EDITORIALS

# The Goldilocks Time for Remdesivir Is Any Indication Just Right?

Emily L. Heil, Pharm.D., and Shyam Kottilil, M.D., Ph.D.

For 2 years, we have been under siege by a lingering global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In an ideal world, widespread access to and acceptance of vaccines to prevent SARS-CoV-2 infection could end the current pandemic; however, given imperfect vaccine uptake and ongoing emergence of variants, it is likely that SARS-CoV-2 will become endemic. Thus, there is a continued need for therapies that can be used early in the disease course to reduce the risk of disease progression, prevent transmission, and be widely distributed to meet global demand. Monoclonal antibodies against the SARS-CoV-2 spike protein have been shown to reduce viral replication and hospitalization.[1,2] Antiviral agents could work similarly to further reduce hospitalizations and mortality from coronavirus disease 2019 (Covid-19). Figure 1 shows current options for Covid-19 therapy.

Remdesivir, a nucleotide analogue prodrug that inhibits the viral RNA-dependent RNA polymerase, was approved by the Food and Drug Administration in October 2020 for adults and select pediatric patients with severe Covid-19 who require hospitalization. In a randomized, double-blind, placebo-controlled trial, it was shown to reduce the median time to clinical improvement from 15 days to 10 days, with a larger benefit seen when treatment was started earlier in the disease course.[3] Remdesivir has since been evaluated in other trials, with mixed results, as the use of systemic glucocorticoids has increased.[4,5] In the most recent DisCoVeRy trial, which showed no clinical benefit of treatment with remdesivir, the median time from symptom onset to initiation of treatment was 9 days, long after the time of the peak viral load in most patients, reinforcing the theory that remdesivir is more likely to have a clinically meaningful benefit before hospitalization than later in the disease course.[5]

Gottlieb et al. conducted a clinical trial the results of which are now published in the *Journal*[6] to evaluate early outpatient remdesivir treatment to prevent progression to severe Covid-19. Unvaccinated patients with confirmed SARS-CoV-2 infection and at least one risk factor for progression to severe disease who had onset of symptoms within 7 days before randomization were assigned to receive a 3-day outpatient course of intravenous remdesivir or placebo. The percentage of patients who had a Covid-19 related hospitalization was significantly lower in the remdesivir group than in the placebo group (0.7% vs. 5.3%; hazard ratio, 0.13; 95% confidence interval, 0.03 to 0.59); these results equate to a difference of 47 fewer hospitalizations per 1000 infections, a clinically significant finding in an overwhelmed health care system. Notably, no deaths had occurred in either group by day 28. However, the change in viral load, determined with the use of nasopharyngeal swabs, from baseline to day 7 in the remdesivir group was similar to that in the placebo group.

Although the findings of this trial represent the most promising of any remdesivir study to date because of the timely administration of the medication, several practical limitations must be noted. First, the exclusion of vaccinated patients limits understanding of the utility or requirement of early antiviral therapy in vaccinated persons with breakthrough infections. Second, the lack of effect of remdesivir on SARS-CoV-2 viral loads reflects that the way in which this medication improves a patient s clinical disease

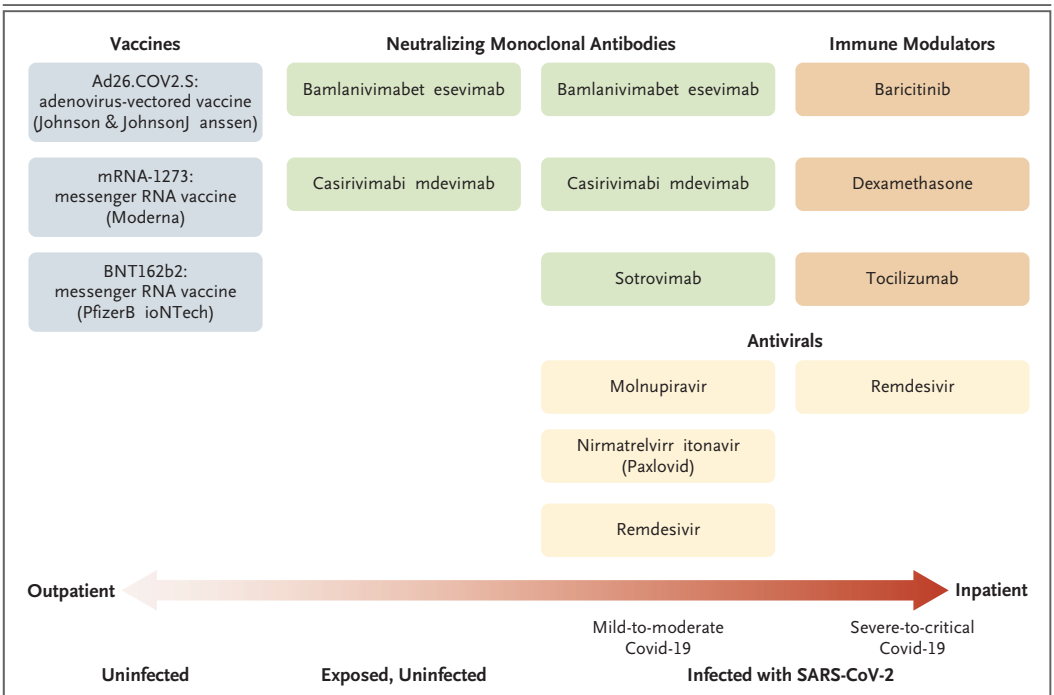


**Figure 1. Current and Pending Therapeutics for Covid-19 in the United States.**

Clinical strategies to reduce morbidity and mortality from coronavirus disease 2019 (Covid-19) are designed according to infection status and the stage of disease. First, for uninfected persons, one of three Covid-19 vaccinations is the most appropriate intervention to prevent development of Covid-19. Second, for those who have a high risk of progression to a more severe case of Covid-19, postexposure prophylaxis with combination neutralizing monoclonal antibodies can be used to preemptively abort development of infection. Third, for those who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there are now multiple approaches to prevent hospitalization. These include neutralizing monoclonal antibodies against the SARS-CoV-2 spike protein and antivirals that block viral replication. This is a critical need that will have a great effect on our ability to curtail this pandemic. Finally, for hospitalized patients, there are antiviral options (remdesivir) and immunomodulator therapies that have been shown to reduce in-hospital mortality. Baricitinib and tocilizumab are indicated for patients with severe-to-critical Covid-19 and elevated markers of inflammation. Tofacitinib can be used instead of baricitinib, and sarilumab can be used instead of tocilizumab.

course is still uncertain. Although SARS-CoV-2 nasopharyngeal viral loads do not reliably predict treatment outcomes in Covid-19, in a randomized, controlled trial of remdesivir conducted by Wang et al., SARS-CoV-2 viral burden (as determined by means of quantitative polymerase-chain-reaction assay of specimens from both the upper and lower respiratory tracts) did not differ between patients in the remdesivir group and those in the control group.[7] So the question arises of whether remdesivir would in fact reduce transmissibility in infected persons (an important consideration in outpatient therapeutics) as compared with monoclonal antibodies or new oral antiviral agents, which are both associated with a more rapid decline in viral burden than placebo.[1,2,8] Evaluation of the effect of remdesivir on viable virus may be required to confirm the mechanism of observed clinical benefit. Finally, the primary challenge for implementing outpatient remdesivir treatment is the pragmatic difficulty of administrating a 3-day course of an intravenous agent. Access to and uptake of single-dose monoclonal antibodies have been challenging, a fact that does not bode well for a 3-day course of outpatient intravenous remdesivir.[9] Although remdesivir administration requires less monitoring than monoclonal antibody administration, the majority of patients in this trial received remdesivir outside of their home or nursing facility, necessitating multiple health care interactions during the time the patients were acutely infected. Agents that could be administrated orally would be vastly easier to implement in the outpatient setting.

The findings of this trial reinforce the need

for timely access to outpatient therapeutics and support the proof of concept for pursuing oral prodrugs of remdesivir s active metabolite. Rapid emergence of variants with adaptive mutations in the spike protein can result in escape from vaccines and monoclonal antibodies, whereas antiviral agents, given the absence of variation in their viral target, are likely to maintain activity, reinforcing the value of antivirals such as remdesivir in curtailing the pandemic.[10] If Covid-19 is here to stay, our focus on prevention through vaccines remains a priority, but therapeutic options to keep vulnerable patients out of the hospital are an important tool in the armamentarium.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy (E.L.H.), and the Institute of Human Virology, University of Maryland School of Medicine (S.K.), Baltimore.

This editorial was published on December 22, 2021, at NEJM.org.

**1.** Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med 2021;384:238-51.
**2.** Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021;325:632-44.
**3.** Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 final report. N Engl J Med 2020;383:1813-26.
**4.** WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 interim WHO Solidarity trial results. N Engl J Med 2021;384:497-511.
**5.** Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis 2021 September 14 (Epub ahead of print).
**6.** Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med 2022;386:305-15.
**7.** Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-78.
**8.** Caraco Y. Phase 2 results from a randomized, controlled, phase 2/3 trial evaluating molnupiravir for treatment of COVID-19 in non-hospitalized adults (MOVe-OUT). Presented at the 31st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Vienna, July 9 12, 2021.
**9.** Anderson TS, O Donoghue AL, Dechen T, Mechanic O, Stevens JP. Uptake of outpatient monoclonal antibody treatments for COVID-19 in the United States: a cross-sectional analysis. J Gen Intern Med 2021;36:3922-4.
**10.** Callaway E. Heavily mutated omicron variant puts scientists on alert. Nature 2021;600:21.

**DOI: 10.1056/NEJMe2118579**


# Risks and Benefits of Janus Kinase Inhibitors in Rheumatoid Arthritis Past, Present, and Future

Jasvinder A. Singh, M.B., B.S., M.P.H.

The Food and Drug Administration (FDA) mandated a safety study to be performed because of possible safety signals detected for the Janus kinase (JAK) inhibitor tofacitinib. As Ytterberg et al. report in this issue of the *Journal*, the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance was a 4-year randomized, open-label, noninferiority, postauthorization, safety end-point trial, in which patients with active rheumatoid arthritis despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor were randomly assigned in a 1:1:1 ratio to receive oral tofacitinib at a dose of 5 or 10 mg twice daily or a subcutaneous tumor necrosis factor (TNF) inhibitor (etanercept or adalimumab).[1]

The risks of major adverse cardiovascular events (MACE) and cancers (excluding nonmelanoma skin cancer [NMSC]) were higher with the combined tofacitinib doses than with a TNF inhibitor, and the noninferiority of tofacitinib was not shown, with hazard ratios of 1.33 (95% confidence interval [CI], 0.91 to 1.94) for MACE and 1.48 (95% CI, 1.04 to 2.09) for cancers. The researchers estimated that during 5 years of treatment, 113 and 55 patients would need to be treated with tofacitinib at a dose of 5 mg twice daily rather than with a TNF inhibitor to result in one additional MACE and cancer, respectively. Efficacy was similar in all three trial groups with respect to multiple patient-centered and clinical outcomes.

What do these results mean? Rheumatoid arthritis is associated with an increased risk of MACE.[2] The use of TNF inhibitors[3] and other traditional and biologic disease-modifying antirheumatic drugs (DMARDs)[4] to treat rheumatoid arthritis is associated with a reduced risk of MACE, presumably through a reduction in inflammation. The most relevant estimates for MACE