International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Potency of TNF-α Inhibitors on HBV Reactivation in patients with HBsAg-/anti-HBc+ : A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - No financial support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202570100

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 July 2025 and was last updated on 24 July 2025.

INTRODUCTION

Review question / Objective P: resolved HBV patients; I: use high potency Tumor Necrosis Factor-alpha; C: use low potency Tumor Necrosis Factor-alpha; O: HBV reactivation.

Rationale Tumor necrosis factor-α (TNF-α) inhibitors differ markedly in their immunosuppressive potency, and APASL guidelines currently recommend potency-based HBV reactivation (HBVr) prophylaxis for HBsAg+ patients despite limited head-to-head evidence. In HBsAg-/anti-HBc+ individuals, who comprise a lower-risk subgroup with an approximate HBVr incidence of 2 %, the influence of inhibitor potency remains unclear: existing cohort studies are small, lack direct comparisons, and yield inconclusive results. No systematic synthesis has yet addressed whether high-potency versus low-potency TNF-α inhibitors differentially affect HBVr risk in this population. A rigorous systematic review and meta-analysis is therefore needed to aggregate and critically appraise available observational data, clarify potency-related risk differences, and identify key predictors (e.g., anti-HBs status), thereby informing evidence-based surveillance and prophylactic strategies for HBsAg-/anti-HBc+ patients.

Condition being studied This study focuses on hepatitis B virus reactivation (HBVr) in individuals with resolved HBV infection—specifically those who are HBsAg-negative but anti-HBc-positive—when treated with tumor necrosis factor-α (TNF-α) inhibitors. Although these patients have cleared active infection, HBV remains dormant in hepatocytes and can resume replication under immunosuppressive therapy. Reactivation is defined by the reappearance or significant rise (≥1 $\log_{10}$) of serum HBV DNA, often accompanied by HBsAg seroreversion and, in some cases, hepatitis flares (ALT elevation). HBVr may lead to clinically significant liver injury, interrupt treatment of the underlying inflammatory disease, and, in severe cases, progress to liver failure. This low-incidence but high-impact event warrants systematic evaluation of how different TNF-α

inhibitor potencies influence reactivation risk to guide prophylaxis and monitoring.

METHODS

Search strategy A comprehensive literature search will be conducted in the following electronic databases from inception through 29 May 2025, without language restrictions:
PubMed (MEDLINE)
Embase
Cochrane Central Register of Controlled Trials (CENTRAL)
For each database, we will combine controlled-vocabulary terms (MeSH in PubMed; Emtree in Embase) and free-text keywords for three concept blocks:
TNF-α inhibitors
MeSH/Emtree: "Tumor Necrosis Factor-alpha" [Mesh] / 'tumor necrosis factor alpha'/exp
Keywords: TNF-α inhibitor*, infliximab, adalimumab, golimumab, certolizumab, etanercept
Hepatitis B virus reactivation
MeSH/Emtree: "Hepatitis B"[Mesh] AND "Reactivation"[Mesh] / 'hepatitis b virus reactivation'/exp
Keywords: HBV reactivation, hepatitis B reactivat*, HBVr
Resolved HBV infection
Keywords: HBsAg negative, HBsAg–, anti-HBc positive, anti-HBc+, HBsAg-/anti-HBc+.

Participant or population We will include studies enrolling adult patients (≥18 years) with resolved hepatitis B infection—defined as HBsAg-negative and anti-HBc-positive—who received one or more tumor necrosis factor-α (TNF-α) inhibitors.

Intervention High-potency agents: infliximab, adalimumab, golimumab, certolizumab.

Comparator Low-potency agent: etanercept.

Study designs to be included We will include primary research studies that report hepatitis B virus reactivation (HBVr) outcomes in HBsAg-/anti-HBc+ patients treated with TNF-α inhibitors. Specifically:Randomized controlled trials (RCTs) comparing different TNF-α inhibitors or TNF-α inhibitors versus controlProspective cohort studiesRetrospective cohort studiesCase-control studiesCross-sectional studies.

Eligibility criteria Include studies on adult (≥18 y) HBsAg-/anti-HBc+ patients treated with clearly defined high- or low-potency TNF-α inhibitors that report HBVr by virological or biochemical criteria and provide extractable incidence or RR data.

Exclude case reports/series, reviews, meta-analyses, conference abstracts, animal studies, pediatric (<18 y) or co-infected (HIV/HCV) populations, and any studies without separate HBsAg-/anti-HBc+ subgroup results.

Information sources Electronic databases: PubMed (MEDLINE), Embase, Cochrane CENTRAL
Trial registries: ClinicalTrials.gov, WHO ICTRP
Manual searches: Reference lists of included studies and relevant reviews.

Main outcome(s) Incidence proportion of HBVr events
Pooled risk ratio (RR) comparing high-potency versus low-potency TNF-α inhibitors.

Additional outcome(s)
Predictive factors for HBVr (e.g., anti-HBs status)
Hepatitis flare events (ALT elevations)
Subgroup-specific RRs by drug, region, age, and study design.

Data management Records will be imported into EndNote for duplicate removal and tracking.
Full-text screening by two independent reviewers.
Data will be extracted into a pre-piloted, password-protected Excel template with built-in validation checks; two reviewers extract independently and reconcile via consensus (third reviewer adjudication as needed).
All datasets and extraction logs will be stored on a secure, access-controlled server with regular backups and version control.

Quality assessment / Risk of bias analysis Observational studies: Assessed with the Newcastle–Ottawa Scale
Randomized trials: Evaluated using Cochrane Risk of Bias 2.

Strategy of data synthesis Use a random-effects model to pool risk ratios (RRs) and incidence proportions via inverse-variance weighting.
Heterogeneity: Assess with the I^2 statistic (≥50 % indicating substantial heterogeneity) and Cochran's Q.

Subgroup analysis Pre-specified by potency, individual drug, region, age group, indication, follow-up duration, sample size, risk-of-bias category, study design, and HBVr definition.

Sensitivity analysis Conduct leave-one-out and, where relevant, compare fixed- versus random-effects results.

Language restriction No Language restriction.

Country(ies) involved Taiwan - Dalin Township, Chia-Yi County 62247, Taiwan.

Other relevant information Nil

Keywords TNF-α inhibitors; hepatitis B virus reactivation; HBsAg-/anti-HBc+; immunosuppressive potency; systematic review; meta-analysis; risk ratio.

Dissemination plans Publication in a peer-reviewed, open-access medical journal.
Presentation at international rheumatology, hepatology, and pharmacy conferences.
Submission of the protocol and final report to INPLASY.
Distribution of summary results to professional societies (APASL, ACR) and via institutional websites and social media.
Deposition of extracted data and meta-analysis code in a public repository

Contributions of each author

Author 1 - Meng-Hsuan Kuo - drafting of the article; acquisition of patients and clinical data, analysis, and interpretation of the data; and critical revision for important intellectual content.
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Author 4 - Chen-Chou Lee - interpretation of the data; critical revision for important intellectual content.