CORRESPONDENCE

Efficacy of Antiviral Agents against the Omicron Subvariant BA.2.75

TO THE EDITOR: Five sublineages of the B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) — BA.1, BA.2, BA.3, BA.4, and BA.5 — are recognized, and BA.5 is currently the predominant variant circulating globally.[1] In India and Nepal, however, the prevalence of a subvariant of BA.2 (designated BA.2.75) is increasing rapidly and is now becoming dominant in Nepal.[2] Moreover, BA.2.75 has been detected in at least 25 other countries, including the United States, Singapore, Canada, the United Kingdom, Japan, and Australia; as such, it has spread across multiple continents.[2-4] The World Health Organization designated BA.2.75 as a "variant of concern lineage under monitoring."

Of additional concern, BA.2.75 may differ antigenically from BA.2. The receptor-binding domain of the spike (S) protein of SARS-CoV-2 is capable of inducing neutralizing antibodies and is the major target for monoclonal antibody–based therapy. BA.2, as compared with the reference strain Wuhan/Hu-1/2019, possesses 16 amino acid substitutions in the receptor-binding domain; BA.2 and BA.2.75 share 14 of these 16 substitutions. However, BA.2.75 possesses 4 amino acid changes in the receptor-binding domain (i.e., G339H, G446S, N460K, and the wild-type amino acid at position 493) that differ from those in BA.2, which suggests that the monoclonal antibodies authorized for emergency use by the Food and Drug Administration (FDA) may be less effective against BA.2.75 than against other SARS-CoV-2 strains and variants.

To assess the efficacy of authorized therapeutic monoclonal antibodies against BA.2.75, we examined their neutralizing abilities against the BA.2.75 variant hCoV-19/Japan/TY41-716/2022 (TY41-716), which was isolated from a person traveling from India to Japan. Whole-genome sequencing of TY41-716 revealed that it possesses nine amino acid changes (K147E, W152R, F157L, I210V, G257S, D339H, G446S, N460K, and Q493 [reversion]) in its S protein as compared with a BA.2 isolate (hCoV-19/Japan/UT-NCD1288-2N/2022) (Fig. S1A in the Supplementary Appendix, available with the full text of this letter at NEJM.org). To quantify neutralization, we performed a live-virus neutralization assay using VeroE6/TMPRSS2 cells and determined the 50% focus reduction neutralization test ($FRNT_{50}$) titers of the monoclonal antibodies. All of the monoclonal antibodies used in this study were synthesized according to publicly available sequences without any modifications (see the Methods section in the Supplementary Appendix).

REGN10987 (marketed as imdevimab) lost neutralizing activity against BA.2.75 (Table 1 and Fig. S1B), whereas REGN10933 (marketed as casirivimab) retained some neutralizing activity against the isolate. REGN10987 in combination with REGN10933 (casirivimab–imdevimab) inhibited BA.2.75; however, the neutralizing activity against BA.2.75 with this combination was less than that against the ancestral strain (SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo) by a factor of 812.5. COV2-2196 (marketed as tixagevimab) and COV2-2130 (marketed as cilgavimab) neutralized BA.2.75. The COV2-2196 plus COV2-2130 combination (tixagevimab–cilgavimab) inhibited BA.2.75 with a low $FRNT_{50}$ value (34.19 ng per milliliter), but the neutralizing activity was less than that against the ancestral strain by a factor of 5.3. The precursor of sotrovimab (S309) neutralized BA.2.75 weakly; however, its activity was less than that against the ancestral strain by a factor of 870.0. Of the monoclonal antibodies we tested, only LY-CoV1404 (marketed as bebtelovimab) efficiently neutralized BA.2.75 ($FRNT_{50}$ value, 6.21 ng per milliliter); however, this value for BA.2.75 was higher than the $FRNT_{50}$ value for the ancestral strain by a factor of 4.4.

Remdesivir, an inhibitor of the RNA-dependent RNA polymerase of SARS-CoV-2, was approved by the FDA for the treatment of coronavi-

Table 1. Efficacy of Monoclonal Antibodies and Antiviral Drugs against Omicron Subvariants in Vitro*

WHO Label (Pango Lineage): Virus Strain	Neutralization Activity of Monoclonal Antibody†								Viral Susceptibility to Drug‡		
	REGN10987, Imdevimab	REGN10933, Casirivimab	COV2-2196, Tixagevimab	COV2-130, Cilgavimab	S309, Sotrovimab Precursor	LY-CoV1404, Bebtelovimab	REGN10987 plus REGN10933	COV2-2196 plus COV2-2130	GS-441524, Remdesivir§	EIDD-1931, Molnupiravir¶	PF-07321332, Nirmatrelvir‖
	nanograms per milliliter									*micromoles*	
Ancestral strain (A): SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo	4.36 ±0.96	2.42 ±0.93	1.91 ±0.95	5.36 ±1.21	32.80 ±11.22	1.40 ±0.79	2.23 ±0.42	6.47 ±2.31	0.98 ±0.30	0.59 ±0.11	1.71 ±0.29
Omicron (BA.2): hCoV-19/Japan/UT-NCD1288-2N/2022	958.28 ±363.87	>50,000	4374.21 ±1483.72	21.59 ±8.57	>50,000	6.09 ±0.67	968.50 ±58.35	43.22 ±8.16	1.32 ±0.21	0.25 ±0.08	1.69 ±0.66
Omicron (BA.5): hCoV-19/Japan/TY41-702/2022	174.37 ±52.55	>50,000	>50,000	54.02 ±20.29	6240.39 ±1883.65	2.43 ±1.26	192.91 ±82.50	123.65 ±55.81	0.45 ±0.09	0.23 ±0.07	1.50 ±0.34
Omicron (BA.2.75): hCoV-19/Japan/TY41-716/2022	>50,000	1153.19 ±104.61	122.31 ±67.08	101.71 ±53.24	28,536.48 ±6444.42	6.21 ±2.80	1811.78 ±600.23	34.19 ±7.60	1.52 ±0.42	0.90 ±0.18	1.78 ±0.35

* Plus–minus values are means ±SD. The antibodies used in this analysis were produced in the authors' laboratories and are not identical to the commercially available products. SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2, and WHO World Health Organization.

† The individual monoclonal antibodies were tested at a starting concentration of 50,000 ng per milliliter as a 50% focus reduction neutralization test titer. The monoclonal antibody combinations were tested at a starting concentration of 10,000 ng per milliliter for each antibody.

‡ The values presented are the 50% inhibitory concentration of the mean micromole value of triplicate reactions.

§ GS-441524 is the main metabolite of remdesivir, an RNA-dependent RNA polymerase inhibitor.

¶ EIDD-1931 is the active form of molnupiravir, an RNA-dependent RNA polymerase inhibitor.

‖ PF-07321332, nirmatrelvir, is an inhibitor of the main protease, also called 3-chymotrypsin-like protease, of SARS-CoV-2.

rus disease 2019. In addition, two antiviral drugs — molnupiravir (another inhibitor of the RNA-dependent RNA polymerase of SARS-CoV-2) and nirmatrelvir (an inhibitor of the main protease, also called 3-chymotrypsin-like protease, of SARS-CoV-2) — are authorized for emergency use by the FDA. We tested whether these antiviral drugs retained efficacy against BA.2.75 by determining the in vitro 50% inhibitory concentration (IC_{50}) values of each compound against this variant. The IC_{50} values were determined with the use of a focus reduction assay in VeroE6/TMPRSS2 cells.

Unlike the amino acid sequence of the reference strain Wuhan/Hu-1/2019, the BA.2.75 isolate encoded the P314L and G662S substitutions in the RNA-dependent RNA polymerase, had a P3395H mutation, and comprised a mixed viral population encoding either P or L at position 3515 in the main protease (Fig. S1C). The susceptibilities of BA.2.75 (TY41-716) to the three compounds were similar to those of the ancestral strain: the IC_{50} value was higher by factors of 1.6, 1.5, and 1.0 with remdesivir, molnupiravir, and nirmatrelvir, respectively (Table 1 and Fig. S1D).

Our data thus suggest that remdesivir, molnupiravir, and nirmatrelvir may be effective against BA.2.75 and that bebtelovimab and tixagevimab–cilgavimab have neutralizing activity against BA.2.75; however, this variant may be less susceptible to casirivimab–imdevimab and sotrovimab in the clinical setting. It is still too early to tell whether BA.2.75 will become the next globally dominant variant. Clinical data on the efficacy of these monoclonal antibodies and antiviral drugs for the treatment of patients infected with BA.2.75 variants are needed, as are data on whether this variant causes more clinically severe disease or is more immune-evasive. In the meantime, when considering treatment options, clinicians should take into account the potential differences in the effectiveness of these monoclonal antibodies in the treatment of patients infected with omicron variants.

Emi Takashita, Ph.D.
National Institute of Infectious Diseases
Tokyo, Japan

Seiya Yamayoshi, D.V.M., Ph.D.
University of Tokyo
Tokyo, Japan

Shuetsu Fukushi, Ph.D.
Tadaki Suzuki, M.D., Ph.D.
Ken Maeda, D.V.M., Ph.D.
National Institute of Infectious Diseases
Tokyo, Japan

Yuko Sakai-Tagawa, Ph.D.
Mutsumi Ito, D.V.M.
Ryuta Uraki, Ph.D.
University of Tokyo
Tokyo, Japan

Peter Halfmann, Ph.D.
University of Wisconsin–Madison
Madison, WI

Shinji Watanabe, D.V.M., Ph.D.
Makoto Takeda, M.D., Ph.D.
Hideki Hasegawa, M.D., Ph.D.
National Institute of Infectious Diseases
Tokyo, Japan

Masaki Imai, D.V.M., Ph.D.
Yoshihiro Kawaoka, D.V.M., Ph.D.
University of Tokyo
Tokyo, Japan
yoshihiro.kawaoka@wisc.edu

Drs. Takashita and Yamayoshi contributed equally to this letter.

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