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Anti-SARS-CoV-2 Therapeutics can Effectively Treat, Prevent COVID-19 Infection (*Evidence updated through 11/30/21*)

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Introduction

Coronavirus disease 2019 (COVID-19) Treatment Guidelines recommend anti-SARS-CoV-2 monoclonal antibodies (mAb) for treatment of mild to moderate COVID-19 infection and for post-exposure prophylaxis (PEP) of COVID-19 infection.[1]

Individuals 12 years of age or older and weighing at least 40 kg who are at high risk of progression to severe COVID-19 are eligible for mAb treatment in outpatient settings. Some of the risk factors for severe COVID-19 infection are outlined in Table 1.[2]

Table 1. Some Risk Factors for Severe COVID-19 Illness.[2]

• Older age
• Obesity
Underlying comorbidities such as: • Cardiovascular disease • Hypertension • Chronic lung disease • Chronic kidney disease • Immunosuppressive conditions • Neurodevelopmental disorders
• People from racial or ethnic minority groups
• People with disabilities
• Pregnancy

The mAbs outlined in Table 2 are available for use by Emergency Use Authorization (EUA) for non-hospitalized individuals.[3-5]

Table 2. Monoclonal Antibodies with EUA for Outpatients.

	Indication	
	Treatment	PEP
Bamlanivimab and Etesevimab	✓	✓
Casirivimab and Imdevimab	✓	✓
Sotrovimab	✓	

Abbreviation: PEP = post-exposure prophylaxis

The EUAs allow for a one-time dose for treatment of COVID-19 infection. The casirivimab and imdevimab mAb combination and the bamlanivimab and etesevimab mAb combination also have EUAs for PEP for individuals who are not fully vaccinated or not expected to mount an adequate immune response to vaccination.[3-5]

Emergency use authorization requests have recently been submitted to the FDA for 3 new products: oral antiviral agents molnupiravir and Paxlovid™ (PF-07321332/ritonavir), and a long-acting mAb, a tixagevimab and cilgavimab.[6-9] A brief summary of these products will be provided at the end of the newsletter.

Monoclonal Antibodies Demonstrate Efficacy, Safety.

Authorization of mAbs for treatment of COVID-19 was based on analysis of phase 3 data from a randomized, double-blind, placebo-controlled trials (Table 3), which demonstrated safety and efficacy in patients at high risk for developing severe COVID-19 infection. *(Note: there is a potential risk of treatment failure from viral variants resistant to bamlanivimab and/or etesevimab. A list of states and territories in which bamlanivimab and etesevimab are not currently authorized based on current prevalence of specific variants is available online from the FDA.)*[3-5]

Table 3. Efficacy of mAbs for Treatment of COVID-19.[3-5]

Primary Endpoint *Day 29*	Casirivimab 600 mg and Imdevimab 600 mg (IV) (n=736)	Placebo (n=748)
COVID-19-related hospitalization or all-cause death	7 (1.0%) RRR 70% (95% CI NR, p=0.0024) NNT 46	24 (3.2%)

Primary Endpoint *Day 29*	Bamlanivimab 700 mg and etesevimab 1400 mg (IV) (n=511)	Placebo (n=258)
COVID-19-related hospitalization or all-cause death	4 (0.8%) RRR 87% (95% CI NR, p<0.0001) NNT 20	15 (5.8%)

Primary Endpoint *Day 29*	Sotrovimab 500 mg (IV) (n=528)	Placebo (n=529)
All-cause hospitalization or death	6 (1.1%) RRR 79% (95% CI, 50 to 91%) NNT 22	30 (5.7%)

Abbreviations: CI = confidence interval; IV = intravenous; NNT = number needed-to-treat; NR = not reported; RRR = relative risk reduction.

The casirivimab and imdevimab combination and bamlanivimab have also demonstrated efficacy in PEP trials.[3,4] Subcutaneous casirivimab 600 mg and imdevimab 600 mg reduced the odds of a positive COVID-19 test after exposure relative to placebo by 81% over 29 days (adjusted OR 0.17; p<0.001).[4] Bamlanivimab was studied without etesevimab for PEP which found that it reduced symptomatic COVID-19 infection relative to placebo over 57 days (adjusted OR 0.43; p<0.001) in exposed individuals.[3] The FDA concluded that it is reasonable to expect that bamlanivimab

and etesevimab together may also be safe and effective for PEP based on the totality of evidence.[3]

All 3 mAbs were well tolerated in clinical trials, with an incidence of infusion-related reactions similar to placebo at about 1%. Few cases of anaphylaxis were reported, and all resolved with treatment.[3-5]

The U.S. Department of Health and Human Services (HHS) currently distributes these treatments to the states and they are available at no charge to the patient. Weekly distribution amounts for each state are determined by HHS based on weekly reports of new COVID-19 cases, hospitalization rates, and current mAb utilization. The COVID-19 Community Vulnerability Index is also considered by the Oregon Health Authority.[10]

More information can be found on the OHA mAb webpage. The OHA can also be contacted with questions at: ORESF8.LogisticsChiefs@dhsoha.state.or.us

Pharmacists Prescribe, Administer REGEN-COV

On August 31, 2021, the Public Health and Pharmacy Formulary Advisory Committee (PHPFAC) for the Oregon Board of Pharmacy approved a protocol for pharmacist prescribing and subcutaneous administration of REGEN-COV. On September 13, the 9th amendment of the Public Readiness and Emergency Preparedness (PREP) Act was declared which also allows licensed pharmacists, qualified pharmacy technicians, and licensed or registered pharmacy interns to administer COVID-19 therapeutics subcutaneously, intramuscularly, or orally in accordance with FDA authorization.[11] The 9th amendment specifically outlines criteria in which these licensed pharmacy personnel may practice.[11] Such licensees are bound to practice within the scope of the PREP Act just as they would be if practicing under the PHPFAC statewide protocol.

New Therapeutic Options Expected Soon

On November 30, the FDA Antimicrobial Drugs Advisory Committee reviewed the EUA submission for molnupiravir oral capsules.[12] The FDA is soon expected to review EUA submissions for Paxlovid™ (PF-07321332/ritonavir) oral combination therapy, and AZD7442, a long-acting mAb combination of tixagevimab and cilgavimab.

Molnupiravir is an oral prodrug of the antiviral ribonucleoside analog N-hydroxycytidine which inhibits coronavirus replication. Evidence for efficacy comes from a 5-day course of molnupiravir studied in non-hospitalized, unvaccinated, non-pregnant, COVID-19-positive adults with 5 days or less of mild or moderate symptoms.[12-15] All participants had at least one risk factor for development of severe infection. Study results found molnupiravir decreases the risk of hospitalization (≥24 hours) or all-cause death through 28 days by 3% versus placebo in this population (6.8% vs. 9.7%, respectively; 95% CI, 0.1 to 5.9%; number needed-to-treat [NNT] = 35).[12-15] Only about 6% of trial participants were located in the United States.[12]

Interim analysis of a 5-day course of Paxlovid™ (PF-07321332/ritonavir), with the same primary endpoint and similar eligibility criteria as the molnupiravir trial, found the drug combination reduced hospitalizations or death through 28 days by 5.7% versus placebo (1.0% vs. 6.7%, respectively; p<0.0001; NNT = 18).[16] Efficacy increased if Paxlovid™ was initiated within 3 days of symptom onset.[16] No deaths were reported in patients who received Paxlovid™ as compared to 1.6% in patients who received placebo. About 45% of trial participants were located in the United States.[16]

Little information is available at this time to make conclusions about the potential real-world safety of these two oral antiviral products. When molnupiravir was reviewed, the Antimicrobial Drug Advisory Committee voiced concerns about potential teratogenicity, genotoxicity, and mutagenesis of molnupiravir, and the effectiveness of the drug in patients with diabetes, in patients with positive baseline antibodies against COVID-19, and in patients with new COVID-19 variants, such as Omicron (B.1.1.529).[12]

AZD7442 (tixagevimab and cilgavimab) is the first mAb cocktail to be studied intramuscularly for both pre-exposure prophylaxis (PrEP) and treatment of COVID-19. In the PrEP trial, more than 75% of participants had co-morbidities that put them at high risk for severe COVID-19 if they were to become infected, including people who are immunocompromised and may have a reduced immune response to vaccination.[17] Participants at the time of screening were unvaccinated adults and had a negative point-of-care SARS-CoV-2 serology test. A one-time injection of AZD7442 reduced the incidence of symptomatic COVID-19 by 83% relative to placebo over 6 months with no cases of hospitalization from COVID-19 or death.[17] In the placebo arm, there were 5 cases of severe COVID-19 and 2 COVID-19-related deaths at 6 months.[17] In an exploratory analysis of the treatment trial in mostly high-risk non-hospitalized adult participants with 3 days or less of mild or moderate symptoms of COVID-19, a one-time injection of AZD7442 reduced the incidence of hospitalization from COVID-19 or all-cause death by 88% relative to placebo through Day 29.[17]

Conclusion

These therapies under EUA provide more tools to potentially prevent the development of severe COVID-19 infection. Both REGEN-COV and AZD7442 provide convenient alternative routes of administration for mAb therapy that do not require intravenous line placement. The new oral antivirals may also provide convenient options for patients who present early with

symptoms from COVID-19 infection. Adequate and accessible supply of COVID-19 tests are critical to the success and utilization of these new therapies. More information on the safety of all of these therapies and their real-world effectiveness against evolving SARS-CoV-2 viral variants will determine their ultimate impact on this pandemic.

The FDA Adverse Event Reporting System (FAERS) Public Dashboard was launched for COVID-19 EUA products. The COVID-19 EUA FAERS Public Dashboard provides weekly updates of adverse event reports submitted to FAERS for drugs and therapeutic biological products used under EUA in COVID-19.[18] Providers using these therapies are encouraged to routinely review this dashboard and are required to submit adverse events potentially related to these therapeutic agents to MedWatch.[19]

Peer Reviewed By: Shimi Sharief, MD, MPH, Senior Health Advisor, Oregon Health Authority

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