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Research Letter

Prevalence of Hepatitis B Core Antibody in Intravenous Immunoglobulin Products by Chemiluminescent Microparticle Immunoassay

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Intravenous immunoglobulin (IVIG) is a diverse collection of antibodies derived from healthy donors. IVIG is used for a myriad of autoimmune disorders, inflammatory conditions, and immunodeficiencies. These products may contain clinically significant antibodies. Previous studies have identified transient positivity of hepatitis B core antibody (HBcAb) after administration of IVIG.[1–3] However, IVIG administration does not increase the risk of reactivation of hepatitis B virus (HBV); hence, obtaining serologies is not standard of care before IVIG administration. In clinical practice, this may lead to inappropriate administration of antiviral therapy and delays in immunotherapy or chemotherapy due to the perceived risk of HBV reactivation with immunosuppressive agents. We aimed to determine the prevalence of hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) in IVIG from commercial sources in the United States using chemiluminescent microparticle immunoassay.

This study was conducted at a single academic center in the United States. Remnants of commercial IVIG from different manufacturers used for patient treatment at the infusion center were obtained for analysis. Assuming a physiological extracellular concentration of IVIG at 8.8 mg/mL for a 70 kg patient, 100 µL of 8.8 mg/mL from IVIG samples were analyzed on Abbott Alinity i (immunoanalyzer). This constituted 53 IVIG samples from Gammagard S/D, Gammagard Liquid, Privigen, and Gamunex-C. Positive and negative discarded serum samples, saline, and IVIG were analyzed on the Abbott Alinity i to determine the concentrations of HBsAb and HBcAb. The analysis of IVIG samples for HBcAb and HBsAb measurements was treated similarly to how a serum sample would be categorized as nonreactive, grayzone, or reactive.

For HBsAb testing, 53/53 (100%) samples tested positive. In testing for total HBcAb, 36/53 tested positive (67.9%), 10/53 were indeterminate (18.9%), and 7/53 were nonreactive (13.2%) (Table 1). Results from HBcAb discarded serum samples as positive control and saline as negative control are shown in Figure 1. The prevalence of HBcAb and HBsAb varied based on the batch of IVIG administered.

In 2022, the rate of chronic HBV in the United States was 5.8 cases per 100,000 people, reflecting an approximate prevalence of 0.3%.[4] This is in comparison to countries with significantly higher endemicity, such as East Asia, where prevalences range from 5% to 10%.[5] HBsAb is a marker for vaccination, and HBcAb is interpreted as a marker of exposure (current or past infection). The natural course of chronic HBV infection can be divided into immune tolerance, immune clearance, low or non-replication, and reactivation phases.[6] HBV reactivation has been reported in 20 to 50% of HBV carriers undergoing immunosuppressive therapy or chemotherapy.[7] Preventive treatment with antivirals is generally suggested prior to considering the administration of agents such as rituximab (a CD20 monoclonal antibody) to reduce the risk of HBV reactivation in patients with evidence of previous hepatitis infection.[8] Manifestations range from asymptomatic aminotransferase elevation to acute hepatic failure secondary to moderate to severe liver tissue inflammation and/or fibrosis.[6] Multiple case reports of positive hepatitis B screening results post-IVIG infusion have been described in the literature. In a single-center cohort study on IVIG in patients with skin disease, all patients had detectable HBsAb, and 70% had HBcAb by week four after IVIG administration; none had evidence of infection by serology prior to treatment with IVIG.[9]

Similarly, a cross-sectional study of HBV antibody prevalence in a cohort of patients receiving immunoglobulin showed that 46.3% of patients tested positive for HBcAb, and 100% of patients tested positive for HBsAb.[10] In this study, titers correlated negatively with time since infusion, likely related to IVIG's half-life (three to four weeks), suggesting passive transfer. Differences in rates of HBcAb positivity according to the product were also described. Another

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Table 1. HBcAb results in IVIG samples

	Nonreactive	Grayzone	Reactive
Number of positive HBcAb IVIG	7	10	36
Percentage of total IVIG	13.2%	18.9%	67.9%

The number and percentage of IVIG samples that fall into the three categories: Nonreactive is defined as values <0.80; Grayzone is defined as values from 0.80 to <1.21; and Reactive is defined as values ≥1.21. HBcAb, hepatitis B core antibody; IVIG, intravenous immunoglobulin.

study assessed the probability of passive transfer in patients with cancer, identifying a predicted probability of HBcAb positivity of 34%, which decreased to 4% after three months.[1] Published reports in the literature reflect the potential for dangerous delays in appropriate therapy resulting from the finding of positive hepatitis B core antibody testing prior to immunosuppressive therapy, including lifesaving chemotherapy, and disease-modifying biologics.[2,11] In our own practice, we have anecdotally encountered several patients referred to Infectious Diseases for positive core total antibody results in anticipation of immunosuppressive therapy for inflammatory disorders, with no known risk factors and negative surface antigen and antibody. All had received IVIG and later cleared the core antibody. This can lead to confusion, stress, and unintended consequences among patients and their referring providers. In some cases, patients had undue delays in immunosuppressive therapy due to concern for possible hepatitis B reactivation, and some received unnecessary antiviral therapy. All of this could be avoided by highlighting the relatively high prevalence of HBcAb in US-sourced IVIG, and if HBV serologic testing, including HBcAb, is undertaken before IVIG is administered.

Notable limitations of this study are related to the limited information available from manufacturers about the content and sources of the IVIG preparation used and the lack of correlation with actual patient outcomes. Given the significant differences in the prevalence of chronic hepatitis B in the United States versus other countries and considering that core total antibody is a marker of HBV exposure, we presume that IVIG sourced from high-prevalence countries would have higher levels of core antibody than US-sourced IVIG. We do not have access to information regarding the content of IVIG sourced outside the US, and in fact, when queried, the relevant manufacturers in this study would not provide more specific information other than that the IVIG products were "US-sourced".

Our findings correlate with multiple case reports of positive hepatitis B screening results in post-IVIG infusion, which could have been secondary to passive transfer. Given the low prevalence of chronic HBV, true infections seem unlikely to explain these findings. Interpretation of these results is complex, as testing for HBV is not generally indicated prior to IVIG administration. The discrepancy identified between the very low prevalence of chronic HBV in the US and the relatively high level of core total antibody in US-sourced IVIG in this study is notable, and we believe it is unique and clinically important, given the increasing number of patients receiving IVIG and immunosuppressive therapies who may be affected by this issue. The high prevalence of HBcAb and HBsAb in our IVIG samples supports serological testing prior to IVIG administration to avoid delays in treatment and may help avoid unnecessary exposure to antiviral therapy for prevention of HBV reactivation in patients undergoing immunosuppressive therapy. Physicians may consider serial testing for conversion to nonreactive based on the half-life of IVIG to confirm

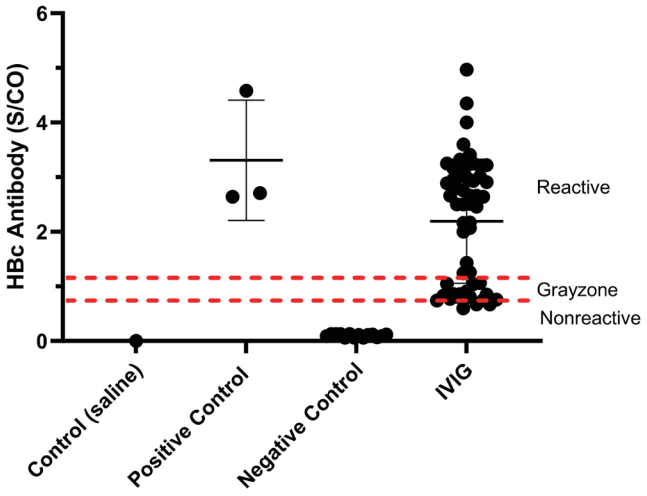

Fig. 1. HBcAb in IVIG and controls. HBcAb, hepatitis B core antibody; IVIG, intravenous immunoglobulin.

that the positivity of hepatitis antibodies on serologic testing is secondary to passive transfer rather than chronic infection. Our results aim to increase awareness among physicians about the possibility of the passive transfer of hepatitis antibodies through IVIG products.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Study design, conceptualization (ASM, KD, LC, JK), methodology, technical support (ASM, RAB), data analysis (ASM, JK, LC, KD, LV), manuscript drafting (LV, WM,), critical revision of the manuscript, and editing (LC, KD, ASM). All authors have read and approved the final manuscript.

Ethical statement

This manuscript does not involve human subjects or animals. Neither involves an individual person's data in any form.

Data sharing statement

All data supporting the findings of this study are available within the paper.

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