

Update on and Future Directions for Use of Anti-SARS-CoV-2 Antibodies: National Institutes of Health Summit on Treatment and Prevention of COVID-19

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As the fourth wave of the SARS-CoV-2 pandemic encircles the globe, there remains an urgent challenge to identify safe and effective treatment and prevention strategies that can be implemented in a range of health care and clinical settings. Substantial advances have been made in the use of anti-SARS-CoV-2 antibodies to mitigate the morbidity and mortality associated with COVID-19. On 15 June 2021, the National Institutes of Health, in collaboration with the U.S. Food and Drug Administration, convened a virtual summit

to summarize existing knowledge on anti-SARS-CoV-2 antibodies and to identify key unanswered scientific questions to further catalyze the clinical development and implementation of antibodies.

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As the fourth wave of the COVID-19 pandemic encircles the globe, there remains a continuing urgent priority to develop safe and effective treatment and prevention strategies for those at risk for infection with SARS-CoV-2, the virus that causes COVID-19, and for those who are already infected. The World Health Organization estimates that as of September 2021 there had been more than 232 million confirmed cases and more than 4.7 million deaths worldwide (1). In the search to identify safe and viable interventions to alleviate morbidity and mortality associated with COVID-19, anti-SARS-CoV-2 antibodies, including convalescent plasma (CP), hyperimmune globulin (HIG), and monoclonal antibodies (mAbs), have been used in a range of health care settings and clinical studies (2). The rationale for administering passive antibody therapy is based on biological plausibility and successful use for treatment of other infectious diseases (3, 4).

To date, the U.S. Food and Drug Administration (FDA) has issued an approval for 1 antiviral drug to treat hospitalized patients and granted Emergency Use Authorizations (EUs) for several single and combination mAbs to treat persons in outpatient settings with mild to moderate COVID-19 who are at risk for clinical progression to severe disease (5) and for 2 mAb combinations for use as post-exposure prophylaxis in certain scenarios (6, 7). Agents that moderate the host immune or inflammatory response are used in later stages of COVID-19 and include dexamethasone, recommended for hospitalized patients requiring supplemental oxygen, as well as tocilizumab (interleukin-6 inhibitor) or baricitinib (Janus kinase inhibitor), recommended for certain patients with severe disease receiving corticosteroids (8). Both tocilizumab and baricitinib have been issued EUs. The FDA has also granted 3 EUs for COVID-19 vaccines (1 of which has now been fully approved) (9). The continuing emergence of SARS-CoV-2 variants has caused clinicians and scientists to reconsider how to proceed with the development and use of anti-SARS-CoV-2 antibodies.

On 15 June 2021, the National Institutes of Health, in cooperation with the FDA, convened the third virtual Summit on COVID-19. The meeting, entitled “Anti-SARS-

CoV-2 Antibodies for Treatment and Prevention of COVID-19—Lessons Learned and Remaining Questions,” highlighted a “snapshot” of the current state of the science and served to inform future directions in this rapidly evolving field (Table 1). The participants included researchers and clinicians from academia, industry, and federal government agencies. The videocast (accessible on <https://videocast.nih.gov/watch=42078>) was open to the public and had more than 1500 participants.

The meeting launched with presentations highlighting the most recent clinical trial data on the use of antibodies to treat or prevent COVID-19 and the global landscape of emerging variants of concern (VOCs).

CONVALESCENT PLASMA

One of the first interventions evaluated to treat patients with COVID-19 was the transfusion of CP, which is blood plasma derived from patients who have recovered from COVID-19. The rationale for use of CP was based on its administration as treatment of Argentine hemorrhagic fever in a clinical trial that provided compelling evidence for the efficacy of CP for viral infections (10), as well as use of CP for treatment in previous influenza and coronavirus outbreaks over several decades (4, 11–14).

Several studies have evaluated the safety and efficacy of CP for treatment of COVID-19. Findings from a retrospective matched cohort study in patients treated with CP soon after admission showed some survival benefit compared with administration later during the disease course (15). A few trials reported efficacy of CP in early-stage disease, but CP treatment did not seem to benefit patients with advanced COVID-19 (15–17). The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (ClinicalTrials.gov: NCT04381936) showed that high-titer CP did not improve survival or other prespecified clinical outcomes in patients hospitalized with COVID-19 (18). Benefits did, however, seem to accrue to immunocompromised patients in some studies (19–21).

In April 2020, the national CP Expanded Access Protocol (EAP) (ClinicalTrials.gov: NCT04374370) was initiated to provide access to a therapy with possible clinical benefit for patients with COVID-19. The EAP was administered

Table 1. NIH Summit on Anti-SARS-CoV-2 Antibodies for Treatment and Prevention of COVID-19: Lessons Learned and Remaining Questions Agenda: 15 June 2021, Virtual Meeting

Summit Sessions	Summit Speakers
Introductory comments	Dr. Francis S. Collins, Director, NIH Dr. Janet Woodcock, Acting Commissioner, FDA Dr. Anthony S. Fauci, Director, NIAID, NIH
State of the science presentations	Convalescent plasma and hyperimmune globulin Dr. Peter Marks, FDA Antibodies for COVID-19 prevention Dr. Myron S. Cohen, UNC at Chapel Hill Antibodies for COVID-19 treatment Dr. Kara Chew, UCLA Dr. Jens Lundgren, Rigshospitalet, University of Copenhagen Mutations/variants of concern Dr. Bette Korber, Los Alamos National Laboratory
Mechanisms of action of functional antibodies that neutralize SARS-CoV-2 and/or eliminate SARS-CoV-2-infected cells	Presenter: Dr. Erica O. Saphire, La Jolla Institute for Immunology Moderator: Dr. Adrian McDermott, NIAID, NIH Dr. Christopher Barnes, Stanford University Dr. Michael Diamond, Washington University in St. Louis Dr. Rachel Liberatore, RenBio Dr. David Montefiori, Duke University Dr. Penny Moore, University of the Witwatersrand Dr. Laura Walker, Adagio Therapeutics
Preclinical delivery, pharmacology, and efficacy of anti-SARS-CoV-2 antibodies	Presenter: Dr. Ralph Baric, UNC at Chapel Hill Moderator: Dr. Connie Schmaljohn, NIAID, NIH Dr. Emmie de Wit, NIAID, NIH Dr. Christopher Ellis, FDA Dr. Tom Hope, Northwestern University Dr. Kevin Saunders, Duke University Dr. Skip Virgin, Vir Biotechnology
Real-world clinical use of anti-SARS-CoV-2 antibodies	Presenter: Dr. Katharine Bar, University of Pennsylvania Moderator: Dr. Rajesh Gandhi, MGH Dr. Ada Adimora, UNC at Chapel Hill Dr. Judith Currier, UCLA Dr. Fred Korley, University of Michigan Dr. Meagan O'Brien, Regeneron Dr. John Redd, HHS Office of the Assistant Secretary for Preparedness and Response Dr. Mark Williams, Eli Lilly
Wrap up and closing comments	Dr. Adrian McDermott, NIAID, NIH Dr. Connie Schmaljohn, NIAID, NIH Dr. Rajesh Gandhi, MGH Dr. Francis S. Collins, NIH

FDA = U.S. Food and Drug Administration; HHS = U.S. Department of Health and Human Services; MGH = Massachusetts General Hospital; NIAID = National Institute of Allergy and Infectious Diseases; NIH = National Institutes of Health; UCLA = University of California, Los Angeles; UNC = University of North Carolina.

by the Mayo Clinic as a single-group clinical protocol treating more than 100 000 patients at about 2700 sites. Although patients received many concomitant treatments over the course of the study, the EAP found that only CP from donor units with high antibody titers was associated with modest clinical benefit based on improvements in 7-day survival in patients who were not intubated, as well as in those who were not intubated, were aged 80 years or younger, and received CP within 72 hours of diagnosis (22).

These studies suggested that CP acts like a conventional antiviral, so benefit may be seen only when CP is administered early in the disease course with donor units containing potent, high-titer antibodies. Disappointingly, however, the C3PO (Convalescent Plasma in Outpatients With COVID-19) trial (ClinicalTrials.gov: NCT04355767) in recently diagnosed outpatients failed to show benefit (23).

ANTI-SARS-CoV-2 mAbs AND HIG

Similar challenges have been encountered in achieving clinically significant improvements in hospitalized

patients treated with mAbs and HIG in addition to standard of care. Anti-SARS-CoV-2 mAbs targeting the spike protein were developed rapidly and integrated into research studies. Hyperimmune globulin is composed of highly purified anti-SARS-CoV-2 antibodies from multiple donors who have recovered from COVID-19, rendering a product whose SARS-CoV-2 neutralization titer is several times higher than that of single-donor CP (24).

In 2 trials, ACTIV-3/TICO (Accelerating COVID-19 Therapeutic Interventions and Vaccines-3: Therapeutics for Inpatients With COVID-19) (ClinicalTrials.gov: NCT04501978) and ITAC (INSIGHT 013: Inpatient Treatment of COVID-19 With Anti-Coronavirus Immunoglobulin) (ClinicalTrials.gov: NCT04546581), patients with COVID-19 hospitalized within 12 days of symptom onset were randomly assigned to an investigational agent or a placebo group, both with standard of care. ACTIV is a public-private partnership among federal agencies, academia, and numerous industry partners managed by the Foundation for the National Institutes of Health (25). Overall, 5 antibody agents were studied in TICO,

including the single mAbs bamlanivimab (Eli Lilly) and sotrovimab (GlaxoSmithKline and Vir Biotechnology), as well as 2 mAb combinations, BRIL-196 plus BRIL-198 (Brii Biosciences) and AZD7442 (AstraZeneca). The fifth agent evaluated was an HIG (CSL Behring, Emergent BioSolutions, Grifols, and Takeda Pharmaceutical), a product that targets multiple epitopes and has been shown to be effective against several SARS-CoV-2 VOCs (26). The first 4 completed evaluations of bamlanivimab, BRIL-196 plus BRIL-198, sotrovimab, and HIG showed that the first 2 did not result in favorable outcomes and the latter 2 resulted in modest but statistically nonsignificant favorable outcomes compared with placebo (27-29). Studies of 2 agents, MP0420 (Molecular Partners-DARPin technology) and AZD7442, are ongoing. Thus, as with CP, it seems that mAbs and HIG administered after multiple days of illness may not be useful.

The results in outpatients were much more encouraging. The safety and efficacy of mAbs to treat COVID-19 in nonhospitalized patients has been evaluated in several clinical trials. The BLAZE-1 (Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies) trial (ClinicalTrials.gov: NCT04427501) evaluated intravenous bamlanivimab for early COVID-19. The phase 2 trial included a preplanned interim analysis (when the last patient randomly assigned to bamlanivimab reached day 11) that showed lower rates of hospitalization and emergency department visits for those receiving bamlanivimab than those receiving placebo, at 1.6% and 6.3%, respectively (30). This trial provided the basis for the first EUA for an mAb to treat COVID-19. Sotrovimab was evaluated in the COMET-ICE (COVID-19 Monoclonal Antibody Efficacy Trial - Intent to Care Early) phase 3 trial (ClinicalTrials.gov: NCT04545060). The trial was stopped early for efficacy because the mAb treatment substantially prevented progression to COVID-19, with an adjusted relative risk reduction of 85% (97.24% CI, 44% to 96%; $P = 0.002$) and with 1% of patients progressing in the sotrovimab group versus 7% in the placebo group (31). The FDA issued an EUA for sotrovimab in May 2021 (32).

The BLAZE-1 extension trial (ClinicalTrials.gov: NCT-04427501) and several trials of REGEN-COV (Regeneron) (ClinicalTrials.gov: NCT04425629) evaluated mAb combinations. The BLAZE-1 extension compared bamlanivimab-etesevimab versus either bamlanivimab alone or placebo in outpatients with mild to moderate COVID-19 (33). Compared with placebo, this mAb combination showed a 70% reduction in rates of hospitalization or death in the phase 3 trial among nonhospitalized patients with COVID-19; specifically, 2.1% of patients in the bamlanivimab-etesevimab group compared with 7.0% in the placebo group were hospitalized or died (absolute risk difference, -4.8 percentage points; [95% CI, -7.4 to -2.3 percentage points]; relative risk difference, $P < 0.001$) (34). The REGEN-COV trials assessed the mAb combination casirivimab-imdevimab delivered intravenously in outpatients. The phase 2 trial showed that participants who were seronegative for SARS-CoV-2 at study entry benefited more from the treatment than those who were seropositive, considering viral and clinical end points (35). The phase 3 trial results for 600 mg of casirivimab plus 600 mg of imdevimab included a reduction in symptom duration and a 70% relative risk

reduction in hospitalizations and deaths; specifically, 1% of patients treated with REGEN-COV versus 3% in the placebo group were hospitalized or died ($P = 0.0024$) (36, 37). A phase 2 dose-ranging trial (ClinicalTrials.gov: NCT04666441) testing intravenous and subcutaneous delivery of casirivimab-imdevimab in outpatients with SARS-CoV-2 infection showed similar viral load reductions independently of the dose and route of administration compared with placebo (36). Additional results were pending at the time of the Summit. Other mAbs are currently under evaluation in the ACTIV-2 (A Study for Outpatients With COVID-19) clinical trial (ClinicalTrials.gov: NCT04518410), including subcutaneous BMS-986414 (C135-LS) plus BMS-986413 (C144-LS) (Bristol Myers Squibb and Rockefeller University), AZD8895 plus AZD1061 (AstraZeneca), and intravenous SAB-185 (SAb Biotherapeutics)—a polyclonal antibody product.

In the prevention setting, mAbs could offer immediate protection for unvaccinated persons exposed to SARS-CoV-2 or those who have no specific exposure but work in high-risk settings. They could also be administered to patients who are unlikely to respond to—or in rare cases those who are allergic to components of—COVID-19 vaccines. Target populations for such preventive use of mAbs may include residents of nursing homes, household contacts, immunocompromised hosts, and certain individuals in high-incidence workplaces.

Nursing homes are areas of particularly high incidence, with nursing home residents and workers making up approximately one third of all COVID-19 deaths in the United States (38). Findings from the phase 3 BLAZE-2 study of postexposure prophylaxis (ClinicalTrials.gov: NCT04497987) served as proof of concept for the use of mAbs in this setting, showing reduced incidence of COVID-19, reduced symptoms, and no deaths among patients in nursing homes who were administered bamlanivimab versus placebo (39).

In the REGEN-COV 2069 phase 3 study (ClinicalTrials.gov: NCT04452318), the combination of casirivimab-imdevimab was administered subcutaneously to all contacts of a household in which 1 member had been diagnosed with COVID-19. Household contacts who received REGEN-COV showed no symptomatic cases of COVID-19 and a 50% reduction in overall rates of infection with SARS-CoV-2 compared with the placebo group (40). Data from the full study showed a relative risk reduction of approximately 81% between the REGEN-COV and placebo groups in the incidence of symptomatic SARS-CoV-2 infection; specifically, 1.5% of patients in the REGEN-COV group versus 7.8% in the placebo group had symptomatic infection (odds ratio, 0.17; $P < 0.001$) (41). The FDA recently expanded the REGEN-COV EUA for postexposure prophylaxis in persons who are at high risk for progression to severe COVID-19 (6).

The Summit included an update on emerging SARS-CoV-2 variants based on data from the Global Initiative on Sharing All Influenza Data as of 9 June 2021 (42). All emerging variants of interest have mutations in the *N*-terminal domain or the receptor-binding domain; many also carry mutations at the furin cleavage site (43). Many of these mutations have been shown to confer partial resistance to convalescent sera and neutralizing antibodies, indicative of immune pressure as a selective force (43). Publicly available databases

Table 2. Current Food and Drug Administration Emergency Use Authorized Anti-SARS-CoV-2 Monoclonal Antibodies to Treat or Prevent COVID-19*

Antibodies	Dose	Route	Developer	Indication	Variants of Concern With Reduced Activity (> 100-fold)	Supporting Trial(s)
REGEN-COV (casirivimab-imdevimab)	600 mg casirivimab, 600 mg imdevimab	IV, SQ	Regeneron	Postexposure prophylaxis	None†	NCT04452318 NCT04519437
REGEN-COV (casirivimab-imdevimab)	600 mg casirivimab, 600 mg imdevimab	IV, SQ (if IV is not feasible)	Regeneron	Treatment	None†	NCT04425629
Bamlanivimab-etesevimab	700 mg bamlanivimab, 1400 mg etesevimab	IV	Eli Lilly	Postexposure prophylaxis	Beta, Gamma, Delta [K417N], Mu‡	NCT04427501 NCT04634409
Bamlanivimab§-etesevimab	700 mg bamlanivimab, 1400 mg etesevimab	IV	Eli Lilly	Treatment	Beta, Gamma, Delta [K417N], Mu‡	NCT04427501
Sotrovimab	500 mg	IV	Vir Biotechnology/ GlaxoSmithKline	Treatment	None	NCT04545060

IV = intravenous; SQ = subcutaneous.

* Data from U.S. Food and Drug Administration. Emergency Use Authorization. Accessed at www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs on 29 September 2021.

† Pseudotyped virus-like particle neutralization data for SARS-CoV-2 variant substitutions with casirivimab and imdevimab together.

‡ Bamlanivimab and etesevimab are not authorized for use in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%. Pseudotyped virus-like particle neutralization data for SARS-CoV-2 variant substitutions with bamlanivimab and etesevimab together (1:2 molar ratio).

§ Bamlanivimab monotherapy Emergency Use Authorization revoked.

|| Pseudotyped virus-like particle neutralization data for SARS-CoV-2 variant substitutions with sotrovimab.

that are searchable and up to date contain information on SARS-CoV-2 therapeutics and resistance, including virus variants and spike mutations versus mAbs (26, 44).

Globally, the Alpha variant emerged in late 2020 and remained dominant until May 2021, when the Delta variant emerged. The Beta variant, which emerged in late 2020 in South Africa, was later detected on all continents; however, its global predominance was hampered by the fast-spreading Alpha and Delta variants. The Delta variant currently has a global presence, with apparent rapid transmission once established in a geographic region (43).

The mutations and variants of SARS-CoV-2 have implications for treatment and vaccine design. Although the EUA for bamlanivimab administered alone was subsequently revoked by the FDA because of the emergence of variants that affect the mAb epitope, other mAb combinations administered together under EUA, including bamlanivimab-etesevimab, sotrovimab, and casirivimab-imdevimab, remain effective against the Delta variant (45). However, when the Delta variant acquired the K417N mutation, the neutralization activity by the bamlanivimab-etesevimab combination was reduced by more than 1000-fold (Table 2) (46). Transitions to global prevalence can occur quickly; the transition to the G clade-SARS-CoV-2 that carries the D614G mutation in the spike protein—in spring 2020 took 6 to 10 weeks. The Delta variant is currently the major variant globally. Although the exact trajectory of future variants cannot be predicted, patterns of convergence and covariation can be studied to determine relevant variants and forms that can occur. This knowledge will inform the improvement of current antibody-based interventions and the design and development of next-generation COVID-19 vaccines.

SESSION 1 KEY THEME: CHARACTERIZATION OF FUNCTIONAL ANTIBODIES TARGETING SARS-CoV-2

Central to the selection of functional antibodies that can be used as potential therapeutic or prophylactic agents

is the characterization of the antibodies that can neutralize SARS-CoV-2 or eliminate SARS-CoV-2-infected cells. This requires a detailed analysis of the specific epitopes targeted by the antibody, delineation of the mechanisms of antiviral effect, characterization of the ability of the antibody to control viruses harboring mutations of concern, and determination of the efficacy of the antibody in animal models followed by evaluation in clinical studies.

The Coronavirus Immunotherapy Consortium (CoVIC) (47) was launched to evaluate potential therapeutic antibodies in side-by-side in vitro analyses using standardized platform assays and in vivo models. Findings from these comparative studies are used to create a profile of antibody activity that correlates with protective clinical efficacy and predicts clinically successful outcomes (47, 48).

To date, CoVIC has compiled 350 candidate therapeutics from more than 50 groups in academia, research institutions, industry and biotechnology companies, and government agencies (47, 48). These antibodies are evaluated by 8 partner laboratories according to CoVIC standardized testing protocols; CoVIC also assesses the ability of their compiled antibodies to retain their neutralizing activity to the VOCs (47, 48).

The session panelists noted an ongoing need to focus on VOCs, particularly on the location of mutations in the spike protein and which antibody classes can be combined to address commonly occurring escape mutants. This gap is being addressed by the ACTIV Tracking Resistance and Coronavirus Evolution initiative, designed to provide actionable information on emerging SARS-CoV-2 variants (49). The panelists also proposed that combining 2 receptor-binding domain binders with 1 N-terminal domain binder would provide more coverage on the spike protein and allow antibody cocktails that are more potent; however, structural factors must be considered to ensure that antibodies with different orientations do not block each other.

A focus on conserved epitopes is also an aspect that needs to be considered for identifying mAbs against variants, especially for development of bispecific antibodies. The panel proposed the use of broadly neutralizing antibody cocktails as a potential approach because target sites for these antibodies on the spike proteins are not routinely recognized by other antibodies (50-52). They noted that additional research is essential to better understand how antibodies with different Fc-mediated effector functions and specificities drive optimal antiviral activity.

The session panelists proposed that as additional mAbs are identified, these should be provided to CoVIC for comparative analysis. They concluded that these critical studies would provide a better understanding of how anti-SARS-CoV-2 antibodies target spike antigens and how mutations in the spike proteins result in immune escape. These research findings will also inform the selection of mAbs with relevant breadth and potency that can be combined as future therapeutics or prevention strategies.

SESSION 2 KEY THEME: PRECLINICAL DELIVERY, PHARMACOLOGY, AND EFFICACY OF ANTI-SARS-CoV-2 ANTIBODIES

The COVID-19 pandemic brought an urgent need to develop animal models to recapitulate the human disease phenotype to better understand the virus pathogenesis and to test therapeutic and preventive interventions. Many models were developed, including mouse, hamster, ferret, and nonhuman primate. Infection with SARS-CoV-2 manifests differently in different animal models. Nonhuman primates are typically a replication model with mild pathology, whereas ferrets and hamsters are useful as transmission models that develop severe disease with weight loss and prolonged recovery. A key goal for these models is to develop cell targets like those that become infected during natural infection in humans, including ciliated cells in the airways and type II alveolar epithelial cells in the alveoli. Current models show evidence of the biphasic disease patterns seen in humans, with early replication followed by clearance and immunopathogenic severe disease; however, the disease course is compressed in small animal models.

The human angiotensin-converting enzyme 2 (HuACE2) is the receptor of SARS-CoV-2 (53, 54). The mouse ACE2 is not sufficient to allow SARS-CoV-2 entry and replication, so mouse systems have been generated to express the HuACE2 gene as a transgene or through viral vectors. The K18 mouse model expresses the HuACE2 under the cytokeratin (K18) promoter (55). The Ad5-HuACE2 transduced mice were widely used to test the ability of multiple mAbs to prevent or treat COVID-19-like disease (56). Another approach was to create a mouse-adapted virus capable of infecting target cells and causing disease (57). Animal models developed to date have been useful in evaluation of mAbs; however, the therapeutic window is very narrow.

The role of the interaction between the Fc portion of antibodies and the Fc receptors can also be evaluated in the transgenic mouse models (58). Interactions between Fc and Fc γ R are required for *in vivo* protective activity of

neutralizing anti-SARS-CoV-2 mAbs by comparing the efficacy of the antibody treatment in animals expressing the human Fc γ R versus genetically defined Fc γ R-null mice. Furthermore, Fc domain variants engineered for selectively enhanced binding to activating Fc γ Rs exhibit improved efficacy using the SARS-CoV-2 mouse-adapted model (58). The Collaborative Cross mice, a recombinant inbred mouse strain (59, 60), have been valuable in addressing the natural genetic variation linked to SARS-CoV-2 pathogenesis. These mice were used to identify the susceptibility loci to extend the therapeutic window. Using a genetic mapping approach, 6 genes associated with susceptibility to infection were identified located on mouse chromosome 9 (Baric RS. Personal communication.). The orthologous genes, at the chromosome 3p21.31 gene cluster, were identified in human genome-wide association studies linked to individuals developing severe COVID-19 (61). The Syrian hamster model has also been used extensively because hamsters are susceptible to the original strain and new variants. These hamsters develop disease and serve as a model of viral transmission between animals (62).

The session panelists suggested that an optimal approach to mitigate variants is to focus on conserved SARS-CoV-2 epitopes, half-life extension of mAbs and Fc-mediated effector function, and use of antibody combinations. The concept of the conserved epitope is important for pandemic preparedness—there is a need to identify and develop mAbs that can protect against other coronaviruses in the future.

The remaining knowledge gaps highlighted during the session included exploring strategies to extend the therapeutic window, identifying correlates of protection from infection and disease, defining characteristics of antibodies essential to providing long-term immunity, defining the effect of antibody biodistribution on its performance, and developing animal models that recapitulate the longer-term effects of SARS-CoV-2 infection.

SESSION 3: REAL-WORLD CLINICAL USE OF ANTI-SARS-CoV-2 ANTIBODIES

This session focused on lessons learned, challenges, and potential future directions for real-world clinical use of anti-SARS-CoV-2 antibodies. Because clinical trials of mAbs have demonstrated efficacy in treatment of early COVID-19 (33-35), resulting in issuance of EUAs for mAb products, much of the discussion centered on these agents.

The panelists discussed challenges encountered regarding delivery and infrastructure both during clinical trials evaluating mAbs and during use as therapeutic agents after EUA. These challenges include the need for an appropriate outpatient setting with sufficient clinical staffing and resources to see trial participants or deliver parenteral mAb treatment to patients from an infection control perspective. This may be amplified when health care resources are stretched, when inpatients with severe disease are prioritized, and where clinical sites are in academic centers rather than community settings. Given the need to administer mAbs early in the disease course, it is necessary to promptly identify eligible patients and to coordinate where they can receive treatment or

participate in a clinical trial. This may be difficult, especially when testing sites are typically in separate locations and clinicians may not always be aware when their patients are being tested for SARS-CoV-2 outside their practice. Mobile medical units that can travel to patients and deliver treatments, as used in the BLAZE-2 trial (39), may overcome certain aspects of these challenges.

Lessons learned and challenges encountered about public health messaging and health inequities were discussed. As knowledge has evolved during the pandemic and mAbs have become available as therapeutic agents, public health messaging to both clinicians and patients has changed. Early in the pandemic, patients were told to isolate at home if they had COVID-19 and were not sick enough to require hospitalization. With the availability of mAbs to treat early COVID-19, certain patients at high risk for progression to severe disease were urged to seek early treatment in the outpatient setting after a positive test result for SARS-CoV-2. Adapting to this evolving messaging was difficult for both patients and clinicians. In addition, there have been numerous barriers to equitable delivery of mAbs, including systemic and structural inequities related to race/ethnicity and socioeconomic status. Geographic and transportation barriers to health care systems can also be important because many infusion centers for administering mAbs are located far from some patients' homes or sites of diagnosis.

Future directions and unanswered questions about the use of anti-SARS-CoV-2 antibodies were addressed. One question raised was whether the availability of routes of administration other than intravenous for antibody treatments could overcome some identified challenges and barriers to implementation. All FDA-authorized mAbs are currently delivered intravenously, with the exception of REGEN-COV, which is also authorized for subcutaneous administration (63). The potential use of mAbs as preventive treatments for immunocompromised persons who do not mount a protective immune response to vaccination was discussed. Although the field has advanced substantially, much remains to be done to achieve certain personalized approaches to treatment, such as rapid point-of-care diagnostic tests to identify variants to ensure that the correct treatment is provided.

CONCLUSION

The Summit highlighted advances that have been made using anti-SARS-CoV-2 antibodies for prevention and treatment of COVID-19. The presenters and panelists illustrated the clinical benefits when potent mAbs are administered early in the disease course for patients at high risk for progression to severe COVID-19. They also discussed ongoing studies to determine the potential benefit of high-titer CP antibodies or HIG in treating patients with COVID-19.

Several key knowledge gaps were identified on the basis of the snapshot of this field, including characterizing the specific spike protein epitopes and conserved regions targeted by anti-SARS-CoV-2 antibodies, delineating the mechanisms of action by which these antibodies bind to the targeted epitopes to prevent or control disease, studying different Fc-mediated effector functions and specificities driving

optimal antiviral activity and pharmacokinetics, developing alternate routes of administration, and improving animal models. The potential effect of mAb infusions on COVID-19 vaccine immunogenicity and efficacy remains unclear. Several preclinical and clinical studies (ClinicalTrials.gov: NCT04852978 and NCT04952402) addressing this issue are ongoing with the support of the U.S. Countermeasures Acceleration Group for the federal COVID-19 response in collaboration with the study product sponsors. The continuing emergence of SARS-CoV-2 variants underscores the critical need to identify classes of mAbs that can be successfully and effectively combined and to develop and evaluate broadly neutralizing antibody cocktails and bispecific antibodies as potential therapeutics. In addition, it is critical to develop solutions to the identified challenges associated with real-world clinical use of antibody therapies. Although this field has rapidly advanced, additional progress is critical for prevention and treatment of COVID-19 in the United States and worldwide.

From Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland (C.B.); Office of the Director, National Institutes of Health, Bethesda, Maryland (R.W.E., J.M.A., F.S.C.); Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland (A.M.L., A.S.F.); and Office of the Commissioner, Food and Drug Administration, Silver Spring, Maryland (J.W.).

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