

Hepatitis B virus Reactivation in Patients Receiving Tocilizumab for Rheumatoid Arthritis: A Long-term, Retrospective Observational Study

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Abstract

Aim To investigate the risk of hepatitis B virus (HBV) reactivation in patients undergoing long-term tocilizumab (TCZ) therapy for rheumatoid arthritis (RA).

Method From January 2011 through August 2019, a total of 134 RA patients who received TCZ at Dalin Tzu Chi Hospital were screened. Patients were excluded if they were < 20 years, without complete data, or received TCZ for less than 3 months. A total of 97 patients were enrolled in this retrospective study. Clinical data, co-medications, and the occurrence of HBV reactivation were recorded.

Results Of the 97 enrolled patients, 7 were HBsAg+ (7.2%), 64 were HBsAg-/HBcAb+ (61%) and 26 were HBsAg-/HBcAb+ (26.8%). The median disease follow-up time was 9 years (range, 1–18 years). TCZ was administered for a median of 29 months (range, 3–91 months). Four patients (4.1%) experienced HBV reactivation after TCZ therapy. Of the 7 HBsAg+ patients, 4 received antiviral prophylaxis and had no HBV reactivation; the remaining 3 patients had no antiviral prophylaxis, and all 3 (100%) experienced early HBV reactivation and hepatitis flare (median time to event, 6 months; range, 5–8 months). Hyper-bilirubinemia occurred in 2 of these 3 patients, with mild prothrombin time prolongation in one. After salvage entecavir treatment, all patients had a favorable outcome. Of the 64 HBsAg-/HBcAb+ patients, only one became positive for serum HBV DNA (2.5×10^7 IU/mL) after 18 months of TCZ treatment (1.6%; 1/64). This patient was immediately treated with entecavir, which prevented hepatitis flare.

Conclusions HBsAg+ RA patients undergoing TCZ treatment are at high risk of HBV reactivation, which is prevented by antiviral prophylaxis. HBsAg-/HBcAb+ patients also are at risk of HBV reactivation. Although their risk of reactivation is lower than that of HBsAg+ patients, strict monitoring of their HBV status is still necessary.

Background

The risk for hepatitis B virus (HBV) reactivation during immunosuppressive therapy in patients with chronic or occult HBV infection is increasingly recognized in different disciplines of medicine, including rheumatology.^{1,2} The consequences of HBV reactivation during immunosuppressive therapy range from an asymptomatic increase in serum HBV DNA levels to fatal hepatic failure.³ In rheumatoid arthritis (RA), HBV can be reactivated by changes in the disease course and by drug use.⁴⁻⁷ Inflammatory arthritis patients receiving biologic disease-modifying antirheumatic drugs (bDMARDs) are thought to have a moderate risk (1–10%) of hepatitis B reactivation.⁷ A previous study reports that without antiviral prophylaxis, HBV reactivation occurs in 62.5% of HBV carriers and 25% of patients with occult HBV infection undergoing treatment with tumor necrosis factor- α blockers.⁸

Tocilizumab (TCZ), a humanized monoclonal antibody that selectively neutralizes both the soluble and membrane-bound forms of interleukin (IL)-6 receptor, is a recently developed biological agent that effectively alleviates RA disease symptoms. IL-6 is a cytokine that plays an important role in regulating immune response and inflammation.⁹ Both the soluble and membrane-bound forms of the IL-6 receptor¹⁰ can induce stress pathways and promote the pathogenesis of autoimmunity.¹¹ Current treatment guidelines suggest that patients with HBV surface antigen-positive (HBsAg+) should initiate antiviral prophylaxis before immunosuppressive or cytotoxic therapy.^{7,12,13} However, determining the risk of TCZ-induced HBV reactivation is difficult due to a lack of prospective controlled studies. Several studies have investigated the risk of HBV reactivation in HBsAg+ patients receiving TCZ.¹⁴⁻¹⁶ Although the data are limited, the risk of HBV reactivation in these patients is as high as 60%

(3/5)¹⁴ and may require liver transplantation for hepatic failure.¹⁶ Further evidence shows that HBV reactivation does not occur in HBsAg+ patients receiving anti-HBV prophylaxis.^{14, 15} Most studies report that HBV reactivation does not occur in HBsAg- / HBV core antibody-positive (HBcAb+) patients,^{14, 17-19} although HBV reactivation with DNA reappearance was observed in Japanese studies of a small number of patients.²⁰⁻²²

Because the number of studies investigating HBV reactivation in RA patients treated with TCZ is limited, the optimal management protocol is still unclear. Therefore, the aim of this retrospective, real-world study is to determine the risk of HBV reactivation with long-term TCZ therapy for RA patients in our hospital.

Methods

Patients

We retrospectively reviewed the medical records of RA patients who had received TCZ therapy between January 2011 to August 2019 at Dalin Tzu Chi General Hospital. The inclusion criteria were as follows: (1) fulfilled the RA classification criteria;^{23, 24} (2) available HBsAg and HBcAb status at diagnosis; and (3) treated with TCZ for at least 3 months. Patients were excluded if they were < 20 years of age or lacked required data. In accordance with international guidelines, TCZ was administered at the standard intravenous dose of 4–8 mg/kg every 4 weeks or subcutaneous dosage of 162 mg every 1–2 weeks.²⁵

Follow up of study population

Medical records were reviewed retrospectively. Baseline characteristics included serum markers of HBV (HBsAg, HBcAb, hepatitis B surface antibody [HBsAb], and HBV DNA), anti-hepatitis C virus antibody (anti-HCV), liver biochemical parameters (serum aspartate aminotransferase [AST]; alanine aminotransferase [ALT]), comorbidity, co-medications, and the occurrence of HBV reactivation. Patients were monitored for ALT/AST levels every 3 months, and HBsAg and HBV DNA tests were checked whenever clinically indicated. Detailed medical records were collected, including immunological profiles, TCZ course, previous and concomitant DMARD therapy, and corticosteroid therapy.

Assessment of HBV reactivation and hepatitis flare

The primary endpoint of this study was the HBV reactivation rate. For HBsAg (+) patients, HBV reactivation was defined as an increase in HBV DNA $> 2 \log_{10}$ over that of baseline or an absolute level of HBVDNA $> 4 \log_{10}$ if baseline data were unavailable.¹² A change in HBV DNA titer from negative to positive or HBsAg seroreversion (HBsAg reappearance) was defined in HBsAg (-)/HBcAb (+).¹² Hepatitis flare was defined as an ALT level elevated at least 3 times that of baseline and >100 U/L.¹²

Statistical analysis

The data were analyzed using SPSS 19.0 for Windows (SPSS Inc, Chicago, IL, USA). Categorical variables are presented as counts and percentages, and continuous variables are presented as the median value and range.

Results

General characteristics of the study subjects

The enrolled patient distribution is illustrated in Figure 1. Of the initial 134 RA patients receiving TCZ, 97 remained after exclusions for missing data regarding HBsAg or HBcAb status (n = 25) or receiving TCZ for less than 3 months (n = 12). Of the included 97 patients, 7 were HBsAg+ (7/97, 7.2%) and 90 were HBsAg- (90/97, 92.8%). Of the HBsAg- patients, 64 were HBsAg-/HBcAb+ (64/90, 71.1%) and 26 were HBsAg-/HBcAb- (26/90, 28.9%). Four patients (4/99, 4.1%) experienced HBV reactivation during TCZ treatment.

The clinical, serological, and virologic characteristics and therapeutic regimens of the patient cohort are shown Table 1. The median age was 64 years (range, 38–87), and 75 (77%) were female. The median disease follow-up time was 9 years (range, 1–18 years). TCZ was administered for a median of 29 months (range, 3–91) in combination with methotrexate (71 patients, 73%) or a low dose of glucocorticoids (90 patients, 94%). Seventy-one (73%) patients had a history of other bDMARD treatment. Most patients had previously received adalimumab (45 patients; 46%) or rituximab (25 patients; 26%).

Clinical Features of HBsAg+ patients with HBV reactivation

The general characteristics of the HBsAg+ patients are shown in Table 1. The median age of these patients was 65 years (range, 56–78 years). They received TCZ with median 16 months (range, 4–66 months). Before using TCZ, patients were previously treated with methotrexate (MTX), glucocorticoids, and at least one type of bDMARDs (Table 1). Adalimumab (3 patients; 43%) and rituximab (3 patients; 43%) were the most common bDMARDs.

Of the 7 HBsAg+ patients, 4 (57.1%) received antiviral prophylaxis and none experienced HBV reactivation or hepatitis flare. In contrast, HBV reactivation and hepatitis flare were noted in all 3 patients without antiviral prophylaxis (Figure 1). Clinical data for the patients with HBV reactivation are shown in Table 2. All were female (median age, 77 years; range, 56–78 years), and the median time to reactivation from the initiation of TCZ treatment was 6 months (range, 5–8 months). Hyperbilirubinemia was noted in 2 of the 3 patients, and mildly prolonged prothrombin time was observed in one patient. No acute liver decompensation (i.e., ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal bleeding) was reported. All 3 of these patients received the antiviral agent entecavir, which achieved sustained viral suppression and smooth recovery with no complications. The time course of HBV reactivation is *described below and shown in Figure 2A–C*.

Case 1

A 56-year-old female who was diagnosed with RA in 2006 was treated with adalimumab from June 2011 to Aug 2012. Because her response to this agent was poor, she started TCZ in Sep 2012. In Jun 2013 (after 5 months of TCZ therapy), routine blood tests showed elevated ALT (155 U/L) and a high viral load (3.7×10^7 IU/mL). Under the diagnosis of HBV reactivation, entecavir (0.5 mg/day) was initiated (Figure 2A). After 2 months of antiviral treatment, the HBV viral load had decreased to 301 IU/mL and the ALT level had normalized. TCZ treatment was continued later, and no further adverse events were noted.

Case2

A 77-year-old-female who was diagnosed with RA in 2004 was treated with etanercept for 5 months and rituximab for 20 months. Because her response was insufficient, she began TCZ in June 2012. In Dec 2012 (after 6 months of TCZ treatment), elevated ALT (698 U/L) and a high viral load (1.6×10^7 IU/mL) were noted (Figure 2B). Entecavir (0.5 mg/day) was initiated under the diagnosis of HBV reactivation. Hyperbilirubinemia (maximum, 24.8 mg/dL) and abnormal ALT level (maximum, 946 U/mL) persisted for 4 weeks. Prolonged prothrombin time (INR, 1.81) was also

observed. The ALT returned to within the normal range about 9 weeks later, and the jaundice improved 23 weeks later. TCZ use was discontinued.

Case 3

A 78-year-old-female who was *diagnosed with RA in 2003 was treated with etanercept for 46 doses starting in Jan 2007 and then switched to rituximab for 13 months*. TCZ was initiated in October 2012. Eight months after the first TCZ, she was sent to our ER due to a urinary tract infection. Routine laboratory tests revealed a slightly elevated ALT level (106 U/L) with an HBV viral load of 1.7×10^8 IU/ mL (Figure 2C). Entecavir (0.5 mg/day) was initiated and TCZ administration was stopped. Hyperbilirubinemia (maximum, 4.3 mg/dL) and abnormal ALT level (maximum, 355 IU/mL) persisted for 20 weeks. Thirty-four weeks later, the HBV viral load was undetectable and ALT had returned to within the normal range. TCZ was no longer used.

Clinical Features of HBsAg⁻/HBcAb⁺ patients with HBV reactivation

The general characteristics of the HBsAg⁻/HBcAb⁺ patients are shown in Table 1. The median age of patients was 67 years (range, 38–87 years). They received TCZ treatment for a median time of 26 months (range, 3–84 months). The most common co-medications were methotrexate (47 patients; 73%) and low- to medium-dose glucocorticoids (64 patients, 100%). Forty-five (70%) patients had a history of other bDMARD treatment. Most patients had previously received adalimumab (31 patients; 48%). With TCZ administration, one HBsAg⁻/HBcAb⁺ patient (1/64; 1.6%) experienced HBV reactivation (Figure 1; Table 2). The time course of HBV reactivation is *described below and shown in Figure 2D*.

Case 4

A 67-year-old-female, diagnosed with RA in 2003, had received etanercept for 35 months, adalimumab for 25 months, and rituximab for 25 months. The last dose of bDMARDs was administrated 17 months before she started TCZ (March 2013). After 18 months of TCZ treatment (Oct 2014,) HBsAg seroreversion with serum HBV DNA appearance (2.5×10^7 IU/mL) was observed. Her serum ALT remained stable without evidence of hepatitis flare (Figure 2D). Entecavir (0.5 mg/day) was initiated, and the HBV viral load was undetectable 22 months later. TCZ treatment was continued.

Discussion

Our results show that RA patients receiving TCZ are at risk of HBV reactivation. The risk was very high for HBsAg⁺ patients who were not administered an antiviral prophylactic agent (3/3; 100%). This risk was eliminated by antiviral prophylaxis. HBV reactivation in HBsAg⁺ patients often occurred within the first year of TCZ treatment (median administration time, 6 months; range, 5–8 months) and was associated with hepatitis flare. We also observed one case of HBV reactivation among HBsAg⁻/HBcAb⁺ patients (1/64; 1.6%).

Patients treated with TCZ are at risk for serious infections, including tuberculosis and other opportunistic bacterial, invasive fungal, and viral infections. The European Society of Clinical Microbiology and Infectious Diseases suggests that TCZ use puts patients at modest risk of overall infection.¹³ Because patients with HBV infection were excluded from pivotal TCZ trials,^{26,27} the risk of HBV reactivation was not well reported. Several studies discuss the clinical presentation and risk of HBV reactivation in HBsAg⁺ patients in the absence of antiviral prophylaxis (Supplement Table 1).^{14,16} A prospective study of 5 HBsAg⁺ RA patients receiving TCZ without antiviral prophylaxis

reports an HBV reactivation rate of 60% (3/5).¹⁴ Together with our observation that all 3 HBsAg+ patients without antiviral prophylaxis experienced HBV reactivation, these data indicate a high HBV reactivation rate among HBsAg+ patients taking TCZ and stress the importance of antiviral prophylaxis in these patients.

The early reactivation of HBV observed in our HBsAg+ patients during TCZ therapy is consistent with other reports (Supplement material Table 1).^{14,16} A case study from the Netherlands reports that one HBsAg+ patient experienced HBV reactivation with fulminant hepatitis 2 weeks after a single dose of TCZ.¹⁶ Although antiviral treatment was immediately administered, hepatic failure ensued, requiring liver transplantation.¹⁶ A prospective study from China reports that HBV reactivation occurred 1–3 months after patients received 3 doses of TCZ, with none experiencing hepatitis flare.¹⁴ After antiviral treatment, all of these patients recovered well. In our study, the median time to reactivation from the first TCZ dose was 6 months (range, 5–8 months). All patients with HBV reactivation developed hepatitis flare up, and 2 even had hyperbilirubinemia (2/3; 67%). After entecavir treatment, we observed improvements in liver function (median time to improvement, 4 months; range, 1–5 months) and hyperbilirubinemia (median time to improvement, 5 months; range, 3–6 months). These reports indicate a short interval between the first dose of TCZ and HBV reactivation (Supplemental Table 1) The reactivation may result in fulminant hepatitis despite early preemptive treatment.

In contrast to the high rate of HBV reactivation in HBsAg+ patients without antiviral prophylaxis, none of the HBsAg+ patients who received antiviral prophylaxis experienced HBV reactivation in our study (Figure 1). A similar result was reported in a retrospective study from Taiwan, with no HBV reactivation occurring in 11 HBsAg+ RA patients receiving TCZ with antiviral prophylaxis.¹⁵ For HBsAg+ RA patients receiving TCZ, close monitoring is not enough. Due to the high risk of HBV reactivation, short interval between TCZ administration and reactivation, and possibility of fulminant hepatitis, our results indicate that antiviral prophylactic agents should be given to HBsAg+ patients before TCZ therapy.

The reported rates of HBV reactivation among HBsAg-/HBcAb+ patients under TCZ treatment are inconsistent. Five studies including a total of 120 patients revealed no HBV reactivation events.^{14,17-19,28} Most of those studies included patients taking multiple types of bDMARDs and only a small number taking TCZ (range, 7–30 patients).^{17-19,28} A prospective study in China investigating the short-term safety of TCZ (3-dose treatment and 3 months of observation)¹⁴ reported no HBV reactivation in HBsAg-/HBcAb+ patients (n = 41). Three Japanese studies^{20,21,29} reported total 4 cases of HBV reactivation among HBsAg-/HBcAb+ RA patients receiving TCZ (Supplement material Table 2). In these small cohorts (range, 4–25 patients), the HBV reactivation rates were 4–25%.^{20,21,29} The viral load in 3 of the 4 cases of HBV reactivation fluctuated between undetectable to detectable, and all cases resolved spontaneously without antiviral treatment. Those results are limited by the small case number and short monitoring time but suggest that TCZ treatment is safe for HBsAg-/HBcAb+ patients.

Our cohort included 64 HBsAg-/HBcAb+ patients who received TCZ for a median time of 26 months (range, 3–84 months). Of these patients, only one experienced HBsAg seroreversion with a high HBV viral load (2.5×10^7 IU/mL); thus, the HBV reactivation rate was 1.6% (1/64) among HBsAg-/HBcAb+ RA patients. This result indicates that HBsAg-/HBcAb+ RA patients receiving TCZ are at risk for HBV reactivation. The monitoring of HBV-DNA and HBV seromarkers every 3–6 months can identify HBV reactivation at an earlier stage and should be suggested in this population.

This study has several limitations. First, the retrospective, observational design precludes the control of numerous factors, and some data are missing. However, our investigation includes the largest cohort of any study of this subject. Because of the large number of person-years of follow up, our findings nonetheless provide important information regarding treatment decisions for prophylaxis and monitoring in this population. Second, our study only enrolled Asian patients; whether our findings are applicable to other populations is uncertain.

Conclusion

RA patients receiving TCZ therapy should be assessed for risk of HBV reactivation using HBV seromarkers. While this risk is very high in HBsAg+ patients, HBV reactivation can be prevented by the administration of antiviral prophylactic agents. For HBsAg-/HBcAb+ patients, the risk of HBV reactivation is lower but still present. We recommend the monitoring of HBV-DNA and HBV markers in this patient population.

Abbreviations

ALT, alanine aminotransferase;

AST, aspartate aminotransferase;

HBV, hepatitis B virus;

HBsAg, HBV surface antigen;

HBcAb, HBV core antibody;

HBsAb, HBV surface antibody;

HCV, hepatitis C virus;

IL, interleukin;

RA, rheumatoid arthritis;

sDMARDs, synthetic disease-modifying antirheumatic drugs;

bDMARDs, biological disease-modifying antirheumatic drugs;

TCZ, tocilizumab;

T. bil, total bilirubin

Declarations

Ethics approval and consent to participate

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by a priori approval by the Ethics Committee of Dalin Tzu Chi General Hospital (approval number B10901013). The requirement for informed consent was waived because this study was retrospective in nature and the data analyzed did not include patient identification.

Consent for publication

Not applicable.

Availability of data and materials

Please contact the author for data requests.

Competing interests

The authors declare no financial and non-financial interests.

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Author contributions

Meng Hsuan Kuo: material support, drafting of the manuscript

Chih-Wei Tseng: statistical analysis, material support, critical revision of the manuscript for important intellectual content

Ming-Chi Lu: critical revision of the manuscript for important intellectual content

Chien-Hsueh Tung: critical revision of the manuscript for important intellectual content

Kuo-Chih Tseng: material support, critical revision of the manuscript for important intellectual content

Kuang-Yung Huang: critical revision of the manuscript for important intellectual content

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Tables

Table 1. Patient baseline characteristics.

	All (N = 97)	HBsAg+ (N = 7)	HBsAg-/HBc Ab+ (N = 64)
Age (years) [#]	64 (38-87)	65 (56-78)	67 (38-87)
Sex, Female n (%)	75 (77%)	5 (71%)	49 (77%)
Follow up time (years) [#]	9 (1-18)	9 (2-14)	9 (1-18)
Duration of TCZ infusion (months) [#]	29 (3-91)	16 (4-66)	26 (3-84)
Anti-HCV (+), n (%)	14 (14%)	1 (14%)	11 (17%)
Antirheumatic therapies before TCZ use, n (%)			
sDMARDs			
Methotrexate	91 (94%)	7 (100%)	62 (97%)
Azathioprine	3 (3%)	0 (0%)	3 (5%)
Cyclosporine	15 (15%)	3 (43%)	9 (14%)
Leflunomide	45 (46%)	3 (43%)	26 (41%)
Sulfasalazine	85 (88%)	6 (86%)	57 (89%)
Glucocorticoid (oral)*	96 (99%)	7 (100%)	63 (98%)
bDMARDs			
Abatacept	10 (10%)	1 (14%)	8 (17%)
Adalimumab	45 (46%)	3 (43%)	31 (48%)
Etanercept	22 (23%)	2 (29%)	11 (17%)
Golimumab	13 (13%)	1 (14%)	8 (13%)
Rituximab	25 (26%)	3 (43%)	12 (19%)
bDMARDs naïve	26 (27%)	0 (0%)	19 (30%)
Concomitant, n (%)			
Methotrexate	71 (73%)	4 (57%)	47 (73%)
Glucocorticoid (oral)*	96 (99%)	7 (100%)	64 (100%)
equivalent dose (mg) [#]	5 (2-10)	5 (2.5-7.5)	5 (2-10)
Low dose	90 (94%)	7 (100%)	58 (91%)

Moderate dose	6 (6%)	0 (0%)	6 (9%)
Azathioprine	1 (1%)	0 (0%)	1 (2%)
Cyclosporine	4 (4%)	1 (14%)	3 (5%)
Leflunomide	21 (22%)	0 (0%)	13 (20%)
Sulfasalazine	45 (47%)	3 (43%)	28 (42%)

#Data are presented as the median (range)

*Glucocorticoids (oral): cortisone, prednisolone, methylprednisolone, dexamethasone

Prednisolone equivalent dose (mg/day): High dose, >20 mg/day \geq 4 wk; Moderate dose, 10-20 mg/day \geq 4 wk; Low dose, <10 mg/day \geq 4 wk

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, HBV surface antigen; HBcAb, HBV core antibody; TCZ, tocilizumab; bDMARDs, biological disease-modifying antirheumatic drugs; sDMARDs, synthetic disease-modifying antirheumatic drugs

Table 2. Clinical features of RA patients who developed HBV reactivation during tocilizumab therapy.

	HBsAg+			HBsAg–/HBc Ab+
data source	Case 1	Case 2	Case 3	Case 4
Age/Sex	56/F	77/F	78/F	67/F
Age at disease onset (year)	11	14	11	15
TCZ dose at reactivation	5	6	8	18
HBsAg	-	-	-	+
HBsAg reversion				
HBsAb	N	N	N	N
Anti-HCV	NA	NA	N	N
HBV DNA (peak, IU/mL)	3.7 x10 ⁷	1.6 x10 ⁷	1.7 x10 ⁸	2.5 x10 ⁷
HBV DNA (initial/peak, IU/mL)	155/155	698/946	106/355	98/107
Bilirubin (initial/peak, mg/dL)	0.6/1.3	2.2/24.8	1.1/4.3	0.5/0.5
HBV reactivation	N	N	Y	N
Ascites	N	N	N	N
Hepatic encephalopathy	N	N	N	N
Hepatitis flare	Y	Y	Y	N
HBV reactivation treatment	ETV 0.5 mg	ETV 0.5 mg	ETV 0.5 mg	ETV 0.5 mg
Outcome	alive & well	alive & well	alive & well	alive & well
Antirheumatic therapies before TCZ				
DMARDs	ADA (14)	ETN (5)/Rituximab	ETN	ETN (35)/ADA

months)		(20)	(46)/Rituximab (13)	(25)/Rituximab (25)/
sDMARDs	MTX/Pd/SSZ/CSA	MTX/Pd/SSZ/LEF/CSA	MTX/Pd/SSZ/LEF	MTX/Pd/SSZ/LEF
oncomitant immunosuppressants				
MTX (mg/week)	0	7.5	7.5	7.5
Prednisolone equivalent dose (mg/day)	5	7.5	7.5	7.5
sDMARDs	N	SSZ	SSZ	SSZ

Entecavir, ETV; NAA, nucleic acid analogue; IFX, infliximab; TAC, Tacrolimus; RA, rheumatoid arthritis; HBV, hepatitis B virus; HCV, hepatitis C virus; F, female; TCZ, tocilizumab; HBsAg, HBV surface antigen; HBc Ab, antibody against HBV core antigen; ALT, alanine aminotransferase; IU, international units; T.bil, Total Bilirubin ;PT, prothrombin time; sDMARD, Pd, prednisolone; MTX, methotrexate; LEF, leflunomide; SSZ, sulfasalazine; CSA, cyclosporine, bDMARDs, ADA, adalimumab; ETN, etanercept; NA, not applicable; N, not happened; Y, happened

Figures

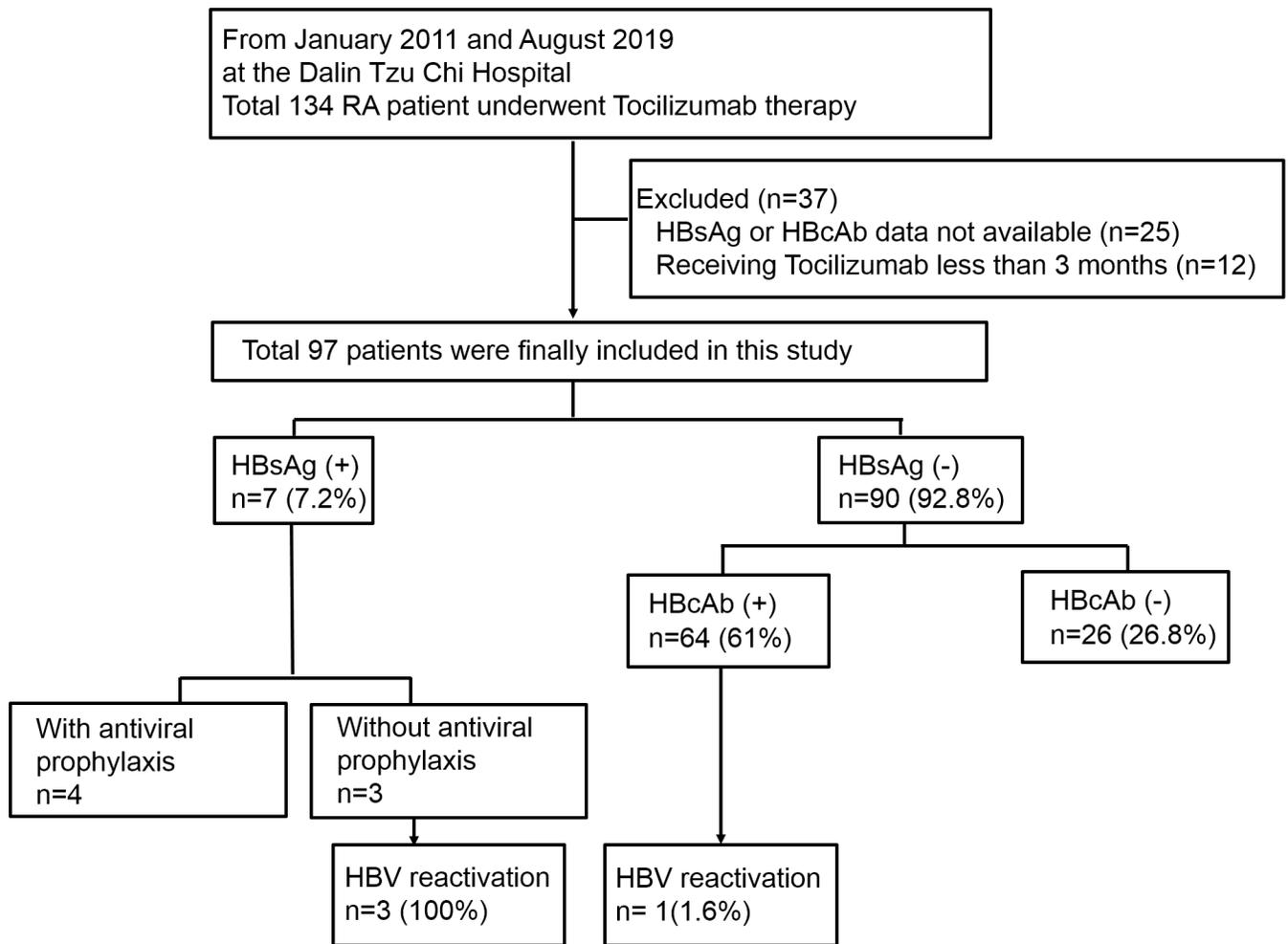


Figure 1

Flow diagram of study cohort characteristics. 2 Flowchart shows the hepatitis B virus (HBV) infection serostatus distribution at baseline and 3 the occurrence of HBV reactivation in rheumatoid arthritis (RA) patients treated with 4 tocilizumab. 5 Abbreviations: HBsAg, HBV surface antigen; HBCAb, HBV core antibody

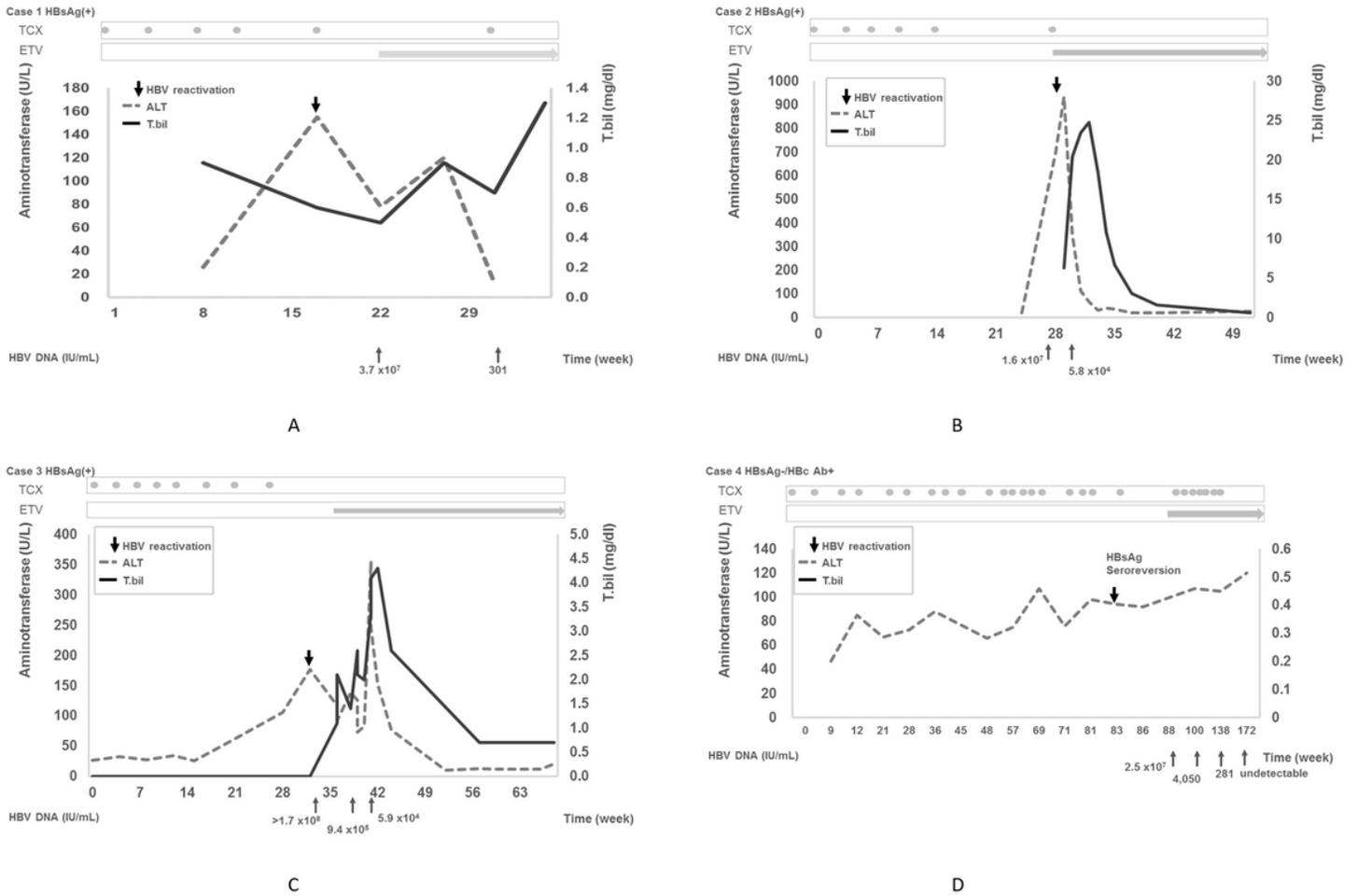


Figure 2

Time course of serum alanine aminotransferase and total bilirubin 1 concentrations in patients experiencing HBV reactivation. 2 Abbreviations: ALT, alanine aminotransferase; T. bil, total bilirubin; HBV, hepatitis B virus; 3 HBsAg, HBV surface antigen; HBcAb, HBV core antibody; TCZ, tocilizumab; ETV, entecavir

Supplementary Files

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- [LaTeXSupportingFiles.pdf](#)