Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2

TO THE EDITOR: The omicron (B.1.1.529) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (Covid-19), has spread rapidly around the world and has already become the predominant variant circulating in many countries. As of February 2022, omicron variants have been divided into four distinct sublineages: BA.1, BA.1.1, BA.2, and BA.3.[1] Most circulating omicron variants belong to sublineage BA.1; however, in Denmark, India, and the Philippines, the sublineage BA.2 is now becoming dominant.[2]

As compared with the Wuhan/Hu-1/2019 reference strain, the sublineage BA.2 of the omicron variant has 16 amino acid substitutions in the receptor-binding domain of the spike (S) protein of SARS-CoV-2,[2] which is the primary target for monoclonal antibody–based therapy. The BA.2 and BA.1 variants share 12 of these 16 substitutions; however, BA.2 has four substitutions in the receptor-binding domain (i.e., S371F, T376A, D405N, and R408S) that differ from those in BA.1. These findings suggest that there may be differences in the effectiveness of monoclonal antibodies against these different omicron sublineages.

Accordingly, we examined the neutralizing ability of therapeutic monoclonal antibodies that have been approved by the Food and Drug Administration, individually and in combination, against the omicron BA.2 subvariant hCoV-19/Japan/UT-NCD1288-2N/2022 (omicron/BA.2; NCD1288), which was isolated from a traveler who arrived in Japan from India. Whole-genome sequencing analysis of the NCD1288 virus stock confirmed that it had the 16 substitutions that are characteristic of the omicron variant in the receptor-binding domain of the S protein, as compared with the Wuhan/Hu-1/2019 reference strain (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

A live-virus focus reduction neutralization test (FRNT) showed that both LY-CoV016 (marketed as etesevimab) and LY-CoV555 (marketed as bamlanivimab), individually and in combination, lost neutralizing activity against omicron/BA.2 (NCD1288) (Table 1). These findings are similar to our previous findings with omicron/BA.1 (hCoV-19/Japan/NC928-2N/2021; NC928)[3] and omicron/BA.1.1 (hCoV-19/Japan/NC929-1N/2021; NC929).[4] BA.1.1, a subvariant of BA.1, has the R346K mutation in the S protein (Table S2). However, REGN10987 (marketed as imdevimab), which was previously shown to lose neutralizing activity against omicron/BA.1 (NC928) and omicron/BA.1.1 (NC929),[3,4] had neutralizing activity against omicron/BA.2 (NCD1288).

In addition, the combination of REGN10987 and REGN10933 (marketed as casirivimab) also inhibited omicron/BA.2 but did not inhibit omicron/BA.1 or omicron/BA.1.1. However, the $FRNT_{50}$ (the titer of monoclonal antibodies required for a 50% reduction in the number of infectious foci) value of this combination therapy was higher by a factor of 43.0 to 143.6 for omicron/BA.2 than for an ancestral strain — SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo (NC002) — and other variants of concern (i.e., the alpha [B.1.1.7], beta [B.1.351], gamma [P.1], and delta [B.1.617.2] variants).

REGN10933, COV2-2196 (marketed as tixagevimab), and COV2-2130 (marketed as cilgavimab) neutralized omicron/BA.2. The COV2-2196–COV2-2130 combination inhibited omicron/BA.2 with a low $FRNT_{50}$ value (14.48 ng per milliliter); however, the $FRNT_{50}$ values of this combination were higher by a factor of 1.4 to 8.1 for omicron/BA.2 than for the ancestral strain and other variants of concern.

S309 (the precursor of sotrovimab), which has been shown to have lower neutralizing activity against omicron/BA.1 and omicron/BA.1.1 than against the ancestral strain and other variants of concern,[3,4] had even less neutralizing activity against omicron/BA.2 in our study. The $FRNT_{50}$ value of this monoclonal antibody was higher by a factor of 12.2 to 49.7 for omicron/BA.2 than

Table 1. Efficacy of Monoclonal Antibodies and Antiviral Drugs against the Omicron/BA.2 Subvariant in Vitro.*

Monoclonal Antibody or Antiviral Drug	hCoV-19/Japan/UT-NCD1288-2N/2022 (Omicron/BA.2)	
	Tested Value	Factor Increase as Compared with the Ancestral Strain
Neutralization activity of monoclonal antibody†		
LY-CoV016, etesevimab	>50,000 ng/ml	>2749
LY-CoV555, bamlanivimab	>50,000 ng/ml	>10,661
REGN10987, imdevimab	68.65±8.84 ng/ml	22.5
REGN10933, casirivimab	1666.19±771.77 ng/ml	597.2
COV2-2196, tixagevimab	395.78±62.37 ng/ml	206.1
COV2-2130, cilgavimab	4.44±2.72 ng/ml	0.6
S309, sotrovimab precursor	1359.05±269.23 ng/ml	49.7
LY-CoV016 plus LY-CoV555	>10,000 ng/ml	>794
REGN10987 plus REGN10933	222.59±64.47 ng/ml	63.1
COV2-2196 plus COV2-2130	14.48±2.04 ng/ml	4.2
Viral susceptibility to drug‡		
GS-441524§	2.85±0.31 μM	2.7
EIDD-1931¶	0.67±0.22 μM	1.3
PF-07321332‖	6.76±0.69 μM	1.9

* Plus–minus values are means ±SD. The antibodies used in this analysis were produced in the authors' laboratory and are not identical to the commercially available products. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant is denoted according to the World Health Organization labels for the Pango lineage.
† The individual monoclonal antibodies were tested at a starting concentration of 50,000 ng per milliliter as a 50% focus reduction neutralization test ($FRNT_{50}$) titer. The monoclonal antibody combinations were tested at a starting concentration of 10,000 ng per milliliter for each antibody. Shown is the factor increase in the $FRNT_{50}$ titers of monoclonal antibodies against the omicron/BA.2 subvariant as compared with that against the ancestral strain, SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo (A).
‡ In this category, the value is the 50% inhibitory concentration (IC_{50}) of the mean micromole value of triplicate reactions. The factor increase in the IC_{50} of drugs against the omicron/BA.2 subvariant as compared with that against the ancestral strain, SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo (A), is shown.
§ 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 (also known as nirmatrelvir) is a protease inhibitor.

for the ancestral strain and other variants of concern.

The susceptibilities of omicron/BA.2 (NCD1288) to remdesivir, molnupiravir, and nirmatrelvir were similar to those of the ancestral strain and other variants of concern (i.e., 50% inhibitory concentration values for these three agents that differed by factors of 2.5 to 4.5, 0.7 to 1.6, and 1.5 to 3.3, respectively) (Table 1).[3] Clinical studies are warranted to determine whether these antiviral therapies are indeed effective against omicron/BA.2 infections. Our data indicate that some therapeutic monoclonal antibodies (REGN10987–REGN10933, COV2-2196–COV2-2130, and S309) have lower neutralizing activity against omicron/BA.2 than against earlier variant strains.

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

Noriko Kinoshita, M.D.
National Center for Global Health and Medicine
Tokyo, Japan

Seiya Yamayoshi, D.V.M., Ph.D.
Yuko Sakai-Tagawa, Ph.D.
University of Tokyo
Tokyo, Japan

Seiichiro Fujisaki, Ph.D.
National Institute of Infectious Diseases
Tokyo, Japan

Mutsumi Ito, D.V.M.
Kiyoko Iwatsuki-Horimoto, D.V.M., Ph.D.

University of Tokyo
Tokyo, Japan

Peter Halfmann, Ph.D.

University of Wisconsin–Madison
Madison, WI

Shinji Watanabe, D.V.M., Ph.D.

National Institute of Infectious Diseases
Tokyo, Japan

Kenji Maeda, M.D., Ph.D.

National Center for Global Health and Medicine
Tokyo, Japan

Masaki Imai, D.V.M., Ph.D.

University of Tokyo
Tokyo, Japan

Hiroaki Mitsuya, M.D., Ph.D.
Norio Ohmagari, M.D., Ph.D.

National Center for Global Health and Medicine
Tokyo, Japan

Makoto Takeda, M.D., Ph.D.
Hideki Hasegawa, M.D., Ph.D.

National Institute of Infectious Diseases
Tokyo, Japan

Yoshihiro Kawaoka, D.V.M., Ph.D.

University of Tokyo
Tokyo, Japan
yoshihiro.kawaoka@wisc.edu

1. World Health Organization. Weekly epidemiological update on COVID-19. February 1, 2022 (https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-february-2022).
2. CoVariants. Overview of variants/mutations. February 3, 2022 (https://covariants.org/per-variant).
3. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of antibodies and antiviral drugs against Covid-19 omicron variant. N Engl J Med. DOI: 10.1056/NEJMc2119407.
4. Uraki R, Kiso M, Imai M, et al. Therapeutic efficacy of antibodies and antivirals against a SARS-CoV-2 Omicron variant. January 19, 2022 (https://assets.researchsquare.com/files/rs-1240227/v1/43f2453c-851d-4f87-ba4f-657687d73757.pdf?c=1642600701). preprint.