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Outpatient Treatment of SARS-CoV-2 Infection to Prevent COVID-19 Progression

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Summary:

COVID-19 can progress from mild to severe disease and death. Reliable and facile treatments are urgently needed to stop disease progression. Here, we discuss the current outpatient treatment landscape and the urgent need for more accessible and effective therapeutic options.

Abstract

As of March 2021, COVID-19 has caused more than 123 million infections, and almost 3 million deaths worldwide. Dramatic advances have been made in vaccine development and non-pharmaceutical interventions to stop the spread of infection. But treatments to stop the progression of disease are limited. A wide variety of "repurposed" drugs explored for treatment of COVID-19 have had little or no benefit. More recently, intravenous monoclonal antibody (mAb) combinations have been authorized by the US FDA for emergency use (EUA) for outpatients with mild to moderate COVID-19 including some active against emerging SARS-COV-2 variants of concern (VOC). Easier to administer therapeutics including intramuscular and subcutaneous mAbs and oral antivirals are in clinical trials. Reliable, safe, effective COVID-19 treatment for early infection in the outpatient setting is of urgent and critical importance. Availability of such treatment should lead to reduced progression of COVID-19.

Five Key words: COVID-19, monoclonal antibodies. antivirals, outpatients

COVID-19 has had devastating consequences since surfacing in December of 2019 with at least 124.3 million cases and 2.7 million deaths worldwide as of the end of March 2021 (1). Over the first year of the pandemic, there has been great progress in understanding the biology, transmission (2, 3) and natural history of SARS-CoV-2 infection (3), and considerable success in the development and distribution of vaccines (4), as well as in the management of hospitalized patients (5). But far less progress has been made in outpatient treatment of COVID-19, the topic we will discuss.

The initial phase of COVID-19 is the acquisition of SARS-CoV-2 in the upper respiratory tract. This can be followed by asymptomatic infection [6], but many patients will develop symptomatic disease with risk of disease progression. A variety of risk factors for severe COVID-19 have been identified with advanced age being among the most important (6), emphasized by the extreme morbidity and mortality of COVID-19 in residents of long-term care facilities (7).

Provocative clinical trial results suggest that inhibition of viral replication during the acute phase of SARS-CoV-2 infection can thwart the progression of COVID-19 (8-13). However, our ability to provide early antiviral treatment(s) to prevent this progression of COVID-19 has been rather dismal. In part, this stems from the logistical barriers to early detection of SARS-CoV-2 infection and our inability to distinguish those who will remain asymptomatic from those who will have symptomatic infection and progressive disease. The limitation in SARS-CoV-2 testing has been well-documented (14), and outside of research and specific surveillance programs, prospective detection of asymptomatic and very early SARS-CoV-2 infection has been difficult. Further, while risk factors for progression of COVID-19 have been established (6, 15), predicting exactly who will progress remains a major challenge, and unfortunately some persons with minimal or no known risk factors develop severe and fatal COVID-19 (5). Therefore, many at risk for progression to severe COVID-19 are not

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diagnosed early and, when they are we remain are unable to predict which are most likely to benefit from treatment.

Another major challenge to early intervention in COVID-19 has been the paucity of therapeutic options. Filling this vacuum, especially early in the pandemic, patients and their providers turned to a wide variety of "repurposed agents" for outpatient treatment. Examples include, vitamin D, zinc, azithromycin, hydroxychloroquine, ivermectin and many other agents that were not subjected to robust clinical evaluation before deployment. When properly evaluated, these agents have not shown clinical benefits. For example, public interest in hydroxychloroquine fueled by political and media figures, stimulated hundreds of clinical trials (16) and off-label use; however, ultimately the Food and Drug Administration (FDA) withdrew its emergency use authorization (EUA) of this agent for treatment of COVID-19 given the absence of benefit and demonstrated potential for harm (17).

The disappointing, disorganized, and distracting experiences related to treatment of COVID-19 over the past year emphasize that traditional methods for drug development are absolutely required to identify safe and effective treatments. These methods include careful consideration of the biological plausibility of an intervention, demonstration of a substantial and reproducible antiviral effect *in vitro* (using validated assay systems), exploration of *in vivo* benefit(s) in small animals (e.g., mice, Syrian Hamsters, ferrets) (18) or non-human primates, assessment of toxicity in pre-clinical and animal studies, and well-designed and efficient randomized clinical trials (8, 11, 13).

COVID-19 prevention and treatment experiments in small animals have been consistently predictive. For example, the antiviral effects of remdesivir (19), molunpiravir (20)(MK 4482/EIDD 2801), and several monoclonal antibodies (mAbs) directed at the SARS-CoV-2 receptor binding domain (18, 21) protected small animals when these agents were given before or shortly after exposure to the virus. Such positive results ultimately led to the development of remdesivir, a mainstay antiviral treatment for hospitalized patients in the US (22), and supported a recent trial demonstrating the antiviral activity molnupiravir in volunteers with mild symptomatic COVID-19 (23), and the FDA EUA for mAbs

for outpatients with COVID-19 (24-26). These examples demonstrate that rigorous steps in drug development can be efficiently followed to provide a relatively rapid response during a pandemic.

To date, the FDA has granted EUA for two mAb combination regimens – casivirimab and imdevimab (25) and bamlanivimab and etesevimab (26). The agency withdrew approval for bamlanivimab as a single agent (27) following the emergence of resistant variants of concern (28). When given very early in the course of symptomatic infection, these mAb regimens demonstrate the ability to reduce the concentration of SARS-CoV-2 detected by the polymerase chain reaction (PCR) in a nasal specimen, while also reducing the risk of more severe illness (8-11, 13). Additional data suggest that those slow to mount a SARS-CoV-2 specific antibody response benefit the most from a mAb (13) and such patients are overrepresented in the high-risk group. In contrast, these agents appear to have little or no benefit in hospitalized patients (29), probably because inflammation and coagulopathy rather than viral replication play a greater pathogenic role during later stage disease.

The mAb treatments currently approved under EUA must increasingly confront SARS-CoV-2 variants of concern (VOC) that may escape neutralization (28, 30-36). The variants include: B.1.17, which is now a dominant strain in the United States, United Kingdom and Western Europe; P1, which is dominant in Brazil; and B.135.1 dominant in sub-Saharan Africa (35, 36). Currently, of the antibodies available through EUA the caseviramab and imdevinamab combination demonstrates the most consistent activity *in vitro* across the predominant VOC (25, 26, 28, 30, 31, 34, 36).

In addition, timely application of mAbs is handicapped in multiple ways. First, current use of EUA mAb requires a documented symptomatic infection (25, 26), but in the US obtaining a SARS-CoV-2 test, receiving results, and then obtaining a referral for treatment in a timely fashion can be difficult, especially in rural locations, for underserved populations, and during a surge of infections. Delayed treatment may reduce or eliminate the benefit of mAbs. This limitation may change with the sale of over the counter home tests in major pharmacy chains, if they are affordably priced (37).

A second challenge is the provision of outpatient treatment to patients with suspected or proven COVID-19. Currently, both mAbs combinations under EUA are given intravenously (Table 1) a major barrier to timely access. Some creative medical centers are administering mAbs in emergency departments or specialized COVID-19 outpatient infusion centers, but epidemic and endemic COVID-19 make this strategy difficult on a large and sustained scale. Easier routes of administration for mAbs, and involvement of commercial pharmacies for delivery, can make mAbs more widely available to those who can benefit most from them. Trials of subcutaneous and intramuscular mAbs are in progress as well (www.riseabovecovid.org, NCT04425629).

These challenges have led to limited utilization of mAbs for COVID-19 treatment that underscore the importance of the development of more patient-friendly routes of antiviral treatment administration, including oral and inhaled agents. The oral agent molnupiravir, which has demonstrated activity *in vitro* and in animal models, is in clinical development (NCT04746183). In a phase 2 study, molnupiravir reduced recovery of replication competent SARS-CoV-2 from nasal specimens (23). In another phase 2 study, single sub-cutaneous injection of peg-interferon-lambda lowered nasopharyngeal RNA shedding to undetectable levels more frequently than placebo, especially in participants with higher viral shedding (38). These are but a few of many antiviral drugs directed at SARS-Cov-2 in different phases of development (39).

Further, the US government's ACTIV-2 program, which is using an adaptive platform designed to find safe and effective antiviral therapies for outpatients with COVID-19, is currently testing not only new mAbs but also novel oral and inhaled agents (Table 2) with more agents in the pipeline (21, 39).

For all RNA viruses, the emergence of resistance with selective pressure is anticipated. Many SARS-CoV-2 variants demonstrate decreased susceptibility to convalescent plasma (40), some vaccine-evoked neutralizing antibodies (30, 32) and, as mentioned, some mAbs (27, 28, 30). Specific host defense defects, which prevent clearance of SARS-CoV-2 infection, appear to facilitate emergence of resistant variants, as well (41). Combination mAb therapy that considers viral protein structure and

drug binding and *in vitro* neutralization or neutralizing mAb that bind to conserved spike protein regions should be prioritized (33, 42). Antiviral agents against non-spike targets, such as molnupiravir, remdesivir, and others (39), should be active across current circulating variants of concern, but vigilance for emergence of drug resistance is essential.

Another emerging consideration is the interaction between early COVID-19 treatments and vaccination, which remains unclear. For example, COVID-19 in a fully vaccinated person suggests either inadequate immune response or infection with a variant capable of evading vaccine-induced immune responses. In both cases, adjunctive antiviral treatment would seem warranted, even if treatment can confuse learning as to whether vaccination alone might have limited COVID-19 progression. Further, the effects of previous use of mAb treatments on subsequent vaccine efficacy is unknown. Theoretically, mAb treatments could blunt immune response to subsequent vaccination; however, after natural infection, vaccination has been found to produce a robust and seemingly uncompromised immune response (43). This issue is under study within ACTIV-2 and the NIH COVID Prevention Network (CovPN). In contrast, recent reports of poor immune response to vaccination in some immune-compromised hosts (44) raises the potential importance of mAbs to provide passive immunity in this population.

Whether the immune response induced by SARS-CoV-2 vaccination impacts viral transmission, via reductions in the level and presence of virus in the upper respiratory tract, is beginning to be understood (45, 46) and the same may hold for early treatment of COVID-19 (9, 12). Ongoing household and close contact studies in which a COVID-19 index case has been treated (NCT04452318 and ACTIV-2) will also address this question. Importantly, based on recent results (9, 12), mAbs currently available by EUA for COVID-19 treatment may ultimately be extended for use as pre- and post-exposure prophylaxis.

In conclusion, antiviral treatment of early COVID 19 is needed to prevent progression of disease, the generation of SARS-CoV-2 VOCs, and secondary transmission. Progress has been made with first-

generation mAbs but these agents are underutilized due to the substantial logistical challenges outlined above, a general lack of provider and patient awareness of this therapeutic option, and gaps in understanding of how best to utilize these agents and identify patients with early infection most likely to derive maximal benefit. In addition, antiviral therapy may help prevent or reduce post-acute sequalae of COVID-19 that occur even in patients who do not require hospitalization (47, 48) . The NIH-sponsored ACTIV-2 study has extended follow-up and added assessments to help address these questions. We are heartened by the on-going efforts to develop antiviral agents that are easier to administer and can enhance uptake in the ambulatory setting. Since every hospitalized patient with severe COVID-19 was at one point an outpatient with early infection, we believe the development of reliable, early, rapid detection and timely treatment of outpatient COVID-19 to be among the most important priorities in our response to the COVID-19 pandemic.

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Table 1. Monoclonal Antibodies U.S. Food and Drug Administration Emergency Use Authorization (EUA) (25, 26)

Date	Product	Isotype	Approved Use	Restrictions	Results
11/21/20	Casirivimab + imdevimab - Administered as soon as possible after positive viral test for SARS-COV-2 and within 10 days of symptom onset - Infused over ≥ 60 minutes followed by a post-infusion observation period of ≥ 60 minutes	Recombinant human IgG1 monoclonal antibodies	Treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19, hospitalization, or both. This includes treatment for those who are 65 years of age or older or who have certain chronic medical conditions.	Not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19	Shown to reduce COVID-19-related hospitalization or emergency room visits in patients at high risk for disease progression within 28 days after treatment when compared to placebo. Viral load reduction in patients treated with casirivimab and imdevimab was larger than in patients treated with placebo at day seven. Evidence that casirivimab and imdevimab administered together may be effective came from the predefined secondary endpoint of medically attended visits related to COVID-19, particularly hospitalizations and emergency room visits within 28 days after treatment. For patients at high risk for disease progression, hospitalizations and emergency room visits occurred in 3% of casirivimab and imdevimab-treated patients on average compared to 9% in placebo-treated patients. The effects on viral load, reduction in hospitalizations and ER visits were similar in patients receiving either of the two casirivimab and imdevimab doses.
02/09/21	Bamlanivimab + etesevimab - Administered as soon as possible after positive viral test for SARS-COV-2 and within 10 days of symptom onset - Infused over ≥ 60 minutes followed by a post-infusion observation period of ≥ 60 minutes	Recombinant neutralizing human IgG1 monoclonal antibodies	Treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19, hospitalization, or both. This includes treatment for those who are 65 years of age or older or who have certain chronic medical conditions.	Not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19	Based on a randomized, double-blind, placebo-controlled clinical trial in 1,035 non-hospitalized adults with mild to moderate COVID-19 symptoms who were at high risk for progressing to severe COVID-19. Of these patients, 518 received a single infusion of bamlanivimab 2,800 milligrams and etesevimab 2,800 milligrams together, and 517 received placebo. The primary endpoint was COVID-19 related hospitalizations or death by any cause during 29 days of follow-up. Hospitalization or death occurred in 36 (7%) patients who received placebo compared to 11 (2%) patients treated with bamlanivimab 2,800 milligrams and etesevimab 2,800 milligrams administered together, a 70% reduction. All 10 deaths (2%) deaths occurred in the placebo group. Thus, all-cause death was significantly lower in the bamlanivimab 2,800-milligram and etesevimab 2,800-milligram group than the placebo group.

Table 2. Antiviral Agents in ACTIV-2			
Agent	Antiviral Class	Route of Administration	Phase of Study
Bamlanivimab (8)	Monoclonal antibody	Intravenous	Completed Phase 3
Brii-196 and Brii-198 (49)	Monoclonal antibody	Intravenous	Phase 3
AZD8895 and AZD1061 (50)	Monoclonal antibody	Intravenous	Phase 2
AZD8895 and AZD1061 (50)	Monoclonal antibody	Intramuscular	Phase 2
Camostat mesylate (51)	Protease inhibitor	Oral	Phase 2
Interferon beta (52)	Immune modulator	Inhaled	Phase 2
SAB 185 (53)	Polyclonal antibody	Intravenous	Phase 2
BMS-986414 and BMS-986413 (54)	Monoclonal antibody	Subcutaneous	Phase 2