Inhibition of SARS-CoV-2 Omicron BA.1 and BA.4 Variants After Fourth Vaccination or Tixagevimab and Cilgavimab Administration in Patients With Cancer

Patients with cancer are at high risk for severe COVID-19 and show impaired immune responses after vaccination.1,2 Specifically, levels of neutralizing antibodies against variants of concern, including Delta (B.1.617.2) and Omicron (B.1.1.529), are lower in patients with cancer than in those without.3 Fourth vaccination dose or administration of monoclonal neutralizing antibodies, such as tixagevimab and cilgavimab, is being considered, although data supporting this strategy are limited, especially in the context of currently circulating variants, such as BA.4.

Methods | To analyze variant-specific humoral immunity after active and passive SARS-CoV-2 immunization in patients with hematologic-oncologic diseases, we compared antibody levels against the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2 hu-1 and Omicron sublineages BA.1 or BA.4 after the third and fourth vaccinations or administration of tixagevimab and cilgavimab in patients with cancer. Moreover, the inhibition of the interaction between these RBDs and the receptor angiotensin-converting enzyme 2 (ACE-2) was evaluated as described previously.3 The study was approved by the institutional review boards of the Medical University of Vienna and the Südtiroler Sanitätsbetrieb. All patients provided written informed consent before serum sampling (eMethods in the Supplement). The study was performed according to the Declaration of Helsinki,4 complying with all applicable amendments and institutional guidelines and national law, and we followed relevant portions of the STROBE reporting guideline.

Results with a 2-sided \( P < .05 \) were considered statistically significant. Statistical analysis was performed using GraphPad Prism, version 9.3 for Mac (Dotmatics).

Results | In total, 72 patients (median [range] age, 74 [48-89] years; 47 men [65.3%], 25 women [34.7%]) were included. Of these patients, 54 (75.0%) received a fourth vaccination (21 had solid tumors, and 33 had hematologic malignant neoplasms) and 18 (25.0%) received tixagevimab and cilgavimab as passive immunization.

We analyzed the levels of anti-RBD antibodies after the third and fourth vaccinations. Median (range) anti-RBD levels increased in patients with hematologic malignant neoplasms undergoing B cell–targeted therapy, particularly against Omicron sublineages BA.1 before vs after fourth vaccination: 0.154 [0.059-1.556] optical density vs 0.969 [0.057-1.306] optical density; \( P = .02 \) and BA.4 (0.245 [0.052-1.270] optical density vs 0.966 [0.052-1.383] optical density; \( P = .02 \)). There were no differences in antibody levels among patients with other hematologic diseases. Similarly, there was a pronounced increase in median (range) anti-RBD levels in patients with solid malignant neoplasms for all investigated variants of concern before vs after the fourth vaccination, including hu-1 (1.157 [0.121-2.210] optical density vs 1.438 [0.213-1.801] optical density; \( P = .02 \), BA.1 (0.721 [0.103-1.486] optical density vs 1.026 [0.146-1.553] optical density; \( P = .003 \)), and BA.4 (0.556 [0.119-1.496] optical density vs 1.220 [0.251-1.423] optical density; \( P = .002 \)). We also investigated the capacity of patients’ serum samples to inhibit RBD and ACE-2 interaction. The inhibitory potential against RBD and ACE-2 interaction was generally stronger for BA.4 than BA.1.
higher after the fourth vaccination than after the third vaccination, especially for sublineages BA.1 and BA.4, in both patients with hematological disease (Figure 1) and those with solid tumors (Figure 2A).

Furthermore, we evaluated the inhibitory capacity of tixagevimab and cilgavimab as a preexposure prophylaxis for RBD and ACE-2 interaction. We observed a difference according to the investigated variant of concern, with median inhibition of 99.9% for hu-1, 34.9% for BA.1, and 15.4% for BA.4 (Kruskal-Wallis P < .001) (Figure 2B).

Conclusion | Study limitations include the relatively small, heterogeneous cohort and variable time points of blood sampling before the fourth vaccination, as some samples were drawn 3 to 4 weeks after the third vaccination and others a few weeks before the fourth vaccination. Moreover, thresholds of antibody levels conferring sufficient protection from SARS-CoV-2 infection remain elusive.

Findings suggest that passive immunization with tixagevimab and cilgavimab may not be effective in blocking Omicron sublineages BA.1 and BA.4. However, there was an increase in humoral immunity after the fourth vaccination. Further prospective studies are needed to corroborate these findings and guide vaccination recommendations.

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