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COVID-19 Therapeutics Update: Where Are We Now? *(Evidence updated through 3/31/23)*

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Introduction

As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to mutate since the original strain was identified, options to treat Coronavirus Disease 2019 (COVID-19) have also changed in the past year. All of the medications listed in Table 1 have received, or had received, approval or emergency use authorization (EUA) by the US Food and Drug Administration (FDA) to treat or prevent COVID-19.

Table 1. Medications Authorized or Approved by FDA from 2020-2022 to Prevent or Treat COVID-19.

Antivirals:
Molnupiravir
Nirmatrelvir – ritonavir
Remdesivir

Immune Modulators:
Anakinra
Baricitinib
Tocilizumab

Monoclonal Antibodies:
Bamlanivimab
Bamlanivimab – estesevimab
Bebtelovimab
Casirivimab – imdevimab
Sotrovimab
Tixagevimab – cilgavimab

COVID-19 Antibodies:
Convalescent plasma

With the emergence of the SARS-CoV-2 Omicron variant and its subvariants[1], the FDA has revoked the Emergency Use Authorization (EUA) of all the monoclonal antibodies so they can no longer be prescribed. The immune modulators are restricted to hospitalized patients with COVID-19 who require supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO). This leaves only the antivirals and convalescent plasma to treat COVID-19 in non-hospitalized individuals at high risk for progressing to severe disease. As the COVID-19 landscape continues to change with an evolving virus and increasing population immunity, this article will present updated research for these outpatient treatments.

Nirmatrelvir and Ritonavir (PAXLOVID)

The FDA granted EUA for nirmatrelvir and ritonavir (NM/r) in December 2021 to treat mild or moderate COVID-19 in individuals at high risk for developing severe disease, including hospitalization or death.[2] The drug product was recently endorsed by an FDA advisory committee for full FDA approval.[3]

Table 2. Nirmatrelvir and Ritonavir Treatment.[2]

Mechanism of Action	Viral protease inhibitor that halts viral replication
Authorized Use	Emergency Use Authorization for treatment of mild to moderate COVID-19
Eligible Population	Age ≥12 years, weight ≥40 kg, at high risk for severe disease
Prescribing Window	Initiate within 5 days of symptom onset
Assessment	Renal impairment; hepatic impairment; drug interactions
Administration Route	Oral
Duration of Therapy	5 days

Authorization of NM/r was based on the Phase 3 trial, EPIC-HR (Table 3).[4] The trial included unvaccinated, non-hospitalized patients with mild or moderate COVID-19 who had at least 1 risk factor for developing severe disease. The trial started in July 2021 and was completed in December 2021. Delta was the predominant circulating SARS-CoV-2 variant during the clinical trial.[4]

Table 3. Results from Phase 3 EPIC-HR Trial.[4]

Primary Endpoint	Nirmatrelvir-ritonavir	Placebo
COVID-19-related hospitalization or all-cause death	0.77%	6.31%
	-5.62% (95% CI, -7.21 to -4.03); NNT = 18 over 28 days if treated within 5 days of symptoms onset	
Abbreviations: CI = confidence interval; NNT = number needed to treat		

In the unpublished Phase 3 trial EPIC-SR, vaccinated patients with COVID-19 treated with NM/r who were at low risk for progressing to severe disease did not experience alleviation of symptoms any faster than those given placebo.[5,6] The study also did not find that NM/r reduced risk of hospitalization from COVID-19 or all-cause death.[5,6] In the unpublished Phase 3 trial EPIC-PEP, post-exposure prophylaxis with NM/r did not provide protection from positive COVID-19 test results in asymptomatic adults exposed to household contacts with COVID-19.[6,7] Therefore, NM/r should be reserved for individuals with mild or moderate COVID-19 who are at high risk for severe disease.

Real world effectiveness and safety of NM/r should be routinely monitored as levels of immunity against COVID-19 change and SARS-CoV-2 variants continue to evolve. From January through March 2022, Clalit Health Services, which covers 52% of the Israeli population, found that NM/r continued to reduce COVID-19-related hospitalizations and death from the B.1.1.529 Omicron variant in people 65 years of age and older, but NM/r did not reduce these events in people 40-64 years of age.[8] Likewise, data from a population-based cohort in Ontario, Canada, also found that NM/r continued to reduce COVID-19-related hospitalizations and death in older vaccinated adults (median age of 77 years).[9] The drug remained well tolerated in those eligible for treatment.[8,9] The FDA has concluded that NM/r has likely retained efficacy at reducing hospitalizations and death in high risk vaccinated individuals or individuals with immunity from previous infection, even with the SARS-CoV-2 Omicron variant and its subvariants.[6]

Rebound phenomenon after treatment with NM/r has been reported in the literature, but cases have been mild and all have resolved without further intervention.[10-12] In a cohort of 484 high-risk patients treated with NM/r, only 4 patients (0.8%) experienced rebound of mild symptoms.[12] The FDA could not identify a clear association between NM/r treatment and COVID-19 rebound in a comprehensive analysis, and data show that this phenomenon is observed in both those treated with NM/r and those not treated.[6]

Treatment with NM/r may help prevent "Long COVID", the disease encompassing the post-acute sequelae of SARS-CoV-2 infection, based on a retrospective study from the US Department of Veterans Affairs.[13] There are also case reports that NM/r helped treat "Long COVID"[14] and this may be an area of study where clinical trials are warranted. Study data will begin to emerge that will help clinicians understand how best to treat these individuals.

Pregnancy is a risk factor for severe COVID-19 and has been associated with higher rates of complications in pregnancy or childbirth, so individuals with COVID-19 who are pregnant are eligible for NM/r.[15] No other oral treatment options are available for patients who are pregnant or breast-feeding. A case series of 47 pregnant patients with mild or moderate COVID-19 at high risk for severe disease (64% had an additional morbidity) were treated with NM/r without serious adverse events.[16] The American College of Obstetricians and Gynecologists advise obstetric care clinicians to consider the use of NM/r in non-hospitalized pregnant individuals with mild to moderate COVID-19, particularly if one or more additional risk factors are present (e.g. body mass index >25, chronic kidney disease, diabetes mellitus, cardiovascular disease).[17] Clinicians should weigh the available data against the individual risks of COVID-19 in pregnancy for each case.[17]

It is not yet known whether longer durations of NM/r treatment are beneficial in patients with mild or moderate COVID-19 who are moderately or severely immunocompromised. Pfizer is currently conducting a randomized clinical trial (EPIC-IC, NCT05438602) that evaluates longer durations of NM/r treatment for immunocompromised individuals with mild or moderate COVID-19.[18]

Molnupiravir (LAGEVRIO)

The FDA granted EUA for molnupiravir in December 2021 to treat mild or moderate COVID-19 in adults at high risk for developing severe disease, including hospitalization or death.[19]

Table 4. Molnupiravir Treatment.

Mechanism of Action	Nucleoside analog that inhibits viral replication by viral mutagenesis
Authorized Use	Emergency Use Authorization for treatment of mild to moderate COVID-19
Eligible Population	Age ≥18 years, at high risk for severe disease, and other treatments not accessible or available
Prescribing Window	Initiate within 5 days of symptom onset
Assessment	Pregnancy status, contraceptive status, breastfeeding status
Administration Route	Oral
Duration of Therapy	5 days

Authorization of molnupiravir was based on the Phase 3 trial, MOVe-OUT (Table 5).[20] The trial included unvaccinated, non-hospitalized adults with mild or moderate COVID-19 who had at least 1 risk factor for developing severe disease. Individuals who were pregnant or breastfeeding were excluded. The trial started in May 2021 and was completed in November 2021. Delta was the predominant circulating SARS-CoV-2 variant during the clinical trial.[20]

Table 5. Results from Phase 3 MOVe-OUT Trial.[20]

Primary Endpoint	Molnupiravir	Placebo
All-cause hospitalization or death	6.8%	9.7%
	-3.0% (95% CI, -5.9 to -0.1); NNT = 34 over 29 days if treated within 5 days of symptoms onset	
Abbreviations: CI = confidence interval; NNT = number needed to treat		

Real world effectiveness and safety of molnupiravir should also be routinely monitored as levels of immunity against COVID-19 change and SARS-CoV-2 variants continue to evolve. From April through August 2022, the United Kingdom's National Health Service conducted an open-label randomized clinical trial in vaccinated patients infected with the B.1.1.529 Omicron variant.[21] Individuals who received molnupiravir instead of usual care did not experience a reduction in all-cause hospitalization or death in the first 28 days, but patients reported a faster time to full recovery of COVID-19 symptoms versus usual care (9 days vs. 15 days).[21] Molnupiravir continued to show a strong safety profile in those who received treatment.[21]

Because molnupiravir induces mutagenesis into the viral genome, there is potential that molnupiravir could drive viral mutations that spread. A study, which has not yet been peer-reviewed, investigated global RNA sequencing databases and found a signature in viral RNA that may be associated with molnupiravir mutagenesis.[22] The study makes a case that molnupiravir could yield mutated SARS-CoV-2 with the capacity to spread, but it is not clear whether molnupiravir can contribute to new infectious variants, or whether it is simply creating weakened viruses unable to spread or cause disease. It is already well understood that SARS-CoV-2 has the capacity to generate plenty of mutations on its own, even in the absence of molnupiravir.[1]

Remdesivir (VEKLURY)

A 3-day course of remdesivir was approved by the FDA in January 2022 for non-hospitalized infants, children and adults with mild or moderate COVID-19 in order to prevent progression to severe disease.[23] Previously, use of remdesivir was limited to hospitalized patients after trials found 5 days of remdesivir provided clinical benefit but did not reduce mortality.[23]

Table 6. Remdesivir Treatment.[23]

Mechanism of Action	Nucleotide analog ribonucleic acid (RNA) polymerase inhibitor that halts viral replication
Approved Use	Approved for treatment of mild to moderate COVID-19
Eligible Population	Age ≥28 days, weight ≥3 kg, at high risk for severe disease
Prescribing Window	Initiate within 7 days of symptom onset
Assessment	Renal impairment, hepatic impairment, prothrombin time
Administration Route	Intravenous infusion
Duration of Therapy	3 days

Approval of remdesivir for outpatient use was based on the Phase 3 trial, PINETREE (Table 7).[24] The trial included unvaccinated, non-

hospitalized children and adults with mild or moderate COVID-19 who had at least 1 risk factor for developing severe disease. The trial started in September 2020 and was completed in April 2021. Delta was the predominant circulating SARS-CoV-2 variant during the clinical trial.[24]

Table 7. Results from Phase 3 PINETREE Trial.[24]

Primary Endpoint	Remdesivir	Placebo
COVID-19-related hospitalization or all-cause death	0.7%	5.3%
	HR 0.13 (95% CI, 0.03 to 0.59); NNT = 22 over 28 days if treated within 7 days of symptoms onset	
Abbreviations: CI = confidence interval; HR = hazard ratio; NNT = number needed to treat		

Real world effectiveness and safety of remdesivir should also be routinely monitored as levels of immunity against COVID-19 change and SARS-CoV-2 variants continue to evolve. A 3-day outpatient course of remdesivir in high-risk patients from Italy who had mild or moderate COVID-19 from February through May 2022 was retrospectively compared to matched controls who did not receive antiviral treatment, including oral antivirals.[25] The study showed that remdesivir continues to significantly reduce the risk of disease progression, including hospitalization.[25] A single-center, prospective cohort study in Toronto, Canada, also found that remdesivir continues to provide significant protection against hospitalization in solid organ transplant patients with mild or moderate COVID-19.[26] Remdesivir has also continued to demonstrate that it is safe and well tolerated.[25,26]

Convalescent Plasma

Convalescent plasma is an antibody-rich blood product donated from people who have recently recovered from COVID-19, preferably from one of the predominant circulating variants. The FDA has granted EUA for use of convalescent plasma in non-hospitalized patients with immunosuppression, which is supported by clinical trials and a systematic review with meta-analysis.[27-30]

Table 8. Convalescent Plasma Treatment.[27]

Mechanism of Action	Direct neutralization of the virus
Authorized Use	Emergency Use Authorization for treatment of COVID-19 in people with immunosuppression
Eligible Population	Adult and pediatric patients with immunosuppression at high risk for severe disease
Prescribing Window	Not specified
Assessment	Prior history of severe allergic reactions or anaphylaxis to plasma transfusion
Administration Route	Intravenous infusion
Duration of Therapy	Based on physician's medical judgement

Conclusion

As SARS-CoV-2 continues to evolve, it is important to continue to study authorized or approved treatments. The COVID-19 antivirals currently available continue to demonstrate real world effectiveness and safety in individuals with mild or moderate COVID-19 since they were originally studied in Phase 3 clinical trials. These treatments may not have the same efficacy as when they were originally studied due to increasing immunity, but they continue to provide real benefit, such as faster resolution of symptoms and decreased risk for hospitalization, especially to those who are older. The National Institutes of Health, which regularly updates their COVID-19 treatment guidelines, gives its strongest recommendation for NM/r, but remdesivir is also a preferred therapy.[31] Molnupiravir is limited as an alternative option because of its presumed lower relative efficacy versus the other antivirals.[31]

NIH COVID-19 Treatment Guidelines[31] for Patients at High Risk of Progressing to Severe COVID-19

Preferred therapies:

- Ritonavir-boosted nirmatrelvir
- Remdesivir

Alternative therapy when preferred therapies are not available or clinically appropriate:

- Molnupiravir

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