SARS-CoV-2 vaccination in patients with GI and hepatobiliary carcinoma: a call for booster vaccination

Bollipo *et al*[1] presented recommendations for SARS-CoV-2 infections in patients with chronic liver diseases (CLDs). Since their publication, at least three SARS-CoV-2 vaccinations are recommended for all persons regardless of comorbidities.[2] Cancer and CLD are associated with impaired immune responses to SARS-CoV-2 vaccines.[3–6] However, patients with GI cancer, especially with hepatobilary carcinoma (HBC), are under-represented in published studies.

In this prospective, longitudinal study, 120 patients with GI cancer, including 32.5% HBC, participated (table 1). Patients under anticancer therapy were analysed compared with patients with GI cancer in follow-up care (≥1 year off anticancer therapy). We present profound data on humoral response rates (SARS-CoV-2 antispike and surrogate neutralisation antibodies (sNAB) using SARS-CoV-2 IgG II Quant chemiluminescent microparticle immunoassay (Abbott Laboratories) and cPass SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript), respectively). Of note, the ELISA analysing levels of sNAB is limited when it comes to current variants of concern (VOCs; BA.1, BA.2, BA.4 and BA.5). Therefore, rates of infections are more important. Cellular response rates were not considered. Linear mixed regression models were used to compare levels of total ($\log_{10}$ transformed) and neutralising antibodies.

Four weeks after second vaccination, levels of SARS-CoV-2 antispike IgG were significantly lower in patients with active GI cancer (2.48 $\log_{10}$ binding antibody unit (BAU)/mL; 95% CI 2.28 to 2.68; p<0.01) and HBC (2.52 $\log_{10}$ BAU/mL; 95% CI 2.25 to 2.78; p<0.01) compared with patients in follow-up care (3.03 $\log_{10}$ BAU/mL; 95% CI 2.77 to 2.28). Titres decreased overtime, and differences diminished (figure 1). However, patients with HBC still showed significantly lower IgG levels compared with patients in follow-up care 12 weeks after second vaccination (2.06 $\log_{10}$ BAU/mL; 95% CI 1.79 to 2.33 vs 2.47 $\log_{10}$ BAU/mL; 95% CI 2.24 to 2.70; p=0.02). Regarding surrogate neutralisation antibody (sNAB) at the same time point, levels were more impaired in patients with HBC (57.80%; 95% CI 47.49 to 68.11; p<0.01) than in patients with GI-cancer (67.81%; 95% CI 58.33 to 77.29; p<0.01) compared with patients in follow-up care (84.88%; 95% CI 76.34 to 93.43) (figure 1). Patients with HBC under chemotherapy showed most extended impairment of SARS-CoV-2 antispike IgG levels (1.94 $\log_{10}$ BAU/mL; 95% CI 1.42 to 2.46) 12 weeks after second vaccination in an univariate analysis. While in patients with GI cancer under chemotherapy levels of SARS-CoV-2 antispike IgG were also lower (2.16 $\log_{10}$ BAU/mL; 95% CI 1.80 to 2.52), patients under therapy with immune checkpoint inhibitors had highest titres (2.27 $\log_{10}$ BAU/mL; 95% CI 1.43 to 3.11) compared with all other types of therapy.

Following first booster vaccination, that is, the third vaccination, titers of SARS-CoV-2 antispike IgG were balanced between patients with GI

Table 1 Patientbaseline characteristics

Patients	GI cancer under treatment (n=52)	HBC* under treatment (n=30)	Off treatment >1 year (n=38)	P value
Age (years)				0.76
Median	66	69	69	
IQR	(61–73)	(62–78)	(61–73)	
Sex				0.33
Women	35.0% (18)	40.0% (12)	50.0% (19)	
Men	65.0% (34)	60.0% (18)	50.0% (19)	
Tumour types				
Cholangiocellular cancer		30.0% (9)	2.5% (1)	0.32
Gallbladder cancer		3.0% (1)	2.5% (1)	
Hepatocellular cancer		67.0% (20)	18.5% (7)	
Colorectal cancer	33.0% (17)		34.5% (13)	0.04
Neurodendocrine tumour	25.0% (13)		2.5% (1)	
Pancreas cancer	21.0% (11)		8.0% (3)	
Gastric cancer	8.0% (4)		16.0% (6)	
Oesophageal cancer	9.0% (5)		13.0% (5)	
GI stromal tumour	4.0% (2)		2.5% (1)	
Intention of treatment				<0.01
Neoadjuvant	9.0% (5)	23.0% (7)		
Adjuvant	23.0% (12)	0.0% (0)		
Palliative	68.0% (35)	77.0% (23)		
Type of treatment				<0.01
Chemotherapy†	42.0% (22)	27.0% (8)		
Targeted therapy	21.0% (11)	10.0% (3)		
Immune checkpoint inhibition	8.0% (4)	0.0% (0)		
Local therapy§	4.0% (2)	33.0% (10)		
Combined therapy¶	25.0% (13)	30.0% (9)		
History of SARS-CoV-2 infection after booster vaccination	7.7% (3)	3.0% (1)	2.5% (1)	0.85
Vaccines				0.98
BNT162b2 (Pfizer and BioNTech)	82.0% (43)	90.0% (27)	82.0% (31)	
AZD1222 (AstraZeneca)	8.0% (4)	7.0% (2)	8.0% (3)	
mRNA-1273 (Moderna)	4.0% (2)	0.0% (0)	5.0% (2)	
AZD1222+BNT162b2/mRNA-1273	4.0% (2)	3.0% (1)	5.0% (2)	
Ad26.COV2.s (Johnson & Johnson, Janssen)	2.0% (1)	0.0% (0)	0.0% (0)	

Baseline characteristics were compared between the three groups using one-way analysis of variance for age and Fisher's exact tests for the categorical variables.
*Cholangiocellular cancer, gallbladder cancer and hepatocellular cancer.
†Mostly with combinations of 5-fluorouracil, platinum derivatives, gemcitabine, taxane or irinotecan
‡Including multikinase inhibitors such as sorafenib, lenvatinib, cabozantinib, epidermal growth factor receptor antibodies or vessel endothelial growth factor antibodies.
§Including transarterial embolisation, radioembolisation or endobiliary/transcutaneous radiofrequency ablation and photodynamic therapy.
¶Chemotherapy+targeted therapy or chemotherapy+local therapy.
HBC, hepatocellular carcinoma.

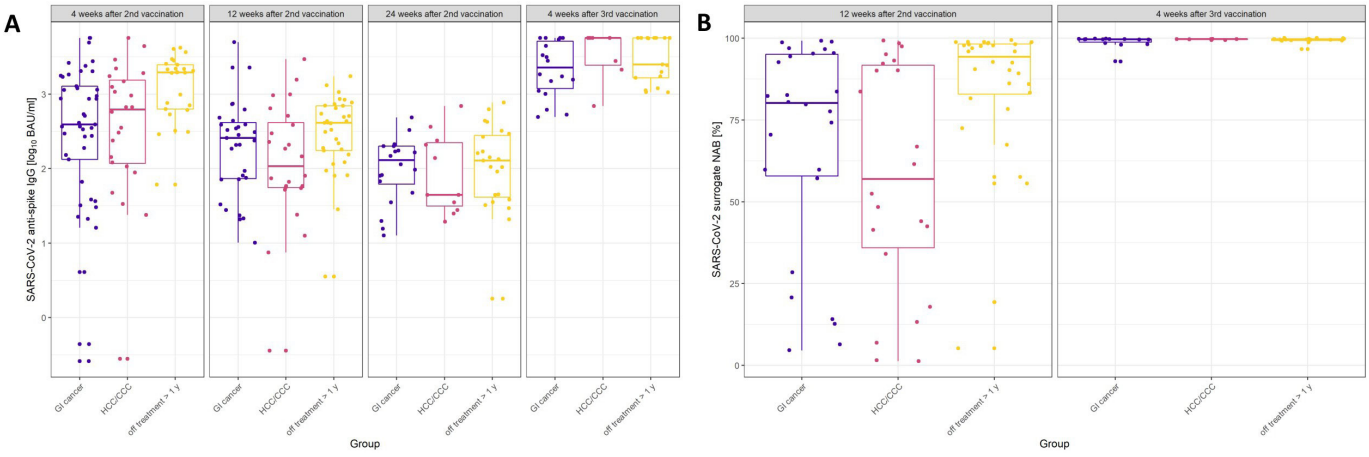

Figure 1 SARS-CoV-2 antibodies. (A) SARS-CoV-2 antispike IgG levels. Log_{10} SARS-CoV-2 antispike IgG titre of patients with GI cancer*, patients with HCC/CCC and patients in follow-up care (off treatment >1 year) at week 4, 12 and 24 following second vaccination and at week four after third vaccination. Length of box represents the IQR (50% of the data), horizontal line shows the median log_{10} SARS-CoV-2 antispike IgG titre. (B) SARS-CoV-2 surrogate neutralisation antibody (sNAB) levels. SARS-CoV-2 sNAB titres of patients with GI cancer*, patients with HCC/CCC and patients in follow-up care (off treatment >1 year) at week 12 following second vaccination and at week 4 after third vaccination. Length of box represents the IQR (50% of the data), horizontal line shows the median SARS-CoV-2 surrogate neutralisation antibody titre. BAU, binding antibody units; CCC, cholangiocarcinoma; HCC, hepatocellular carcinoma. *Colorectal cancer, neurodendocrine tumours, pancreas cancer, gastro-oesophageal-junction cancer, gastric cancer, oesophageal cancer and GI stromal tumours.

cancer (3.28 log_{10} BAU/mL; 95% CI 3.01 to 3.56; p=0.29), HBC (3.36 log_{10} BAU/mL; 95% CI 2.94 to 3.78; p=0.60) and patients with GI cancer in follow-up care (3.50 log_{10} BAU/mL; 95% CI 3.21 to 3.79). This was also true for sNAB (98.87%; 95% CI 85.95 to 100 or 99.64%; 95% CI 79.9 to 100; p=0.95% and 99.40%; 95% CI 87.68 to 100; p=0.98, respectively) (figure 1). Mild infections with SARS-CoV-2 were detected in five patients after booster vaccination.

In line with recent data on patients with solid tumours,[3] immunogenicity after second vaccination for SARS-CoV-2 in patients with GI cancer under anticancer therapy, particularly under chemotherapy, was significantly reduced. The capacity to develop adequate response rates, above all concerning sNAB, was more pronounced than in previous reports including all kind of solid tumours[3] and was most impaired in patients with HBC. Patients with CLD showed reduced immunogenicity for different vaccines including those for SARS-CoV-2.[4–6] Underlying cirrhosis in most patients with HBC also contributes to impaired immune responses.[7] Differences between antibody levels were overcome by third vaccination with only rare infections thereafter highlighting the importance of booster vaccinations especially for patients at high-risk for impaired SARS-CoV-2 immunogenicity. As waning immunity overtime can be assumed[8] and clinical benefits of a fourth vaccine dose have been proved,[9] additional booster vaccinations after further antibody assessment in the vulnerable group of patients with GI cancer/ HBC should be recommended. In future studies, long-term SARS-CoV-2 immunogenicity, effects of additional booster vaccinations and new SARS-CoV-2 VOC (like BA.5 at the very moment) showing antibody escape from vaccines[10] have to be considered.

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