Humoral responses to BNT162b2 SARS-CoV-2 and hepatitis B vaccines are associated in patients on maintenance hemodialysis: a single-center experience in Belgium

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Maintenance hemodialysis (HD) patients are at high-risk for life-threatening coronavirus disease 2019 (COVID-19) [1]. Recent studies have documented a strong humoral response after SARS-CoV-2 vaccination in this population [2], even in older patients [3], in contrast to kidney transplant recipients [4]. Previous reports have also shown a poor humoral response after hepatitis B virus (HBV) vaccination in chronic kidney disease patients with comorbidities (*e.g.* older age, diabetes, immunosuppression) [5] [6]. We therefore hypothesized that this weak response to the HBV vaccine could serve as a potential indicator of response to SARS-CoV-2 vaccination. However, data linking humoral responses to both vaccines remains scarce and contradictory [7] [8].

We retrospectively studied the association between the humoral response to HBV and BNT162b2 spike mRNA vaccines in a cohort of adult patients on in-center maintenance (≥3 months) HD at Cliniques universitaires Saint-Luc and its satellite site. We excluded 58 patients who had a history or serologic evidence of HBV (n=27) or SARS-CoV-2 infection (n=15), refused vaccination (n=11) or had an incomplete HBV vaccination (n=5). Demographics, dialysis vintage, diabetes status, immunosuppressive treatment if applicable and time since last SARS-CoV-2 and HBV vaccine administrations were recorded. In each patient, a single sample was tested simultaneously with five electro-chemiluminescent immunoassays (Roche Elecsys): SARS-CoV-2 recombinant nucleocapsid antigen antibody (anti-SARS-CoV-2 N), SARS-CoV-2 spike protein receptor-binding domain antibody (anti-SARS-CoV-2 RBD), Hepatitis B surface antigen and antibody (HBsAg and anti-HBs Ab) and Hepatitis B core antibody (anti-HBc Ab). Patients were divided into groups depending on their HBV and SARS-CoV-2 vaccine response status. Patients with an anti-HBs Ab titre >10 IU/ml after three doses of Engerix-B® or Fendrix® and an anti-SARS-CoV-2 RBD Ab titre ≥0.8 U/ml after two doses of BNT162b2 SARS-CoV-2 vaccine were considered responders to the HBV and SARS-CoV-2 vaccines, respectively. Groups were compared using unpaired t test, Mann-Whitney U test and Fisher's exact test, as appropriate. All tests were two-tailed and a P-value <0.05 was considered significant.

Fifty-four patients (median age 72 years, 56% men, 91% Caucasians, on dialysis for a median of 47.0 months, 39% diabetics, 19% on immunosuppressive treatment) were included (Table 1). Serum

samples were collected 4.1 months [interquartile range (IQR) 4.1–5.0] after the second dose of the SARS-CoV-2 vaccine. Responders to the SARS-CoV-2 vaccine did not differ from non-responders regarding demographics, dialysis vintage and diabetes. However, patients were less likely to respond to the SARS-CoV-2 vaccine if treated with immunosuppressive medications and in case of non-response to the HBV vaccine (Table 1, Figure 1). Anti-HBs and anti-SARS-CoV-2 RBD Ab titres were correlated (Spearman, r=0.34, p=0.01). Out of the five patients who did not respond to the SARS-CoV-2 vaccine, one was on tacrolimus and mycophenolate mofetil, two were on maintenance rituximab and low-dose methylprednisolone and two were on tacrolimus alone. Out of the five patients on immunosuppressive therapy who responded to the SARS-CoV-2 vaccine, three were on low-dose methylprednisolone and two on tacrolimus alone.

Our study shows a significant association between humoral responses after HBV and SARS-CoV-2 vaccines in a small cohort of patients on maintenance HD. HBV vaccine non-responders may therefore benefit from a systematic SARS-CoV-2 serological follow up and potential intensification of the vaccine schedule. Furthermore, this study highlights the poor vaccine response of immunosuppressed patients, including those treated with rituximab, as recently reported [9].

A definite strength of this study is its novelty in assessing and correlating immunization responses to both HBV and SARS-CoV-2 vaccines among maintenance hemodialysis patients with a subgroup of patients on immunosuppressive therapy. The small sample size is a clear limitation.

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Table 1. Characteristics of the patients

Characteristics	All patients (N = 54)	SARS-CoV-2 vaccine responders (N = 49)	SARS-CoV-2 vaccine non-responders (N = 5)	P-Value
Age – median [IQR] years	72 [62–81]	73 [63–81]	55 [55–67]	0.14
Gender: male – no. (%)	30 (56)	27 (55)	3 (60)	1.00
Race: Caucasian / African – no. (%)	49 (91) / 5 (9)	45 (92) / 4 (8)	4 (80) / 1 (20)	0.40
Dialysis vintage – median [IQR] months	47.0 [23.6 – 78.8]	46.2 [23.7 – 76.6]	68.8 [20.6 – 110.1]	0.72
Diabetes – no. (%)	21 (39)	20 (41)	1 (20)	0.64
Immunosuppressive treatment – no. (%)	10 (19)	5 (10)	5 (100)	<0.001
HBV vaccine response – no. (%)	39 (72)	38 (78)	1 (20)	0.02

FIGURE 1: Level of anti-HBs antibodies (Ab) (A) and HBV vaccine response status (B) stratified for the presence vs. absence of humoral response to SARS-CoV-2-19 vaccination.