS	6 centers	China	RA, AS, PsA	98	88.8%	YES	YES	LAM	NA	GOOD
Nakamura 2014 (7)	2014	ROS	single center	Japan	RA	251	22.7%	NO	NO	---	74.00%	FAIR
Biondo 2014 (32)	2014	POS	Single center	Italy	RA, AS, PsA	169	11.8%	YES	NO	---	65.00%	FAIR
Ballanti 2014 (33)	2014	ROS	Single center	Italy	RA	344	7.6%	YES	YES	LAM	15.60%	FAIR
Laurenti 2013 (8)	2013	Case series	Single center	Italy	PsA	NA	NA	NO	YES	LAM	NA	FAIR
Giardina 2013 (34)	2013	POS	Single center	Italy	RA, AS, PsA	57	33.3%	YES	YES	LAM	59.64	FAIR
Tan 2012 (35)	2012	ROS	7 centers	Korea	RA, AS	NA	NA	YES	YES	LAM/ENT	NA	GOOD
Ryu 2012 (36)	2012	POS	Single center	China	RA	476	45.2%	YES	YES	LAM	NA	FAIR
Kim 2012 (37)	2012	ROS	Single center	USA	RA	NA	NA	YES	YES	ENT, TEN	NA	FAIR
Cho 2012 (9)	2012	Case series	Single center	Taiwan	PsA	NA	NA	YES	YES	ENT	NA	FAIR
Urata 2011 (38)	2011	ROS	Single center	Japan	RA	428	31.5%	YES	NO	---	38.50%	FAIR
Tamori 2011 (10)	2011	POS	Single center	Japan	RA	NA	NA	YES	YES	---	74	FAIR
Prignano 2011 (11)	2011	ROS	Single center	Italy	PsA	300	3.7%	YES	NO	---	NA	FAIR
Mori 2011 (12)	2011	ROS	Single center	Japan	RA	239	25.9%	YES	YES	ENT	63.3	FAIR
Lan 2011 (5)	2011	ROS	Single center	Taiwan	RA	106	83.0%	YES	YES	LAM	100	FAIR
Vassilopoulos 2010 (13)	2010	POS	Single center	Greek	RA, AS, PsA	131	25.2%	YES	YES	LAM, ENT, TEN	NA	FAIR
Caporali 2010 (14)	2010	POS	2 centers	Italy	RA, AS, PsA	732	9.8%	YES	NO	---	64.2	FAIR
Kalyoncu 2009 (39)	2009	ROS	Single center	Turkey	Mixed rheuma	NA	NA	YES	YES	LAM	45.5	FAIR
Chung 2009 (15)	2009	ROS	Single center	Korea	RA, AS, PsA	103	7.8%	YES	NO	---	NA	FAIR
Chapin 2009 (16)	2009	ROS	Single center	France	RA, AS, PsA	504	4.2%	YES	NO	---	NA	FAIR

* **Abbreviations:** POS, prospective observational study; ROS, retrospective observational study; RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis; NA, not applicable; LAM, Lamivudine; TEN: Tenofovir; ADE, Adenovir; ENT, Entacavir; Quality, Newcastle-Ottawa Quality Assessment; F=Fair; G=Good

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Lab evidence = YES: In addition to HBsAg, HBcAb and HBV DNA, a study also reported or included ALT/AST, HBeAg or liver biopsy for differential diagnosis.

Table 2

Pooled HBV reactivation rates in inflammatory arthritis patients with resolved hepatitis B

Resolved HBV*	Antiviral prophylaxis (-)			
	N	Event	Pooled Rate,% (95%CI)	P value**
Summary	1,032	16	1.6 (0.8–2.6)	0.27
TNF-alpha inhibitors	629	8	1.4 (0.5–2.6)	0.26
Non-TNF biologics	69	3	6.1 (0.0–16.6)	0.08
Non-biologic DMARDs	334	5	1.7 (0.2–4.2)	0.23

* Resolved HBV: HbsAg (-), HbcAb (+);

** P value for study heterogeneity within DMARD classes.

In all studies included in this meta-analysis, no patient with resolved HBV was treated with antiviral prophylaxis.

Abbreviations: TNF: tumor necrosis factor; DMARD: Disease Modifying Anti-Rheumatic Drugs.

Table 3

Pooled HBV reactivation rates in inflammatory arthritis patients with chronic HBV infection, with or without antiviral prophylaxis

Chronic* HBV	Antiviral prophylaxis (+)				Antiviral prophylaxis (-)			
	N	Event	Pooled Rate,% (95%CI)	P value**	N	Event	Pooled Rate,% (95%CI)	P value**
Summary***	99	10	9.0 (4.1–15.5)	0.02	160	24	14.6 (4.3–29.0)	<0.001
TNF-alpha inhibitors	57	2	4.4 (0.4–11.7)	0.73	64	11	15.6 (2.3–35.7)	0.05
Non-biologic DMARDs	29	8	27.1 (12.4–44.8)	0.09	58	13	22.4 (8.1–40.8)	0.11

* Chronic HBV: HbsAg (+);

** P value for study heterogeneity within drug classes. TNF: tumor necrosis factor

*** Numbers do not add-up because there was only one study for chronic HBV infection patients receiving non-TNF biologic DMARDs (17) without (N=38) and with (N=13) antivirals, which was not eligible for subgroup analyses. No reactivation was observed in this study.