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Short Communication

mRNA COVID-19 vaccines induce superior immunoglobulin A titers in patients with cancer compared with viral vector vaccines: implications for immunization strategies

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ABSTRACT

Objectives: Immunoglobulin (Ig) A antibodies are involved in mucosal immunity and eliminate pathogens immediately at the point of entry. Vaccine-induced IgA antibodies could contribute to an additional layer of protection against SARS-CoV-2 for infection-prone patients with cancer. This might be particularly relevant for patients with cancer because they mount reduced IgG antibody titers after dual-dose BNT162b2 COVID-19 vaccination and even lower responses after double-dose ChAdOx1 vaccination than healthy individuals. However, data on vaccine-induced IgA antibodies are scarce, especially in patients with cancer.
Methods: This study compares SARS-CoV-2 anti-spike (S1) IgA antibodies after dual-dose BNT162b2 vs ChAdOx1 vaccination in patients with cancer. SARS-CoV-2 anti-S1 IgA antibodies were quantified in serum samples collected 7 days after the second vaccination dose (N = 213) (IEQ-CoVS1RBD-IgA-1-RB enzyme-linked immunosorbent assay kit, RayBiotech) and analyzed with colorimetric detection. In addition, correlations with different aspects of humoral immunity were assessed (neutralizing and IgG antibodies).
Results: Significantly lower anti-S1 IgA antibody titers were reported in patients with cancer after dual-dose ChAdOx1 than BNT162b2 vaccination. Moreover, patients with cancer who received dual-dose BNT162b2 vaccination had a significant 16.44-fold increased chance to mount detectable IgA antibodies compared with patients receiving ChAdOx1 vaccination.
Conclusions: These findings highlight the potential role of boosters or alternative strategies to sustain mucosal immunity.

Introduction

The importance of immunoglobulin (Ig) G antibodies in humoral immunity against SARS-CoV-2 is well established [1]. In addition to IgG, IgA antibodies also play a role in protection against SARS-CoV-2 infection [2]. IgA antibodies act as a first line of defense and eliminate pathogens immediately at the point of entry (e.g. respiratory and gastrointestinal tracts) [3]. In the context of influenza, IgA serum levels have been correlated with the efficacy of vaccination [4], and influenza-specific IgA are more effective in preventing infections in mice and humans than influenza-specific IgG [3]. Functional studies further highlight the strong neutralizing capacity of IgA at epithelial surfaces, emphasizing its critical role in immune defense against SARS-CoV-2 [3,5]. Although mucosal protection is primarily mediated by secretory IgA, serum IgA measurements offer a practical and informative proxy for assessing vaccine-induced responses when direct mucosal sampling is not feasible [3]. Therefore, the level of IgA in serum may serve as an indicator of the host immune response. As SARS-CoV-2 is evolving toward an endemic virus, mapping all parts of the vaccination-induced immune response, including IgA responses, becomes increasingly relevant. We hypothesized that IgA responses are enhanced after vaccination, independent of vaccine type. However, the role of IgA antibodies against SARS-CoV-2 remains unclear, with a lack of studies on IgA production upon COVID-19 vaccination, especially in the context of patients with cancer who already have reduced SARS-CoV-2 IgG antibody responses after COVID-19 vaccination compared with healthy individuals [6], particularly, after ChAdOx1 vaccination [7]. Because patients with cancer frequently experience

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immunologic dysregulation as a result of the disease and the immunosuppressive effects of anti-neoplastic therapy, the presence of IgA antibodies might be particularly relevant for this patient group. This study maps vaccine-induced anti-spike (S1) IgA antibodies after dual-dose vaccination with BNT162b2 or ChAdOx1 in patients with cancer receiving active anti-neoplastic treatment.

Methods

Blood samples 7 and 28 days post-second dose from 213 patients included in the prospective B-VOICE (EudraCT 2021-000300-38) and Tri-VOICE plus (EudraCT 2021-003573-58) studies were retrospectively analyzed within the current study *Cellular and humoraL immune responses after COVID-19 Vaccination in cancER patients* (CLOVER) (EC number 5460). Clinical data and data regarding humoral immunity (SARS-CoV-2 anti-S1 IgG antibodies and *in vitro* neutralizing antibody titers [NT50]) obtained within these studies [6,7] were used to assess correlations between different aspects of humoral immunity. All patients were assigned to a cohort based on the type of anti-neoplastic treatment they were receiving at time of the first vaccine dose administration. Data of four different cohorts are reported: chemotherapy, immunotherapy, targeted/hormonal therapy, and patients receiving treatment for hematologic malignancies. Anti-S1 receptor binding domain (RBD) SARS-CoV-2 IgA antibodies were assessed in serum samples collected 7 days after the second vaccine dose administration. Samples were analyzed based on availability without previous stratification by tumor type or treatment. IgA antibodies were quantified with an enzyme-linked immunosorbent assay (ELISA) by use of the RayBio COVID-19 S1 RBD protein Human IgA ELISA kit (RayBiotech). Serum samples were thawed on the day of analysis and processed according to manufacturer instructions (IEQ-CoVS1RBD-IgA-1-RB ELISA kit). Samples were analyzed in duplicate via colorimetric detection at 450 nm, with an iMARK Microplate absorbance reader (BioRad), connected to a computer equipped with the Microplate Manager 6 Software. A value greater than 21.4 U/ml was considered positive. Log-transformed IgA titers were compared using a *t* test and a two-way analysis of variance with post hoc Tukey test. Responders were compared with the use of the Fisher exact test. A two-sided $P < 0.05$ after Bonferroni–Holm correction for multiple testing was considered statistically significant. All statistical analyses were performed using the statistical software program R (version 4.3.2).

Results

Patients received dual-dose vaccination with an interval of 21 days (21 ± 2 days for 95% and 24-27 days for 5% of the patients) for the BNT162b2 vaccine and 12 weeks (12 weeks ± 10 days for 90% and 8-10 weeks for 10% of the patients) for the ChAdOx1 vaccine. The overall studied population was majorly female (149; 70.0%) and diagnosed with a solid tumor (187; 87.7%). Detailed demographics of the enrolled patients are included In Table 1. In our cohort of patients with cancer, we observed significantly lower anti-S1 RBD SARS-CoV-2 IgA antibody titers after ChAdOx1 vaccination (N = 57; geometric mean titer 12.17 U/ml [95% confidence interval {CI} 10.84-13.67]) than BNT162b2 vaccination (n = 156; geometric mean titer 52.02 U/ml [95% CI 41.19-65.69]) 7 days after second dose administration ($P < 0.001$) (Figure 1a). After dual-dose BNT162b2 vaccination, 96 (61.5%) patients had detectable antibodies, compared with five (8.8%) after ChAdOx1 vaccination. This indicates that patients that received dual-dose BNT162b2 vaccination had a significant 16.44-fold increased chance to mount a detectable IgA antibody response compared with patients receiving ChAdOx1 vaccination ($P < 0.001$). A subanalysis of treatment cohorts revealed significantly lower post-vaccination IgA antibody titers after ChAdOx1 than BNT162b2 vaccination in patients receiving targeted/hormonal therapy (12.44 U/ml [95% CI 10.03-15.43] vs 91.09 U/ml [95% CI 69.08-120.10], $P < 0.001$) and chemotherapy (13.56 U/ml [95% CI 9.52-19.31] vs 33.66 U/ml [95% CI 21.95-51.62], $P = 0.034$). In contrast, IgA antibody titers did not significantly differ between both vaccine types in patients receiving immunotherapy and patients with hematologic malignancies, treatment cohorts in which also BNT162b2 vaccination elicits very limited IgA antibodies (Figure 1b). Possible correlations between IgA antibodies and other immunologic markers were also investigated. Here, we describe correlations between immunologic markers after BNT162b2 vaccination because the low overall IgA titers after ChAdOx1 vaccination limits interpretability in this cohort. Significant moderate correlations were observed between anti-S1 RBD SARS-CoV-2 IgA and IgG antibodies on days 7 ($r = 0.40$, $P < 0.001$, Supplement Figure 1a) and 28 ($r = 0.51$, $P < 0.001$, Supplement Figure 1b) after second dose respectively. In addition, a weak but significant correlation was also observed between IgA antibody titers and NT50 titers against the Wuhan-1 variant ($r = 0.35$, $P < 0.001$; Supplement Figure 1c), the main circulating variant at time of vaccination.

Discussion

BNT162b2 and ChAdOx1 vaccines can induce anti-S1 SARS-CoV-2 IgG antibodies in patients with cancer [7]. However dual-dose BNT162b2 elicits higher IgA antibody titers than ChAdOx1 vaccination. This difference might be explained by the different delivery mechanisms and type of genetic material used in both vaccines. It is important to note that certain anti-neoplastic therapies, including chemotherapy and B-cell depleting agents, have also been shown to impair humoral immune responses, including IgA production [8]. Underlying mucosal dysfunction, often present in patients with cancer receiving radiotherapy or systemic treatments [9], may also contribute to lower IgA titers. Although reduced IgG antibody titers after ChAdOx1 vaccination in patients with cancer have been previously described [7], to the best of our knowledge, this is the first study to compare IgA responses after BNT162b2 messenger RNA and ChAdOx1 viral vector vaccination in patients with cancer. A similar trend was observed in a study performed by Selma-Royo *et al.*, in which the presence of SARS-CoV-2–specific IgA antibodies in breast milk was found to be dependent of the vaccine type [10]. In addition, messenger RNA vaccination is associated with mucosal immunity in patients with cancer without previous SARS-CoV-2 vaccination [11,12].

This study provides valuable insights; however, several limitations should be considered. First, no baseline IgA levels were measured, despite the availability of baseline IgG levels. Although baseline IgA levels could have provided additional context, they were not assessed due to the established IgA-IgG correlation observed by Abril *et al.* [13] and confirmed in this study, combined with low baseline IgG levels that would likely result in many values falling below the detection limit. Second, the unequal distribution of vaccine types across treatment cohorts resulted in small sample sizes for some subgroups, which could affect the power of certain comparisons. Third, although serum IgA levels offer a practical and informative proxy for mucosal immunity, it should be acknowledged that they may not fully capture mucosal protection. Lastly, although clinical correlates such as breakthrough infections would provide valuable insights into vaccine efficacy, the study period coincided with a lockdown period. As a result, very few breakthrough infections were reported [14] and further analysis of breakthrough infections was not pursued.

The observed weak or absent IgA responses in certain treatment cohorts highlights the need for tailored vaccination strategies enhancing mucosal immunity to ensure optimal protection. Nev-

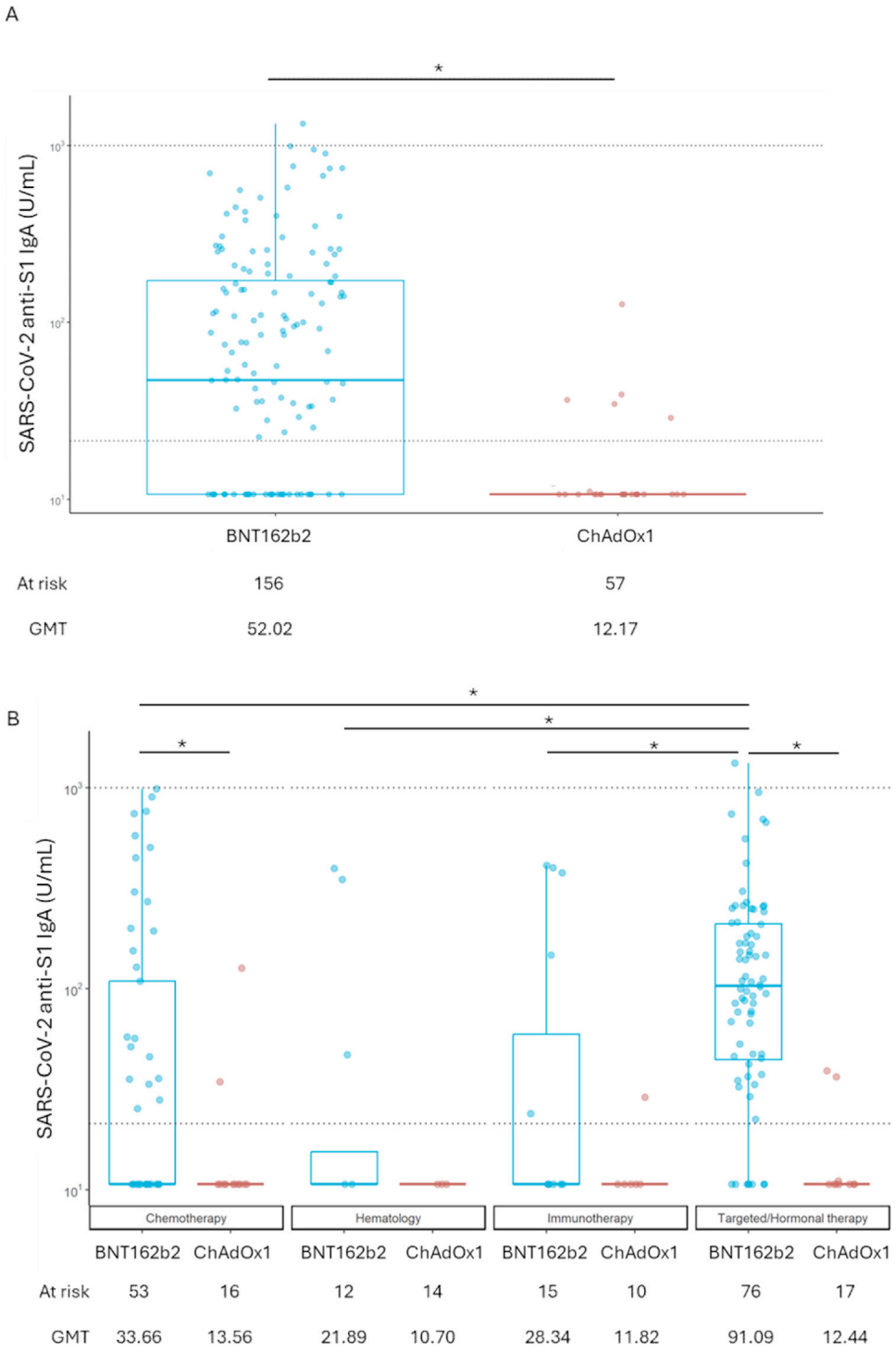

Figure 1. Comparison of anti-S1 SARS-CoV-2 IgA antibody titers 7 days after the second vaccine dose administration. Boxplots of anti-S1 SARS-CoV-2 IgA antibody titers 7 days after the second dose administration in the entire study population (panel a) and in different treatment cohorts (panel b) per vaccine type (BNT162b2 in blue vs ChAdOx1 in red). Each dot represents an individual IgA measurement. Anti-S1 RBD IgA antibody titers were quantified using the RayBio COVID-19 S1 RBD protein Human IgA enzyme linked immunosorbent assay kit (RayBiotech). The measuring interval is 21.40-1000.00 U/ml. Values below the lower limit of quantification (LLQ) were imputed half of it (10.70 U/ml), and values above the upper limit of quantifictaion (ULQ) were imputed 33% above the upper limit of detection (1330.00), with dotted lines indicating LLQ and ULQ, respectively. Log transformed data are presented and analyzed using a *t* test (a) or two-way analysis of variance (b) with *indicating $P < 0.05$. Color should not be used for any figures in print.
GMT, geometric mean titer; Ig, immunoglobulin; RBD, receptor binding domain.

ertheless, it is important to note that although BNT162b2 induces higher IgA antibody titers than ChAdOx1 vaccination, both vaccine types have been shown to be effective in preventing severe COVID-19. Lower IgA antibody titers induced by viral vector vaccines do not necessarily translate to lower overall protection or vaccine efficacy; other immunologic aspects such as cellular immunity, also play a crucial role in immunity. In addition, studies incorporating mucosal sampling (e.g. nasal swabs) are required to enhance clini-

Table 1
Demographics: demographics of the patients at time of study enrolment.

	ChAdOx1 (N = 57)	BNT162b2 (N = 156)	Overall (N = 213)
Gender			
Female	35 (61.4%)	114 (73.1%)	149 (70.0%)
Male	22 (38.6%)	42 (26.9%)	64 (30.0%)
Age			
Mean (SD)	57.9 (9.31)	60.9 (12.0)	60.1 (11.4)
Median [min, max]	60.0 [36.0, 75.0]	61.0 [31.0, 88.0]	61.0 [31.0, 88.0]
Tumor type			
Hematologic malignancy	14 (24.6%)	12 (7.7%)	26 (12.2%)
Solid tumor	43 (75.4%)	144 (92.3%)	187 (87.8%)
Therapy			
Chemotherapy	16 (28.1%)	53 (34.0%)	69 (32.4%)
Hematological treatment	14 (24.6%)	12 (7.7%)	26 (12.2%)
Immunotherapy	10 (17.5%)	15 (9.6%)	25 (11.7%)
Targeted/Hormonal therapy	17 (29.8%)	76 (48.7%)	93 (43.7%)

cal relevance and to further elucidate the role of IgA responses in vaccine-induced protection.

Conclusion

Our results indicate that although IgA plays an important early role in neutralizing SARS-CoV-2 [15], its levels after dual dose are low in patients with cancer, especially after ChAdOx1 vaccination. These findings emphasize the need for boosters or alternative strategies to sustain mucosal immunity. This knowledge is crucial for guiding clinical decisions and public health policies regarding vaccination protection strategies for patients with cancer.

Declarations of competing interest

T. Vandamme reports consultancy, advisory roles, and honoraria from AstraZeneca outside the scope of presented work. The other authors report no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval statement

This retrospective study was approved by the ethics committee of the Antwerp University Hospital (EC number 5460). Moreover, the prospective studies of which we now retrospectively analyzed blood samples were approved by the central ethics committee of the Antwerp University Hospital and the Federal Agency for Medicine and Health Products (EudraCT nos. 2021–000300–38 and 2021–003573– 58 and EC nos. 2021–0543, 2021.0541, and 2021.0110). All studies were executed in accordance with Good Clinical Practice and the Declaration of Helsinki [ICH GCP E6(R2)].

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Author contributions

Conceptualization: YD, MP, PvD, TV; Data curation: YD, LV; Formal analysis: YD; Funding acquisition: YD, LV, MP, TV; Investigation: YD, LV; Methodology: YD, TV, LV; Project administration: YD, LV; Resources: MP, PvD, TV; Supervision: MP, PvD, TV, LV; Visualization: YD; Writing original draft: YD; Writing: review and editing: LV, MP, PvD, TV.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107939.

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