

Risk of hepatitis B virus reactivation following treatment with abatacept: A retrospective study of international pharmacovigilance databases

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Summary

Background Abatacept is a selective T-cell costimulation modulator approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis. Reports were recently published on hepatitis B virus reactivation (HBVr) in patients who were treated with abatacept. However, the literature is limited to case reports and series, and no study has investigated the relationship between HBVr and abatacept using extensive population-based databases.

Methods Using the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database, we collected all cases of HBVr between Jan 1, 2006 and June 30, 2021, for abatacept and other drugs. Disproportionality was analysed using the reporting odds ratio (ROR), which was considered significant when the lower limit of the 95% CI was >1. We also conducted a confirmatory analysis in the European pharmacovigilance database, EudraVigilance.

Findings During the study period, 77,669 adverse cases were reported for abatacept use. There were 2889 reports of HBVr with any drug during this period, of which 55 were reported with abatacept. The ROR for HBVr with abatacept was significantly elevated at 4.80 (95% CI 3.68–6.27). All 55 cases of HBVr with abatacept were reported as serious adverse events. Of them, six individuals were hospitalised and four died. Among 832 reports of HBVr with any drug in EudraVigilance, 43 were reported with abatacept; the ROR was 8.99 (95% CI 6.61–12.23).

Interpretation We identified a positive signal between abatacept exposure and HBVr. Future prospective studies should further confirm the relationship and provide evidence to develop strategies involving pre-treatment screening, monitoring, and utilisation of antiviral prophylaxis when using abatacept in patients with rheumatic diseases.

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Keywords: Hepatitis B virus reactivation; Abatacept; FAERS; EudraVigilance

Introduction

Hepatitis B virus (HBV) infection is a major global health problem. It can cause liver diseases, ranging from acute to chronic hepatitis, cirrhosis, and hepatocellular carcinoma.¹ Based on recent estimates by WHO, approximately 300 million people worldwide suffer from chronic HBV infection, with 1.5 million new infections each year.² However, the vast majority of infected

people are unaware that they have chronic HBV infection, or have been exposed to HBV.³

HBV reactivation (HBVr) refers to an abrupt increase in HBV replication in patients with inactive or resolved HBV infection.⁴ HBVr can occur spontaneously but is more frequent in the context of immune suppression or cancer chemotherapy for the management of rheumatological conditions, dermatological conditions, inflammatory bowel disease, organ transplantation, or malignancies.⁴ The manifestations of HBVr range from asymptomatic with only serological or biochemical changes to symptomatic, including liver failure and death.^{4,5} Once HBVr occurs, an interruption in medical therapy might be required for the underlying disease.⁶

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Research in context

Evidence before this study

We searched PubMed on Sept 4, 2021 for publications since database inception using the terms “abatacept” AND “hepatitis B”. The literature for abatacept and hepatitis B virus (HBV) reactivation are limited to case reports and series. Pharmacovigilance databases allow for signal detection between a drug and an adverse drug reaction.

Added value of this study

Our study is the first to investigate the relationship between HBV reactivation and abatacept by using extensive population-based databases. Using the United States Food and Drug Administration Adverse Event Reporting System, we identified a strong positive signal between abatacept exposure and HBV reactivation, and we confirmed it in another pharmacovigilance database EudraVigilance.

Implications of all evidence available

Our study suggested caution should be taken with abatacept use in patients with chronic HBV infection or those with resolved HBV infection and will help prompt utilisation of antiviral prophylaxis and early recognition of HBV reactivation in this population.

Abatacept is a soluble fusion protein that comprises the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the Fc portion of immunoglobulin G1.⁷ CTLA-4, naturally expressed on the surface of T-cells, is a costimulatory molecule that negatively regulates T-cell activation.^{8,9} Abatacept acts as a potent inhibitor of T-cell activation and is approved for treating rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis. However, as CTLA-4 can interfere with HBV-specific T-cell responses, which are crucial for virus clearance, abatacept can cause HBVr in susceptible patients, including patients with chronic HBV infection and those with resolved HBV infection.¹⁰

HBVr events related to abatacept are reported occasionally in case reports,^{11–13} but no definitive data have been established. Therefore, we aimed to investigate the possible relationship between HBVr and abatacept use in clinical practice, using real-world pharmacovigilance data from the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

Methods

Study design and participants

The FAERS is a post-marketing safety surveillance system for drugs and therapeutic biologic products.¹⁴

Healthcare professionals, consumers, and manufacturers submit reports to FAERS. The FDA receives voluntary reports directly from healthcare professionals (e.g., physicians, pharmacists, nurses, and others) and consumers (e.g., patients, family members, lawyers, and others). Healthcare professionals and consumers can also report to the products' manufacturers. If a manufacturer receives a report from a healthcare professional or consumer, it is required to send the report to the FDA as specified by regulations. The reports include information on patient demographics, medication use, adverse events (AEs), indications, outcomes, and report sources. All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The FAERS database receives reports from both the USA and other countries and contained more than 22 million reports from 1968 to June, 2021. The database allows for signal detection and quantification of an association between a drug and an adverse drug reaction. Our study inquired data from the FAERS public dashboard between the first quarter of 2006 and the second quarter of 2021 because abatacept was approved in late December 2005.

Procedures

AE data for patients who received abatacept during the period above were queried using “abatacept”. HBVr in this population was queried using “hepatitis B reactivation”. HBVr cases among patients treated with abatacept were compared to all HBVr events reported in the database due to other drugs and biological products. The same comparison was made with rituximab, a CD20 antibody for the treatment of lymphoma and rheumatoid arthritis, as well as tumour necrosis factor (TNF) inhibitors including adalimumab, certolizumab, etanercept, golimumab, and infliximab for the treatment of autoimmune diseases.⁶ Increased HBVr risks with rituximab and TNF inhibitors have been well documented as high and moderate, respectively.⁶

When available, the following clinical characteristics of reported cases were also collected and analysed: sex, age, reporter type, report countries, reporting year, indications, concomitant product names, and reaction outcomes. Duplicate reports were removed according to the unique case ID and the case characteristics. Cases were compiled into Microsoft Excel 2019.

Statistical analysis

Disproportionality signal analysis was performed by calculating the reporting odds ratio (ROR) with its 95% CI. The ROR is defined as the ratio of two odds. The numerator consists of the odds of the number of reports of HBVr to the interested drug and to other drugs. The denominator consists of the odds of the number of reports of other AEs (non-HBVr) to the interested drug

and to other drugs (Supplementary material, Appendix 1).¹⁵ If the value of ROR is x for abatacept, it means the odds of reporting HBVr with abatacept use is x times of reporting the AE with other medications use in FAERS. When the lower limit of the 95% CI of the ROR was > 1 with at least three cases, the ROR was considered significant. We chose the ROR because it is considered superior to other disproportionality measures.¹⁶ The likelihood of association between interested drugs (abatacept, rituximab, adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) and HBVr was assessed using the two-sided Chi-square or Fisher's exact tests, as warranted. We also conducted a confirmatory analysis in the European pharmacovigilance database, EudraVigilance.¹⁷ EudraVigilance is the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the European Economic Area. EudraVigilance receives data from case reports filed by national drug regulatory agencies and pharmaceutical companies. EudraVigilance first operated in December 2001, although there are cases from Jan 1, 1995 onwards.

All analyses were conducted using Stata/SE 12.0 (StataCorp LP, College Station, TX, US) and statistical significance was defined as $p < 0.05$. Ethical approval and informed consent were not required because the FAERS and EudraVigilance databases are open to the public and patient records are anonymised and deidentified. This study adhered to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement (Supplementary material, Appendix 2).¹⁸

Role of the funding source

The funding source had no role in any aspect of this study including study design, data collection, analysis and interpretation, and the decision to submit for publication. JW, XZ, XG, and WW had full access to the data

and all authors were responsible for the decision to submit for publication.

Results

There were 19,281,040 AE reports between Jan 1, 2006 and June 30, 2021 in FAERS. Among them, 77,669 (0.40%) cases were related to abatacept. During this period, in FAERS there were 2889 (0.015%) reports of HBVr with any drug, of which 55 (1.90%) were reported with abatacept. The ROR for HBVr with abatacept was significantly elevated at 4.80 (95% CI 3.68–6.27; $p < 0.001$; Table 1). The evolution of ROR over time showed that the disproportionality remained constant for the association of abatacept and HBVr (Supplementary material, Fig. S1). Stratified analyses by sex, age, reporter, and reporter region showed that the ROR for HBVr with abatacept was significantly elevated in each stratum (Supplementary material, Table S1).

The disproportionality was also observed in EudraVigilance (Supplementary material, Table S2 and Fig. S2). Among 832 reports of HBVr with any drug, 43 were reported with abatacept; the ROR was 8.99 (95% CI 6.61–12.23; $p < 0.001$) for abatacept in EudraVigilance.

Out of the 55 cases of HBVr with abatacept reported to FAERS, 31 (56.36%) were female, 10 (18.18%) were male, and 14 (25.45%) had sex unspecified. Median age of the case series was 72.5 years. The most common indication for abatacept use was rheumatoid arthritis (90.91%). Most cases were from Japan (34 cases), followed by the USA (5 cases), Italy (5 cases), Taiwan (4 cases), and Canada (2 cases). All patients suffered from serious AEs of HBVr, including six hospitalisations and four deaths with available follow-up. 13 (23.64%) cases had one or more AEs other than HBVr. All individuals who died had additional AEs other than HBVr (Supplementary material, Table S3). Details of the 55 cases of HBVr with abatacept are listed in Table 2.

In 60% (33/55) of cases with HBVr, abatacept was the only suspected drug. In the remaining 40% of cases

Drug	Total AEs	AEs of HBVr	ROR (95% CI)	<i>p</i> value
All drugs in FAERS	19,281,040	2889	—	—
Abatacept	77,669	55	4.80 (3.68–6.27)	< 0.001
Rituximab	117,018	776	60.54 (55.75–65.74)	< 0.001
Adalimumab	501,102	22	0.29 (0.19–0.44)	< 0.001
Certolizumab	63,784	4	0.42 (0.16–1.11)	0.072
Etanercept	516,031	39	0.50 (0.36–0.68)	< 0.001
Golimumab	44,258	23	3.49 (2.31–5.26)	< 0.001
Infliximab	147,129	37	1.69 (1.22–2.33)	0.001

Table 1: AEs of HBVr related to abatacept, rituximab, adalimumab, certolizumab, etanercept, golimumab, and infliximab between January 1, 2006 and June 30, 2021 in FAERS.

AEs: adverse events; CI: confidence interval; FAERS: the United States Food and Drug Administration Adverse Event Reporting System; HBVr: hepatitis B virus reactivation; ROR: reporting odds ratio.

Characteristics	Abatacept (%)	Rituximab (%)	Adalimumab (%)	Certolizumab (%)	Etanercept (%)	Golimumab (%)	Infliximab (%)
Number	55	776	22	4	39	23	37
Sex							
Male	10 (18.18%)	364 (46.91%)	9 (40.91%)	0 (0%)	9 (23.08%)	2 (8.70%)	6 (16.22%)
Female	31 (56.36%)	143 (18.43%)	7 (31.82%)	1 (25.00%)	14 (35.90%)	11 (47.83%)	9 (24.32%)
Not specified	14 (25.45%)	269 (34.66%)	6 (27.27%)	3 (75.00%)	16 (41.03%)	10 (43.48%)	22 (59.46%)
Median age, years (range)	72.5 (47–87), n = 36	64 (7–92), n = 482	54 (22–80), n = 15	44, n = 1	61 (32–73), n = 22	75.5 (71–85), n = 12	63 (20–85), n = 15
Indication for use							
Rheumatoid arthritis	50 (90.91%)	19 (2.45%)	7 (31.82%)	1 (25.00%)	16 (41.03%)	20 (86.96%)	16 (43.24%)
Unknown indication	5 (9.09%)	25 (3.22%)	0 (0%)	1 (25.00%)	3 (7.69%)	0 (0%)	3 (8.11%)
Other indications	0 (0%)	732 (94.33%)*	15 (68.18%)	2 (50.00%)	19 (48.72%)	3 (13.04%)	18 (48.65%)
Suspected drug							
One drug only	33 (60.00%)	90 (11.60%)	8 (36.36%)	2 (50.00%)	23 (58.97%)	9 (39.13%)	13 (35.14%)
Including other drugs	22 (40.00%)	686 (88.40%)	14 (63.64%)	2 (50.00%)	16 (41.03%)	14 (60.87%)	24 (64.86%)
Type of reaction							
Serious	55 (100%)	773 (99.61%)	22 (100%)	4 (100%)	39 (100%)	23 (100%)	37 (100%)
Non-serious	0 (0%)	3 (0.39%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other reactions							
No	42 (76.36%)	225 (28.99%)	2 (9.09%)	1 (25.00%)	19 (48.72%)	15 (65.22%)	11 (29.73%)
1 other reaction	7 (12.73%)	231 (29.77%)	8 (36.36%)	0 (0%)	8 (20.51%)	3 (13.04%)	7 (18.92%)
2 or more other reactions	6 (10.91%)	320 (41.24%)	12 (54.55%)	3 (75.00%)	12 (30.77%)	5 (21.74%)	19 (51.35%)
Outcome [§]							
Died	4 (7.27%)	297 (38.27%)	7 (31.82%)	1 (25.00%)	3 (7.69%)	2 (8.70%)	11 (29.73%)
Hospitalised	6 (10.91%)	148 (19.07%)	7 (31.82%)	1 (25.00%)	2 (5.13%)	5 (21.74%)	7 (18.92%)
Other outcomes	54 (98.18%)	589 (75.90%)	15 (68.18%)	4 (100%)	38 (97.44%)	21 (91.30%)	30 (81.08%)
Reporter							
Healthcare professional	52 (94.55%)	720 (92.78%)	21 (95.45%)	3 (75.00%)	35 (89.74%)	22 (95.65%)	36 (97.30%)
Consumer	3 (5.45%)	45 (5.80%)	1 (4.55%)	1 (25.00%)	4 (10.26%)	0 (0%)	1 (2.70%)
Not specified	0 (0%)	11 (1.42%)	0 (0%)	0 (0%)	0 (0%)	1 (4.35%)	0 (0%)
Areas							
Asia	38 (69.09%)*	373 (48.07%)	12 (54.55%)	0 (0%)	16 (41.03%)	17 (73.91%)	16 (43.24%)
Europe	9 (16.36%)*	214 (27.58%)	6 (27.27%)	3 (75.00%)	11 (28.21%)	3 (13.04%)	10 (27.03%)
Americas	8 (14.55%)*	162 (20.88%)	4 (18.18%)	1 (25.00%)	10 (25.64%)	3 (13.04%)	11 (29.73%)
Other/not specified	0 (0%)	27 (3.48%)	0 (0%)	0 (0%)	2 (5.13%)	0 (0%)	0 (0%)
Year initial report received							
2008	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.56%)	0 (0%)	0 (0%)
2009	0 (0%)	0 (0%)	1 (4.55%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2010	0 (0%)	1 (0.13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2011	0 (0%)	1 (0.13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2012	5 (9.09%)	12 (1.55%)	1 (4.55%)	0 (0%)	2 (5.13%)	0 (0%)	2 (5.41%)
2013	2 (3.64%)	72 (9.28%)	5 (22.73%)	1 (25.00%)	1 (2.56%)	2 (8.70%)	7 (18.92%)
2014	1 (1.82%)	41 (5.28%)	2 (9.09%)	0 (0%)	0 (0%)	0 (0%)	2 (5.41%)
2015	2 (3.64%)	78 (10.05%)	1 (4.55%)	1 (25.00%)	4 (10.26%)	3 (13.04%)	2 (5.41%)
2016	6 (10.91%)	98 (12.63%)	2 (9.09%)	0 (0%)	4 (10.26%)	4 (17.39%)	5 (13.51%)
2017	16 (29.09%)	90 (11.60%)	5 (22.73%)	1 (25.00%)	6 (15.38%)	7 (30.43%)	5 (13.51%)
2018	8 (14.55%)	80 (10.31%)	2 (9.09%)	1 (25.00%)	10 (25.64%)	4 (17.39%)	10 (27.03%)
2019	8 (14.55%)	113 (14.56%)	1 (4.55%)	0 (0%)	3 (7.69%)	2 (8.70%)	2 (5.41%)
2020	7 (12.73%)	147 (18.94%)	1 (4.55%)	0 (0%)	8 (20.51%)	1 (4.35%)	1 (2.70%)
2021 [†]	0 (0%)	43 (5.54%)	1 (4.55%)	0 (0%)	0 (0%)	0 (0%)	1 (2.70%)

Table 2: Characteristics of patients with HBV related to abatacept, rituximab, adalimumab, certolizumab, etanercept, golimumab, and infliximab between January 1, 2006 and June 30, 2021 in FAERS.

* Cases from Asia: Japan 34 and Taiwan 4; cases from Europe: Italy 5, Belgium 1, Spain 1, France 1, and Romania 1; cases from Americas: US 5, Canada 2, and Colombia 1.

Including 639 cases (82.35%) treated for lymphoma or chronic lymphocytic leukemia.

§ Cases with serious reactions could have one or more of the following outcomes: died, hospitalised, and others.

† From January 1, 2021 to June 30, 2021.

FAERS: the United States Food and Drug Administration Adverse Event Reporting System; HBV: hepatitis B virus reactivation.

(22/55), abatacept was suspected with concomitant use of one or more immunosuppressive agents. Methotrexate and prednisolone were the most commonly used drugs concomitantly (Supplementary material, Table S4).

There were 776 reported cases of HBVr related to rituximab in FAERS, with a significantly elevated ROR of 60.54 (95% CI 55.75–65.74; $p < 0.001$). Compared with abatacept and rituximab, fewer HBVr cases were reported for adalimumab, certolizumab, etanercept, golimumab, and infliximab, with the ROR for HBVr ranging from 0.29 to 3.49. Among them, only golimumab and infliximab had significantly elevated ROR (Table 1). Characteristics of patients with HBVr related to rituximab, adalimumab, certolizumab, etanercept, golimumab, and infliximab are shown in Table 2.

Discussion

Abatacept, modulating T-cell activation through the CTLA-4 pathway, has shown good clinical responses in many rheumatic diseases. It has been approved by the US FDA for the treatment of adult rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and adult psoriatic arthritis. Recently, the FDA granted abatacept a breakthrough therapy designation for the prevention of moderate-to-severe acute graft-versus-host disease in patients who are being treated with hematopoietic stem cell transplants from unrelated donors.¹⁹ Since the CTLA-4 pathway is also involved in the initiation and perpetuation of other rheumatic diseases,²⁰ abatacept has been attempted in these conditions, especially in refractory cases with inadequate responses to conventional therapies.²¹

Due to immunosuppressive potency, however, abatacept may result in unintended downstream consequences such as development of new infections or reactivation of underlying infections.²² Since abatacept approval, HBVr has been reported in patients treated with it.^{11–13} To our knowledge, no previous study has investigated the relationship between HBVr and abatacept use by using extensive population-based databases. To do this, we performed disproportionality analysis in the pharmacovigilance database FAERS and validated it in another database EudraVigilance. Data mining of pharmacovigilance databases might provide previously unknown or not well-established, but clinically important associations, and give us useful suggestions to guide clinical decision making.²³ It is especially more advantageous in the case of rare adverse events such as HBVr as our study focused on. In this study, we found that the odds of reporting HBVr with abatacept use is 4.80 times that of reporting the AE with other medication use in FAERS and 8.99 times in EudraVigilance, respectively. These disproportionately high frequencies represent possibly important signals between abatacept use and the increased HBVr risks.

There are some case reports of HBVr in patients with rheumatoid arthritis with abatacept use, including those with resolved HBV infection before abatacept initiation.^{11–13} However, evidence from retrospective cohort studies is inconsistent. Previous three cohorts only observed one case of HBVr during abatacept treatment in 65 patients with rheumatoid arthritis with resolved HBV infection without antiviral prophylaxis (0/9, 0/19, and 1/39, respectively).^{24–26} Recently, a study from China with longer treatment follow-up (median 12.7 years) showed that six out of 69 cases experienced HBVr during abatacept treatment, with an HBVr incidence of 9.38 per 1000 person-years.²⁷ Abatacept use was found to be independently associated with increased risk of HBVr (adjusted hazard ratio: 60.57, 95% CI 6.99–525.15).²⁷ This study supports our findings based on international pharmacovigilance databases. Since HBVr relatively rarely happens, studies with longer follow-ups or using extensive population-based databases are more likely to detect a positive association between HBVr and abatacept use, while studies with shorter follow-ups are less likely to detect the association.

As our study showed, abatacept-associated HBVr can be serious or even fatal. All 55 cases of HBVr with abatacept identified in FAERS were reported as serious adverse events, which means clinically significant hepatitis. Death occurred in four of them (7.3%). The mortality rate is higher than other reports of HBVr (0–4%).²⁸ This high mortality rate in our study could be related to the under-reporting of asymptomatic or mild patients of HBVr in FAERS.

The case series in our study implies that patients with old age (range, 47–87 years) and concomitant use of immunosuppressive agents may be more susceptible to the development of HBVr, as the median age of the case series was 72.5 years and 40% of cases (22/55) had concomitant use of immunosuppressive agents other than abatacept. Older age has been mentioned as a risk factor associated with HBVr,⁵ while evidence lacked for concomitant use of immunosuppressive agents, although, theoretically, it would exacerbate the impairment of immune control of HBV. Further studies can explore whether there is an additive effect when more immunosuppressive agents are used together.

Rituximab, a CD20 antibody used for the treatment of B-cell lymphoma and refractory rheumatoid arthritis, has been clearly shown to increase HBVr risk in susceptible patients.²⁹ HBVr risk by TNF inhibitors (e.g., adalimumab, certolizumab, etanercept, golimumab, and infliximab), used for the treatment of rheumatoid arthritis and other autoimmune diseases, have also been well-demonstrated.⁶ Rituximab and TNF inhibitors are respectively classified as high- and moderate-risk agents by American Gastroenterological Association (AGA).⁶ Our study compared reported HBVr in patients using rituximab and TNF inhibitors to abatacept during the

same period. ROR with abatacept (ROR, 4.80) is lower than rituximab (ROR, 60.54) but higher than TNF inhibitors (ROR, 0.29–3.49) (Table 1). A recent retrospective cohort study including 489 Chinese patients with rheumatoid arthritis and resolved hepatitis B also showed that abatacept is second to rituximab at risk of HBVr, followed by TNF inhibitors.²⁷ The incidence rates of HBVr for rituximab, abatacept, and TNF inhibitors were 17.72, 9.38, and 0.99 per 1000 patient-years, respectively.²⁷ Although abatacept and TNF inhibitors are currently classified as the same risk group that is moderate-risk group for HBVr by AGA,⁶ more concern may need to be given to abatacept as the above data suggested.

CTLA-4 is one of the major coinhibitory molecules that negatively regulates T-cell activation.^{8,9} Previous studies demonstrated that HBV clearance and immune surveillance depends on effective and vigorous HBV-specific CD4+ and CD8+ T-cells.^{30–32} Upregulation of CTLA-4 expression is associated with T-cell exhaustion and HBV persistence in patients with chronic HBV infection.^{10,33} An *ex vivo* study using blood collected from individuals with chronic HBV infection have demonstrated that blockade of CTLA-4 leads to improved HBV-specific CD8+ T-cell function.³⁴ Taking together, abatacept might decrease the function of pre-existing HBV-specific CD4+ and CD8+ T-cells and results in a high risk of HBVr in susceptible patients.

Antiviral prophylaxis can substantially reduce HBVr risk in patients with positive hepatitis B surface antigen (HBsAg) receiving rituximab, abatacept, or TNF inhibitors and is strongly recommended in these patients.^{28,35–37} For previously resolved hepatitis B (HBsAg-negative/anti-HBc-positive), antiviral prophylaxis is also strongly recommended in subjects treated with rituximab due to high HBVr risk but not very clear in those with abatacept or TNF inhibitors who were classified as moderate-risk group.^{28,35–37} Antibody to HBsAg (anti-HBs) can neutralise the virus and is thought to provide immunological protection against HBV infection or re-infection. With the treatment of immunosuppressive agents, levels of anti-HBs may firstly decline, then anti-HBs disappears, indicating loss of protection against HBV, and finally HBVr develops presented with HBV-DNA and HBsAg reappearance.⁴ Therefore, HBVr usually occurs in patients with low levels or absence of anti-HBs.³⁸ According to Chen et al. if the baseline anti-HBs was less than 100 mIU/mL, the long-term cumulative risk of HBVr was as high as 35.4% to 62.5% in abatacept treated patients with resolved hepatitis B.²⁷ Thus, besides monitoring HBsAg and HBV-DNA, management strategy should incorporate the level of anti-HBs in patients with resolved hepatitis B when using abatacept.

The main strength of this study is our ability to detect a serious adverse event that was not observed during the clinical trial stage for abatacept. In clinical trials

evaluating abatacept, the number of enrolled participants with resolved hepatitis B was relatively small and follow-up was not long enough to observe HBVr events. To the best of our knowledge, this is the largest published series of abatacept-associated HBVr cases to date. The data from these cases and the significant signal detected in this study suggests caution should be taken with abatacept use in susceptible patients and will help prompt utilisation of antiviral prophylaxis and early recognition of HBVr in these patients.

As with many studies based on pharmacovigilance databases, our study has some limitations. First, due to the voluntary nature of reporting to FAERS and EudraVigilance, underreporting is expected and reporting bias exists.³⁹ These databases allow signal mining for a specific drug and adverse drug reaction of interest but are not enough to establish their relationship. A causal relationship does not necessarily exist even if disproportionality analysis results are significant. Second, incidence and prevalence of HBVr cannot be calculated, as the total number of patients using these drugs is undetermined. Third, FAERS and EudraVigilance are not independent sources of information and there is a certain overlap of cases between these two databases. Fourth, missing and incomplete information, including medication dosages, timeline to event occurrence, prior chemotherapy, antiviral prophylaxis, antiviral treatment after the notice of reactivation, and patient characteristics including baseline HBV status were not reported in FAERS and EudraVigilance and these may act as contributory factors to reactivation. In addition, abatacept is often a drug that is used in patients with many comorbidities because it is considered to have excellent safety. Therefore, it is possible that patients selected for abatacept treatment are more frail and therefore more exposed to HBVr.

Using FAERS, we identified an association between abatacept exposure and HBVr and validated it in EudraVigilance. Future prospective studies should further confirm the relationship and provide evidence to develop strategies involving pre-treatment screening, monitoring, and utilisation of antiviral prophylaxis when using abatacept in patients with rheumatic diseases.

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Contributors

JW, XZ, XG, and WW conceived of and designed the study. JW and WW acquired the data. JW, XZ, and XG conducted the statistical analyses. All authors interpreted the data. JW, XZ, XG and WW drafted the manuscript. All authors reviewed and contributed revisions to

the final version of the paper. JW, XZ, XG, and WW accessed and verified the data. All authors approved the final version of the paper and were responsible for the decision to submit for publication.

Data sharing

All data can be freely accessed through the FAERS and the Eudravigilance websites.

Declaration of interests

We declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101425.

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