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BRIEF REPORT

Product Choice Affects Risk of False-Positive Hepatitis B Virus Serology During Immunoglobulin Replacement Therapy

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Hepatitis B virus (HBV) core antigen antibodies passively transferred from immunoglobulin products used for replacement or immunomodulation may lead to unnecessary antiviral treatment for patients who are also starting immunosuppressive treatment. We have systematically assessed the contents of 93 commercial immunoglobulin batches and show that there are consistent product-specific differences in the levels of HBV core antigen antibodies and that choice of immunoglobulin product may have an impact on false-positivity rates.

Keywords. Common variable immunodeficiency; HBV core antigen antibodies; Hepatitis B virus; Immunoglobulin replacement therapy; Passive immunity.

Donor-derived immunoglobulin (Ig) products are used as immunomodulatory treatment for autoimmune diseases and as Ig replacement therapy (IgRT) for patients with increased infectious susceptibility due to primary or secondary antibody deficiency. The IgG specificities represented in each batch reflect the immune status of the plasma donor population. One thousand or more donors are pooled for each product batch, which makes the content insensitive to individual variation. However, manufacturers of Ig products may systematically acquire plasma from certain sources, which could influence the content of specific IgG in their products. The aim of this study was to test if commonly used Ig products are associated with differences in specific IgG content that are consistent over time. Here we focused on hepatitis B virus (HBV) serology because false-positive results, due to passive transfer from Ig products, can be particularly problematic for patients in need of immunosuppressive therapy (IST).

Patients with common variable immunodeficiency (CVID) generally receive IgRT due to increased infectious susceptibility but can occasionally develop lymphoproliferative disease, which is associated with poor prognosis and requires IST [1, 2]. Moreover, several autoimmune diseases are treated with intravenous Ig before long-term IST is started [3]. To avoid HBV reactivation while on IST, screening for HBV infection is performed before treatment is started [4]. Two serological tests are routinely performed for HBV: HBV core antigen IgG (anti-HBc), a marker of current or past infection, and HBV surface antigen IgG (anti-HBs), a marker of past infection or vaccination. If screening yields a positive result for anti-HBc, it is not possible to distinguish chronic HBV infection from false-positive results from donor-derived Ig products. In this situation it is often advised to initiate prophylactic antiviral treatment, which is associated with increased costs and potential adverse events [5, 6]. Thus, there is a solid rationale to study whether specific IgRT products are associated with anti-HBc reactivity.

MATERIALS AND METHODS

Ninety-three commercial Ig batches used at the Immunodeficiency Unit at Karolinska University Hospital were prospectively sampled and later analyzed. Three manufacturers referred to as A, B, and C were represented with 1 or more products referred to as A_1, A_2, A_3, B_1, C_1, and C_2. Product IgG concentration ranged from 100 to 200 g/L, but the concentration of all samples was adjusted to 25 g/L by dilution with phosphate-buffered saline prior to analysis. The production dates ranged from May 2017 to April 2022. Antibodies were analyzed on a Cobas 8000 workflow using the kits Elecsys Anti-HBc II and Elecsys Anti-HBs II (Roche, Basel, Switzerland) in an accredited clinical laboratory. Anti-HBc II is a qualitative assay based on a competitive principle resulting in inhibition of the signal by anti-HBc in the sample, termed the cutoff index. The assay classifies samples as positive or negative but, for the purpose of this study, we plotted the obtained signal from the Ig products as an approximation of the anti-HBc content. Patient serum samples were analyzed with the same assay as part of their clinical care.

RESULTS

Anti-HBc values varied dependent on product type ($P = 1.7 \times 10^{-8}$, Kruskal-Wallis 1-way analysis of variance; Figure 1*A*)

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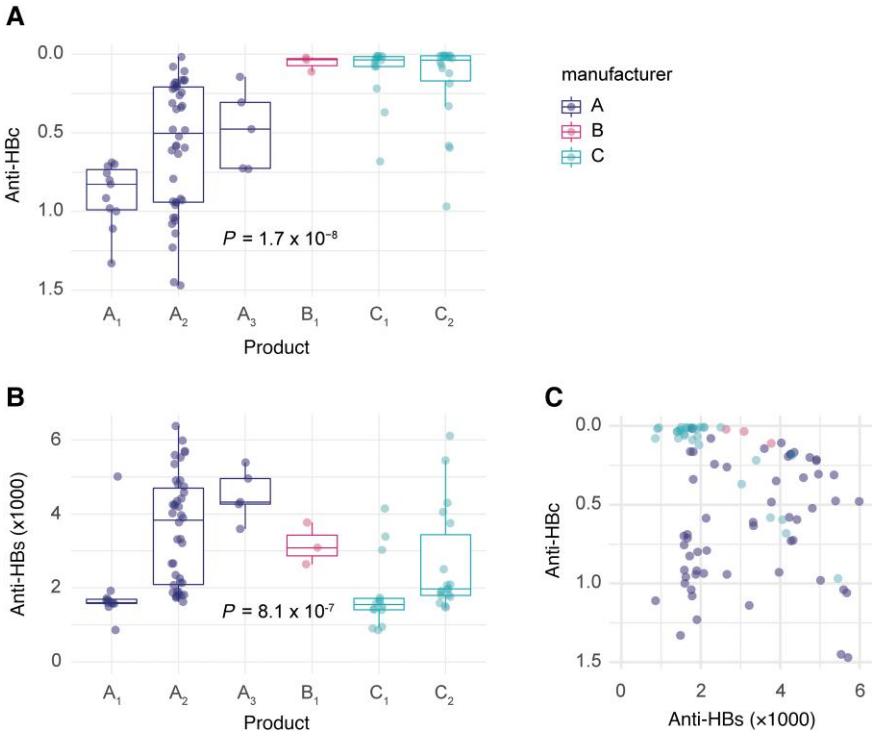

Figure 1. Anti–hepatitis B virus core antigen (HBc) (*A*) and anti–hepatitis B virus surface antigen (HBs) (*B*) immunoglobulin G (IgG) in immunoglobulin products from 3 manufacturers referred to as A, B, and C. Dots represent unique production batches. Anti-HBc was assessed using a competitive assay and samples with high IgG quantities give results that approach zero. *P* values were calculated for the 6 products using Kruskal-Wallis 1-way analysis of variance. (*C*) The correlation between anti–HBc and anti–HBs values in individual immunoglobulin products from the three manufacturers was assessed.

Table 1. Anti–Hepatitis B Core Antigen Results in Patients With Common Variable Immunodeficiency Who Had Changed to Another Immunoglobulin Replacement Therapy Product

				IgRT Product		Anti-HBc Result		
Patient	Age, y	Sex	Indication for IST	Before	After	Before	After	Reanalysis[a]
1	24	F	GLILD	C_1	A_2	Positive	Negative	16 d
2	60	F	AID, LPD	C_1	A_1	Positive	Negative	106 d
3	61	M	LPD	C_1	A_1	Positive	Negative	142 d

Abbreviations: AID, autoimmune disease; F, female; GLILD, granulomatous lymphocytic interstitial lung disease; HBc, hepatitis B virus core antigen; IgRT, immunoglobulin replacement therapy; IST, immunosuppressive treatment; LPD, lymphoproliferative disease; M, male.

[a]Reanalysis is the time that had passed between product change and blood sampling for reanalysis of anti-HBc.

and manufacturer ($P = 1.6 \times 10^{-9}$). Interestingly, products from manufacturer A consistently contained lower quantities of anti-HBc compared to manufacturer C. We could also observe consistent differences within the various products from manufacturer A, with product A_1 containing lower amounts of anti-HBc antibodies compared to A_2 and A_3 ($P = .01$, Wilcoxon signed-rank test). The 3 batches from manufacturer B had similarly high quantities of anti-HBc as the batches from manufacturer C. Next, the levels of anti-HBs were assessed (Figure 1*B*), which also displayed product-dependent variation with the lowest values in A_1 and C_1. There was a weak negative correlation between anti-HBc and anti-HBs quantities when considering all batches together ($r = -0.28$, $P = .007$, Spearman correlation; Figure 1*C*), but this correlation essentially originated from the products from manufacturer C ($r = -0.41$, $P = .02$). To assess the clinical relevance of these product-specific differences in anti-HBc quantities, we identified patients on IgRT at our clinic with a positive result for anti-HBc (Table 1). Three patients were identified, and all were treated with C_1 at the time of testing. Importantly, the IgRT products were then switched to A_1 or A_2 and negative anti-HBc results were obtained for all 3 patients upon reanalysis.

DISCUSSION

Reactivation of chronic HBV infection due to IST is a concern, but the risk is difficult to assess in patients on Ig treatment, including patients with CVID or autoimmune diseases. Given the serum half-life of IgG from IgRT of up to 41 days [7], false-positive serological results may remain for months after treatment cessation. If a patient is screened positive for anti-HBc, IST may be withheld or prophylactic antiviral treatment started. It has previously been shown that intravenous or subcutaneous IgRT occasionally is the cause of misleading anti-HBc results, and it has been suggested that manufacturer-specific donor selection could be a potential cause [8–10]. HBV seroconversion after commencement of IgRT was analyzed in 80 patients in a previous study by Ramsay et al [9]. Anti-HBc results were negative in all patients at baseline, but 37 of 80 (46.3%) had seroconverted after 6 months. Interestingly, among the IgG products that were not associated with seroconversion in that study is manufacturer A, which had a relatively low signal for anti-HBc in our study. Moreover, all products from manufacturer B and C in the study of Ramsay et al were associated with higher rates of seroconversion, also consistent with our results [9].

Ideally, HBV serology should be performed before starting treatment with donor-derived IgG, and if a positive serological result is obtained within 3–4 months after starting the treatment, this is likely passively transferred antibodies. However, for patients who receive long-term continuous IgRT, this strategy is usually not appropriate. However, in this report we show that switching to an Ig product known to contain insignificant amounts of anti-HBc antibodies may be an option.

Notes

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Patient consent. All patients provided written informed consent prior to inclusion in the study. The study was approved by the Swedish Ethical Review Board (dnr 2011/116-31 + 2020/00125).

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Potential conflicts of interest. All authors: No reported conflicts.

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