

NARRATIVE REVIEW

Comparative evaluation of authorized drugs for treating Covid-19 patients

Towhidul Islam¹  | Moynul Hasan² | Mohammad Saydur Rahman² |
Md. Rabiul Islam¹ 

¹Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh

²Department of Pharmacy, Jagannath University, Dhaka, Bangladesh

Correspondence

Md. Rabiul Islam, Department of Pharmacy, University of Asia Pacific, 74/A Green Rd, Farmgate, Dhaka 1205, Bangladesh.
Email: robi.ayaan@gmail.com

Abstract

Background and Aims: Vaccines are the first line of defense against coronavirus disease 2019 (Covid-19). However, the antiviral drugs provide a new tool to fight the Covid-19 pandemic. Here we aimed for a comparative evaluation of authorized drugs for treating Covid-19 patients.

Methods: We searched in PubMed and Google Scholar using keywords and terms such as Covid, SARS-CoV-2, Coronavirus disease 2019, therapeutic management, hospitalized Covid-19 patients, Covid-19 treatment. We also gathered information from reputed newspapers, web portals, and websites. We thoroughly observed, screened, and included the studies relevant to our inclusion criteria. We included only the United States Food and Drug Administration (FDA) authorized drugs for this review.

Results: We found that molnupiravir and paxlovid are available for oral use, and remdesivir is for only hospitalized patients. Paxlovid is a combination of nirmatrelvir and ritonavir, nirmatrelvir is a protease inhibitor (ritonavir increases the concentration of nirmatrelvir), and the other two (remdesivir and molnupiravir) are nucleoside analog prodrugs. Remdesivir and molnupiravir doses do not need to adjust in renal and hepatic impairment. However, the paxlovid dose adjustment is required for mild to moderate renal or hepatic impaired patients. Also, the drug is not allowed for Covid-19 patients with severe renal or hepatic impairment. Preliminary studies showed oral antiviral drugs significantly reduce hospitalization or death among mild to severe patients. Moreover, the US FDA has approved four monoclonal antibodies for Covid-19 treatment. Studies suggest that these drugs would reduce the risk of hospitalization or severity of symptoms. World Health Organization strongly recommended the use of corticosteroids along with other antiviral drugs for severe or critically hospitalized patients.

Conclusion: All authorized drugs are effective in inhibiting viral replication for most SARS-CoV-2 variants. Therefore, along with vaccines, these drugs might potentially aid in fighting the Covid-19 pandemic.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Health Science Reports* published by Wiley Periodicals LLC.

KEYWORDS

antivirals, Covid-19, dexamethasone, molnupiravir, monoclonal antibody, paxlovid, remdesivir, SARS-CoV-2

1 | INTRODUCTION

The first reported severe acute respiratory syndrome due to coronavirus-2 (SARS-CoV-2) was in Wuhan, China, in December 2019. Coronavirus disease 2019 (Covid-19) seriously threatened the global healthcare systems. The world has seen more than 505 million confirmed cases with more than 6.2 million related deaths in more than 200 countries, areas, or territories as of April 21, 2022. Since the first outbreak of SARS-CoV-2 in China and the declaration of the pandemic, scientists all over the globe surged to develop treatment options and preventive measures for the Covid-19.¹ People of all ages are prone to get infected by a coronavirus. However, most of the total cases occurred in middle-aged adults aged 30–69 years.² Transmissibility, hospitalization, and mortality depend on age, sex, race, and comorbidity of patients. Obesity, older age, and chronic diseases are risk factors for developing severity of Covid-19 patients.² The world observed a revolutionary outcome from the Covid-19 vaccine pipeline. Today, many vaccines have been approved and are in different stages of clinical trials. Vaccines are the first line of defense against Covid-19.^{3–6} There is also a need for antivirals for therapeutic purposes. However, antiviral drugs are designed for SARS-CoV-2 involve various strategies to inhibit viral replication. For example, viral attachment to host cell inhibitor candidates targets spike proteins of SARS-CoV-2 and human angiotensin-converting enzyme 2 (ACE2) receptor interaction-mediated viral entry.^{7–9} Another strategy involves inhibiting viral proteases, main protease (M^{Pro})¹⁰ or 3-like proteases (3CL^{Pro}), and papain-like protease (Pl^{Pro}).^{11,12} Furthermore, RNA-dependent RNA polymerase (RdRp) also emerged as a target in anti-SARS-CoV-2 drug design.¹³ Recently, only a few drugs are available against SARS-CoV-2 for preventative (tixagevimab/cilgavimab) and curative (sotrovimab, bebtelovimab, molnupiravir, and remdesivir, nirmatrelvir/ritonavir) purposes. Here, we aimed for a comparative evaluation of the United States Food and Drug Administration (USFDA)-approved antivirals for treating Covid-19 patients based on current knowledge. We summarized and presented the comparative dosage regimen, benefits, and risks of authorized drugs for Covid-19 therapy. Among numerous experimental drugs directly or indirectly used in Covid-19, we included the specific drugs/combinations authorized for emergency use by the US FDA. We have searched in PubMed and Google Scholar using keywords and terms such as Covid, SARS-CoV-2, coronavirus disease 2019, therapeutic management, hospitalized Covid-19 patients, Covid-19 treatment. We also gathered information from reputed newspapers, web portals, and websites. Studies relevant to our inclusion criteria were thoroughly observed, screened, and included. We excluded information about experimental drugs except for FDA authorization. Primary screening was carried out

based on title and abstract, and then we screened out articles based on relevancy, article type, and published year.

2 | REMDESIVIR

Remdesivir (DB14761) is the first US FDA-approved antiviral to treat Covid-19. In October 2020, the US FDA approved it for emergency use on individuals aged more than 12 years and over 40 kg.¹⁴ Now, remdesivir is approved for temporary use in more than 50 countries.¹⁵ Remdesivir has been developed and considered a broad-spectrum antiviral during past outbreaks caused by coronaviruses (Middle East respiratory syndrome [MERS]/SARS) and filoviruses (Ebola). It has been reported to possess therapeutic efficacy and prophylactic activity in several nonclinical models of SARS/MERS.¹⁶ The US company Gilead Sciences discovered remdesivir (GS-5734) as an intravenous (IV)-administered 1'-cyano-substituted nucleotide analog prodrug. It acts as a viral RNA synthesis inhibitor (interferes RdRp), and its base portion resembles adenosine. Biochemical studies revealed its mechanism. A 5'-hydroxyl group when substituted with phosphoramidite, it stimulates the drug delivery into the cell and its hydrolysis unveils monophosphate form. Then, it undergoes intracellular phosphorylation to form active (triphosphate) metabolites.¹⁷ Also, the US FDA authorized a combination of remdesivir with baricitinib for emergency use.¹⁸ Till now, clinical trials concluded that remdesivir in a 3–5-day-long dose regimen facilitates recovery from moderate to severe Covid-19 symptoms by shortening the hospital stay. Also, it reduces the risk of hospitalization.¹⁹ Studies also reported its efficacy against most variants of coronavirus.²⁰ Several studies supported that there is a clear safety profile of remdesivir. According to a group of scientists focusing on renal, cardiac, and hepatic safety, they found remdesivir causing no significant changes in glomerular filtration rate and liver enzymes even in impaired patients. However, they observed a reduction in heart rate, but there was no cardiovascular system (CVS) toxicity even with severe CVS comorbidity.²⁰ A recent review article also found a similar safety profile. Multiple-dose of remdesivir resulted in reversible hepatocellular enzyme elevations, but there was no renal or hepatic toxicity. According to the most recent and the largest clinical trial, no significant adverse drug reactions (ADR) and mortality occurred with remdesivir treatment. ADRs could have resulted from Covid-19 severity rather than remdesivir treatment.²¹ Despite being a safe IV drug, its stability and oral bioavailability are yet to be improved.²² Scientists also surged to develop remdesivir delivery via a noninvasive route of administration. It would allow the initiation of antiviral treatments from the early event of diagnosis. By deuteration, Xie et al.²³ designed a tri-isobutyryl ester prodrug

(VV116) of GS-441524 (RVn: the active metabolite of remdesivir). VV116 showed satisfactory efficacy against SARS-CoV-2 in the Vero E6 cell line with oral bioavailability of about 80% in preclinical studies. In addition, it showed chemical stability over high humidity, lights, and temperature.²³ Another promising orally bioavailable remdesivir-like prodrug candidate is ODBG-P-RVn.²⁴ It also showed efficacy on five different cell lines.²⁵ Along with IV remdesivir, oral Rvn prodrugs would be game-changers in the early treatment of Covid-19.

3 | MOLNUPIRAVIR

The USFDA has approved molnupiravir (DB15661) for emergency use in treating Covid-19 patients in December 2021. It is a prescription-only orally-available drug approved for treating mild-to-moderate adult Covid-19 patients with a high risk for developing complications and hospitalization.²⁶ It also secured efficacy against various strains of SARS-CoV-2.²⁷ Cox et al.²⁸ developed molnupiravir (MK-4482/EIDD-2801), an isobutyryl ester prodrug of β -D-N4-hydroxycytidine analog (cytidine and uridine). It shows broad-spectrum anti-RNA virus activity by inducing error catastrophe during replication. Like remdesivir, it needs RdRp²⁹ and targets cellular kinases. However, it acts as a mutagenic agent rather than a chain terminator.³⁰ It promptly converts to its triphosphate form MTP and acts as a substrate for viral RdRp in the cellular environment. Tautomeric variants of molnupiravir can cause mutations during G-to-A and C-to-U transitions and finally lead to inhibition of viral replication.³¹ Moreover, molnupiravir with favipiravir³² or dihydroorotate dehydrogenase inhibitors such as IMU-838/vidofludimus and BAY2402234³³ has shown synergistic effects in preclinical studies, yet to be clinically established. However, molnupiravir lacks ADR data as it is hard to distinguish between treatment-related adverse events and Covid-19-related adverse events. As of December 26, 2021, we still have a small amount of safety data. On the basis of some evidence on mammalian cells, molnupiravir is assumed to be mutagenic and genotoxic.³⁴ However, considering the risk-benefit and totality of data, the UK authorized molnupiravir.³⁵ Moreover, a systematic review article summarized the molnupiravir-associated ADRs. The most common side effects were nausea, headache, insomnia, diarrhea, elevated ALT, and so forth, in mild-to-severe patients, which indicates the drug is safe and well-tolerated at a desired therapeutic concentration in plasma. However, most studies are still ongoing to find safety data.³⁶ There are several advantages to being orally administered drug over IV remdesivir. However, further studies should clarify its long-term genotoxicity and other potential ADRs.

4 | PAXLOVID (RITONAVIR-BOOSTED NIRMATRELVIR)

M^{Pro} (also called 3CL^{Pro}) and PL^{pro} processes (by proteolytic digestion) viral polyproteins pp1a and pp1ab to generate functional viral proteins to facilitate replication. Thus, proteases have become a possible drug target in antiviral development.^{37,38} Several studies

reported nirmatrelvir (DB16691, PF-07321332) as a potential protease inhibitor for Covid-19 treatment. Positive results were observed with viral protease 3CL^{Pro}.^{37,39} In December 2021, USFDA approved under brand name Paxlovid (Pfizer), a combination of nirmatrelvir and ritonavir for emergency use in Covid-19 treatment.⁴⁰ Ritonavir (DB00503) is an HIV protease inhibitor.⁴¹ Unlike nirmatrelvir, ritonavir cannot inhibit protease of SARS-CoV-2. It inhibits cytochrome P450 and P-glycoprotein. Therefore, this drug enhances the half-life of nirmatrelvir.⁴² Consequently, nirmatrelvir concentration remains higher in the binding sites.⁴³ Pfizer reported paxlovid reduces hospitalization or death rate by 89% among mild-to-severe Covid-19 patients.⁴⁴ Also, paxlovid appeared more effective when compared to molnupiravir.⁴⁵ However, in terms of ADRs, treatment-associated mild adverse events were reported between paxlovid and placebo groups at 19% and 21%, respectively.⁴⁶ Scientists are also hoping that the therapeutic efficacy of paxlovid will remain at a safety margin as the omicron variant of SARS-CoV-2 emerges.⁴⁷ As ritonavir is a hepatic and renal enzyme cytochrome P450 and multidrug-resistant protein P-glycoprotein inhibitor, it might have several drug-drug interactions. Therefore, we should take additional cautions for Covid-19 patients who have a comorbidity of other diseases or immune/hepatic/renal impairment.^{42,48,49} Paxlovid has proven itself effective, but, more importantly, the safety profile of this combination drug should provide long-term reliability.

5 | MONOCLONAL ANTIBODIES AND SOTROVIMAB

Monoclonal antibodies have attracted the focus of scientists from the early stage of Covid-19 pandemic. The US FDA has authorized (for emergency use) four monoclonal antibodies to treat Covid-19 patients with a high risk of hospitalization or progressing severity. They are casirivimab (DB15941) plus imdevimab (DB15940), bamlanivimab (DB15718) plus etesevimab (DB15897), tixagevimab (DB16394) plus cilgavimab (DB16393), and sotrovimab (DB16355).⁵⁰ However, during the Omicron wave, the FDA paused the recommendation of casirivimab plus imdevimab and bamlanivimab plus etesevimab because of the significant reduction in susceptibility.^{51,52} Sotrovimab (previously VIR-7831, GSK4182136 was developed by GlaxoSmithKline and Vir Biotechnology Inc.) sustained its recommendation among the monoclonal antibodies by FDA,⁵³ WHO,⁵⁴ and UK.⁵⁵ Genetically engineered human monoclonal antibody sotrovimab possess the ability to act longer duration. It has proven therapeutic efficacy against many variants of concern.⁵⁶ However, it did not exert any potential improvement in hospitalized or oxygen-required patients.⁵⁷ Sotrovimab showed its safety according to clinical trial NCT04545060 funded by Vir Biotechnology and GlaxoSmithKline in 868 patients (among them, sotrovimab group n=430 and placebo group n=438). In the above study, 17% of participants from sotrovimab group reported adverse events, and the rate was 19% for the placebo group. Therefore, research reports supported sotrovimab as a safer option for treating Covid-19 patients.⁵⁶

TABLE 1 Comparative evaluation of USFDA approved antiviral drugs for treating Covid-19 patients

Drug	Dose	Mode of action	Benefits	Limitations
Remdesivir ⁶⁴	Hospitalized adults and children (aged ≥ 2 years and weight ≥ 40 kg): Loading dose—200 mg iv, maintenance dose—100 mg iv once daily on second to fifth days. Should administer through IV infusion over 30–120 min. Hospitalized children (weight: 3.5–<40 kg): Loading dose—5 mg/kg iv, maintenance dose—2.5 mg/kg iv once daily on second to fifth days. Should administer through IV infusion over 30–120min.	<ul style="list-style-type: none"> • A prodrug • Adenosine analog • Targets RdRp • Inhibits viral replication 	<ul style="list-style-type: none"> • One of the earliest effective antiviral drugs • Effective against major variants • Widely authorized for emergency use • There are no serious renal, hepatic, and CVS adverse events observed • Combination with the anti-inflammatory drug also authorized for emergency use • Reduction of heart rate was observed however it was not fatal even in impaired patients 	<ul style="list-style-type: none"> • Only administered through IV during hospitalization • Effective treatment when treated in the early stages • No oral dosage forms are available due to their poor bioavailability • Prophylaxis of hospitalization is not possible • Nonserious reversible hepatocellular enzyme elevations observed • There is no data for use in pregnancy
Molnupiravir ⁶⁵	800 mg (four 200-mg capsules) orally every 12h for 5 days.	<ul style="list-style-type: none"> • A prodrug • Tautomers of its active form resemble cytidine and uridine • Acts via mutagenic activity on virus rather than terminating chains • Resulting in retardation of viral replication and maturation 	<ul style="list-style-type: none"> • Oral dosage form and can be used for prophylaxis along with curative purposes • Active against SARS-CoV-2 variants of concern (VOCs) in vitro and in animal models • Combinations also show synergistic effects • Can be taken with or without food • No dose adjustment is required in patients with renal or hepatic impairment • No drug–drug interactions identified • Less serious adverse events that indicate safety 	<ul style="list-style-type: none"> • Animal studies assumed that it may cause genotoxicity and mutagenesis to host cells • Treatment should be initiated within 5 days of onset of symptom • The most common side effects were nausea, headache, insomnia, diarrhea, elevated ALT, and so forth • There is no data for use in pregnancy
Paxlovid (combination of nirmatrelvir and ritonavir) ⁶⁶	Only for adults: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days	<ul style="list-style-type: none"> • Combination of two protease inhibitors • Each drug inhibits main protease or M^{pro} or 3CL^{pro} of SARS-CoV-2 • It is assumed that ritonavir helps nirmatrelvir by preventing its hepatic metabolism 	<ul style="list-style-type: none"> • Administered orally with or without food • Reduced hospitalization or death by 89% among mild-to-severe patients • Most of the ADRs were mild to moderate • Paxlovid appeared to be more effective compared to molnupiravir 	<ul style="list-style-type: none"> • Initiation of antiviral treatment as soon as possible after the diagnosis of Covid-19 and within 5 days of onset of symptoms • Nirmatrelvir must be coadministered with ritonavir • Dose reduction is required for moderate renal and hepatic impairment • Not recommended in patients with severe renal and hepatic impairment

TABLE 1 (Continued)

Drug	Dose	Mode of action	Benefits	Limitations
Monoclonal antibodies ^{49–56,67}	<ul style="list-style-type: none"> Casirivimab plus Imdevimab: Before arise of Omicron VOC, single IV dose (casirivimab 600 mg plus imdevimab 600 mg) was authorized for mild to moderate Covid-19 patients with high risk of hospitalization and/or progression of severity. If IV infusion is not feasible or in cases with possibility of delay treatment, USFDA also authorized four subcutaneous injections of casirivimab plus imdevimab 2.5 ml per injection. Bamlanivimab plus etesevimab: In clinical studies, bamlanivimab 700 mg plus etesevimab 1400 mg; bamlanivimab 2800 mg plus etesevimab 2800 mg was observed to be administered in nonhospitalized patients with mild to moderate Covid-19. Sotrovimab: For treatment of nonhospitalized (aged above 12 and weighing above 40 kg) mild-to-moderate Covid-19 patients who are at high risk of progression to severity or hospitalization, single IV dose of sotrovimab administered within 10 days of symptom onset. 	<ul style="list-style-type: none"> Casirivimab plus Imdevimab: Recombinant human mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. Bamlanivimab plus etesevimab: Neutralizing mAbs that bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2. Tixagevimab plus cilgavimab: Recombinant human anti-SARS-CoV-2 mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. Sotrovimab: Originally identified in 2003 by a survivor of SARS-CoV infection. It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2. 	<ul style="list-style-type: none"> Authorized for the treatment of nonhospitalized patients with a high risk of hospitalization or progressing severity. Other mAbs: Bamlanivimab plus etesevimab or casirivimab plus imdevimab recommended for non-Omicron VOCs. Sotrovimab sustained its recommendation (by USFDA, WHO, and UK). Sotrovimab possesses the ability to act longer duration. Also, it shows therapeutic efficacy against many VOCs. 	<ul style="list-style-type: none"> The USFDA paused the recommendation of casirivimab plus imdevimab and bamlanivimab plus etesevimab because of the significant reduction in susceptibility upon arise of Omicron VOC. Sotrovimab did not exert any potential improvement in hospitalized or oxygen-required patients. Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe Covid-19; however, the products may be available through expanded access programs for patients who either have not developed an antibody response to SARS-CoV-2 infection or are not expected to mount an effective immune response to infection.
Baricitinib ^{17,57–61,68}	<ul style="list-style-type: none"> Dose depends on eGFR. All dose given per oral, once daily. When eGFR (ml/min/1.73 m²): <ul style="list-style-type: none"> ≥60: 4 mg 30–<60: 2 mg 15–<30: 1 mg Not recommended when eGFR is less than 15. 	<ul style="list-style-type: none"> Orally administrable Janus kinases inhibitor. Cellular entry of SARS-CoV-2 is inhibited by baricitinib whereas remdesivir retards viral replication. Baricitinib plus Remdesivir synergism inhibits cytokine storm, inflammation, SARS-CoV-2 replication, and load. 	<ul style="list-style-type: none"> Existing drug (indicated for RA) with well-studied safety profile. FDA authorized emergency use of remdesivir/baricitinib combination as anti-SARS-CoV-2 therapy. Upon rising of Omicron VOC, WHO strongly recommended the use of corticosteroids along with remdesivir/baricitinib for severe cases. A combination of remdesivir/baricitinib proved superior to remdesivir monotherapy. 	<ul style="list-style-type: none"> Baricitinib/remdesivir/recombinant human ACE2 combination was reported to possess synergism, which results in lowering the required dose of individual drugs. This finding might

(Continues)

TABLE 1 (Continued)

Drug	Dose	Mode of action	Benefits	Limitations
				be helpful in ADR management.

Abbreviations: 3CL^{pro}, 3C-like protease; ACE2, angiotensin-converting enzyme 2; ADR, adverse drug reaction; ALT, alanine aminotransferase; Covid-19, coronavirus disease 2019; CVS, cardiovascular system; eGFR, estimated glomerular filtration rate; IV, intravenous; JAK, Janus kinase; mAbs, monoclonal antibodies; M^{pro}, main protease; RA, rheumatoid arthritis; RBD, receptor-binding domain; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; USFDA, United States Food and Drug Administration; WHO, World Health Organization.

6 | BARICITINIB

Baricitinib (DB11817) is an orally administrable Janus kinases (JAKs) inhibitor indicated for rheumatoid arthritis. However, like several examples of JAK inhibitors, it also shows antiviral, antibacterial, and antifungal activities as side effects.⁵⁸ In the second half of 2020, the USFDA authorized emergency use of remdesivir/baricitinib combination as anti-SARS-CoV-2 therapy.¹⁸ WHO strongly recommended corticosteroids with remdesivir/baricitinib for severe Covid-19 cases from Omicron wave.⁵⁴ Baricitinib intracellularly suppresses JAK1/JAK2 and consequently inhibits proinflammatory signal of several cytokines. Besides, baricitinib is assumed to interrupt the passage and intracellular assembly of SARS-CoV-2 into the target cells mediated by the ACE2 receptor.⁵⁹ In combination therapy, cellular entry of SARS-CoV-2 is inhibited by baricitinib whereas remdesivir retards viral replication. Therefore, in severe cases, the synergistic effect of this combination is reported to be beneficial in the management of cytokine storm, inflammation, SARS-CoV-2 replication, and viral load.⁶⁰ Some scientists recommended baricitinib over another JAK inhibitor, ruxolitinib for its abundant availability in low-cost generic versions.⁶¹ In terms of safety concerns, there is plenty of safety data. For example, Kalil et al.⁶² concluded remdesivir/baricitinib combined therapy is superior to remdesivir monotherapy in the case of hospitalized patients. They did not find any significant difference in adverse events among placebo, control, and combination patient groups. Although there is a possibility regarding the risk of secondary infections, immunosuppression, and thrombosis in worst cases.⁶² Furthermore, baricitinib/remdesivir/recombinant human ACE2 combination was reported to possess synergism that lowers the required dose of individual drugs. This finding might be helpful in ADR management.⁶³ We presented the comparative evaluation of USFDA-approved antiviral drugs for treating Covid-19 patients in Table 1.

7 | CONCLUSION

Preventive and curative approaches against Covid-19 will bring significant benefits despite of having some negligible risks. Oral antiviral medications have several advantages over IV antivirals. Safety, treatment in early stages to prevent hospitalization. More importantly, oral medication is the most convenient way for outpatients. However, oral antivirals might develop genotoxicity and mutagenesis to host cells. Also, it lacks safety data on pregnancy and some chronic complications. The virus is changing itself and creating new challenges for the efficacy of oral antivirals.⁶⁹⁻⁷¹ Early diagnosis and initiation of treatment are vital success factors for oral antivirals in Covid-19 treatment. Preliminary studies showed that authorized drugs for Covid-19 therapy significantly reduce hospitalization or death among mild to severe patients. We can anticipate that the pandemic phase of Covid-19 might be ended after this massive Omicron waves; however, the Covid-19 will continue.⁷²⁻⁷⁵ Therefore, along with vaccines, these drugs might potentially aid in fighting the Covid-19 pandemic.

AUTHOR CONTRIBUTIONS

Towhidul Islam and Moynul Hasan conceived and wrote the first draft. Mohammad Saydur Rahman revised and gave intellectual input to the manuscript. Md. Rabiul Islam supervised, edited, and revised the manuscript. All the authors approved the final version for submission.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

It was an analysis of online available aggregate data. This study does not require formal ethical approval.

TRANSPARENCY STATEMENT

This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

ORCID

Towhidul Islam  <http://orcid.org/0000-0002-8402-0740>

Md. Rabiul Islam  <https://orcid.org/0000-0003-2820-3144>

REFERENCES

- Islam MR. The SARS-CoV-2 Omicron (B.1.1.529) variant and the re-emergence of COVID-19 in Europe: an alarm for Bangladesh. *Health Sci Rep.* 2022;5(2):e545. doi:10.1002/hsr2.545
- Rahman MA, Shanjana Y, Tushar MI, et al. Hematological abnormalities and comorbidities are associated with COVID-19 severity among hospitalized patients: experience from Bangladesh. *PLoS One.* 2021;16(7):e0255379. doi:10.1371/journal.pone.0255379
- Islam MR. Urgent call for mass immunization against coronavirus in Bangladesh. *Sci Prog.* 2021;104(4):368504211058562. doi:10.1177/00368504211058562
- Islam MR, Hasan M, Nasreen W, Tushar MI, Bhuiyan MA. The COVID-19 vaccination experience in Bangladesh: findings from a cross-sectional study. *Int J Immunopathol Pharmacol.* 2021;35:20587384211065628. doi:10.1177/20587384211065628
- Hossain MJ, Rahman S, Emran TB, Mitra S, Islam MR, Dhama K. Recommendation and roadmap of mass vaccination against COVID-19 pandemic in Bangladesh as a lower-middle-income country (LMIC). *Ach Razi Inst.* 2021;76:1823-1830. doi:10.22092/ARI.2021.356357.1824
- Sohan M, Hossain MJ, Islam MR. The SARS-CoV-2 Omicron (B.1.1.529) variant and effectiveness of existing vaccines: what we know so far. *J Med Virol.* 2022;94(5):1796-1798. doi:10.1002/jmv.27574
- Chen Z, Du R, Galvan Achi JM, Rong L, Cui Q. SARS-CoV-2 cell entry and targeted antiviral development. *Acta Pharm Sin B.* 2021;11(12):3879-3888. doi:10.1016/j.apsb.2021.05.007
- Muralidar S, Gopal G, Visaga Ambi S. Targeting the viral-entry facilitators of SARS-CoV-2 as a therapeutic strategy in COVID-19. *J Med Virol.* 2021;93(9):5260-5276. doi:10.1002/jmv.27019
- Tharappel AM, Samrat SK, Li Z, Li H. Targeting crucial host factors of SARS-CoV-2. *ACS Infect Dis.* 2020;6(11):2844-2865. doi:10.1021/acsinfectdis.0c00456
- Sacco MD, Ma C, Lagarias P, et al. Structure and inhibition of the SARS-CoV-2 main protease reveal strategy for developing dual inhibitors against M^{pro} and cathepsin L. *Sci Adv.* 2020;6(50):eabe0751. doi:10.1126/sciadv.abe0751
- Anirudhan V, Lee H, Cheng H, Cooper L, Rong L. Targeting SARS-CoV-2 viral proteases as a therapeutic strategy to treat COVID-19. *J Med Virol.* 2021;93(5):2722-2734. doi:10.1002/jmv.26814
- Ma C, Sacco MD, Xia Z, et al. Discovery of SARS-CoV-2 papain-like protease inhibitors through a combination of high-throughput screening and a FlipGFP-based reporter assay. *ACS Cent Sci.* 2021;7(7):1245-1260. doi:10.1021/acscentsci.1c00519
- Wang Y, Anirudhan V, Du R, Cui Q, Rong L. RNA-dependent RNA polymerase of SARS-CoV-2 as a therapeutic target. *J Med Virol.* 2021;93(1):300-310. doi:10.1002/jmv.26264
- FDA. FDA approves first treatment for COVID-19. FDA news release. 2020. Accessed December 25, 2021. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19>
- Gilead. Remdesivir global marketing authorization 1. 2021. Accessed December 25, 2021. <https://www.gilead.com/purpose/advancing-global-health/covid-19/veklury-global-marketing-authorization>
- Naveed M, Uddin S, Khan M, Khan Z. Remdesivir for the treatment of COVID-19: a need for combined in vivo and in vitro studies to evaluate the efficacy. *J Pharm Pract.* 2021;34(3):343-346. doi:10.1177/0897190021997001
- Götte M. Remdesivir for the treatment of Covid-19: the value of biochemical studies. *Curr Opin Virol.* 2021;49:81-85. doi:10.1016/j.coviro.2021.04.014
- FDA. Coronavirus (COVID-19) update: FDA authorizes drug combination for treatment of COVID-19. FDA news release. 2020. Accessed December 25, 2021. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-combination-treatment-covid-19>
- Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med.* 2021;386:305-315. doi:10.1056/NEJMoa2116846
- Poliseno M, Gallo C, Cibelli DC, et al. Efficacy and safety of remdesivir over two waves of the SARS-CoV-2 pandemic. *Antibiotics.* 2021;10(12):1477. doi:10.3390/antibiotics10121477
- Lin HXJ, Cho S, Meyyur Aravamudan V, et al. Remdesivir in coronavirus disease 2019 (COVID-19) treatment: a review of evidence. *Infection.* 2021;49(3):401-410. doi:10.1007/s15010-020-01557-7
- Humeniuk R, Mathias A, Kirby BJ, et al. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of remdesivir, a SARS-CoV-2 replication inhibitor. *Clin Pharmacokinet.* 2021;60(5):569-583. doi:10.1007/s40262-021-00984-5
- Xie Y, Yin W, Zhang Y, et al. Design and development of an oral remdesivir derivative VV116 against SARS-CoV-2. *Cell Res.* 2021;31(11):1212-1214. doi:10.1038/s41422-021-00570-1
- Lo MK, Shrivastava-Ranjan P, Chatterjee P, et al. Broad-spectrum in vitro antiviral activity of ODBG-P-RVn: an orally-available, lipid-modified monophosphate prodrug of remdesivir parent nucleoside (GS-441524). *Microbiol Spectr.* 2021;9(3):e0153721. doi:10.1128/Spectrum.01537-21
- Schooley RT, Carlin AF, Beadle JR, et al. Rethinking remdesivir: synthesis, antiviral activity, and pharmacokinetics of oral lipid prodrugs. *Antimicrob Agents Chemother.* 2021;65(10):e0115521. doi:10.1128/AAC.01155-21
- FDA. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment of COVID-19 in certain adults | FDA. FDA news release. 2021. Accessed December 26, 2021. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain>

27. Abdelnabi R, Foo CS, De Jonghe S, Maes P, Weynand B, Neyts J. Molnupiravir inhibits replication of the emerging SARS-CoV-2 variants of concern in a hamster infection model. *J Infect Dis*. 2021;224(5):749-753. doi:10.1093/infdis/jiab361
28. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. *Nat Microbiol*. 2021;6(1):11-18. doi:10.1038/s41564-020-00835-2
29. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med*. 2021;386:509-520. doi:10.1056/NEJMoa2116044
30. Zhao Y, He G, Huang W. A novel model of molnupiravir against SARS-CoV-2 replication: accumulated RNA mutations to induce error catastrophe. *Signal Transduct Target Ther*. 2021;6(1):410. doi:10.1038/s41392-021-00837-4
31. Wang Z, Yang L. Broad-spectrum prodrugs with anti-SARS-CoV-2 activities: strategies, benefits, and challenges. *J Med Virol*. 2021;94:1373-1390. doi:10.1002/jmv.27517
32. Abdelnabi R, Foo CS, Kaptein SJF, et al. The combined treatment of molnupiravir and favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. *EBioMedicine*. 2021;72:103595. doi:10.1016/j.ebiom.2021.103595
33. Stegmann KM, Dickmanns A, Heinen N, et al. N4-hydroxycytidine and inhibitors of dihydroorotate dehydrogenase synergistically suppress SARS-CoV-2 replication. *bioRxiv*. Published online June 28, 2021. Accessed on May 26, 2022. doi:10.1101/2021.06.28.450163
34. Zhou S, Hill CS, Sarkar S, et al. β -D-N4-hydroxycytidine inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. *J Infect Dis*. 2021;224(3):415-419. doi:10.1093/infdis/jiab247
35. Whitley R. Molnupiravir—a step toward orally bioavailable therapies for Covid-19. *N Engl J Med*. 2021;386:592-593. doi:10.1056/NEJMe2117814
36. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. *Diabetes Metab Syndr*. 2021;15(6):102329. doi:10.1016/j.dsx.2021.102329
37. Boras B, Jones RM, Anson BJ, et al. Preclinical characterization of an intravenous coronavirus 3CL protease inhibitor for the potential treatment of COVID19. *Nat Commun*. 2021;12(1):6055. doi:10.1038/s41467-021-26239-2
38. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. *Science*. 2021;374(6575):1586-1593. doi:10.1126/science.aba4784
39. Ahmad B, Batool M, Ain QU, Kim MS, Choi S. Exploring the binding mechanism of PF-07321332 SARS-CoV-2 protease inhibitor through molecular dynamics and binding free energy simulations. *Int J Mol Sci*. 2021;22(17):9124. doi:10.3390/ijms22179124
40. FDA. Coronavirus (COVID-19) Update: FDA authorizes first oral antiviral for treatment of COVID-19 | FDA. FDA news release. 2021. Accessed December 26, 2021. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19>
41. Hoetelmans RM, Meenhorst PL, Mulder JW, Burger DM, Koks CH, Beijnen JH. Clinical pharmacology of HIV protease inhibitors: focus on saquinavir, indinavir, and ritonavir. *Pharm World Sci*. 1997;19(4):159-175. doi:10.1023/a:1008629608556
42. Heskin J, Pallett SJC, Mughal N, et al. Caution required with use of ritonavir-boosted PF-07321332 in COVID-19 management. *Lancet*. 2022;399(10319):21-22. doi:10.1016/S0140-6736(21)02657-X
43. Woodley M. RACGP—what is Australia's potential new COVID treatment? NEWSGP. 2021. Accessed December 26, 2021. <https://www1.racgp.org.au/newsgp/clinical/what-is-australia-s-potential-new-covid-treatment>
44. Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. *BMJ*. 2021;375:n2713. doi:10.1136/bmj.n2713
45. Couzin-Frankel J. Antiviral pills could change pandemic's course. *Science*. 2021;374(6569):799-800. doi:10.1126/science.acx9605
46. García-Lledó A, Gómez-Pavón J, González Del Castillo J, et al. Pharmacological treatment of COVID-19: an opinion paper. *Rev Esp Quimioter*. 2021;35:115-130. doi:10.37201/req/158.2021
47. Wang Z, Yang L. In the age of Omicron variant: paxlovid raises new hopes of COVID-19 recovery. *J Med Virol*. 2021;94:1766-1767. doi:10.1002/jmv.27540
48. Lange NW, Salerno DM, Jennings DL, et al. Nirmatrelvir/ritonavir use: managing clinically significant drug-drug interactions with transplant immunosuppressants. *Am J Transplant*. 2022. doi:10.1111/ajt.16955
49. Mazaherpour H, Sofian M, Farahani E, et al. Comparing outcomes of two antiviral therapy combinations among COVID-19 patients. *Biomed Res Int*. 2022;2022:1522426. doi:10.1155/2022/1522426
50. NIH. Anti-SARS-CoV-2 monoclonal antibodies | COVID-19 treatment guidelines. National Institutes of Health: COVID-19 treatment guidelines. 2022. Accessed February 4, 2022. <https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/>
51. Bamlanivimab/etesevimab. Public Health Emergency. 2022. Accessed February 4, 2022. <https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/default.aspx>
52. REGEN-COV. Public Health Emergency. Accessed February 4, 2022. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/cas_imd/Pages/default.aspx
53. Cavazzoni P. Coronavirus (COVID-19) update: FDA limits use of certain monoclonal antibodies to treat COVID-19 due to the Omicron variant | FDA. FDA STATEMENT. 2022. Accessed February 4, 2022. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron>
54. Kmietowicz Z. Covid-19: WHO recommends baricitinib and sotrovimab to treat patients. *BMJ*. 2022;376:o97. doi:10.1136/bmj.o97
55. Mahase E. Covid-19: UK approves monoclonal antibody sotrovimab for over 12s at high risk. *BMJ*. 2021;375:n2990. doi:10.1136/BMJ.N2990
56. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. doi:10.1056/nejmoa2107934
57. Self WH, Sandkovsky U, Reilly CS, et al. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. *Lancet Infect Dis*. 2021;22:622-635. doi:10.1016/S1473-3099(21)00751-9
58. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis*. 2013;72(suppl 2):ii111-ii115.
59. So JM, Umeh C, Noriega S, Stratton E, Aseri M, Gupta RC. Use of baricitinib in combination with remdesivir and steroid in COVID-19 treatment: a multicenter retrospective study. *Cureus*. 2021;13(12):e20620. doi:10.7759/cureus.20620
60. Zhang X, Zhang Y, Qiao W, Zhang J, Qi Z. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. *Int Immunopharmacol*. 2020;86:106749.
61. Saj F, Kayal S, Dubashi B, Ganesan P. Baricitinib: two birds with one stone. *Indian J Hematol Blood Transfus*. 2022;1-2. doi:10.1007/s12288-022-0

62. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med*. 2021;384(9):795-807.
63. Vitiello A, Ferrara F. Association and pharmacological synergism of the triple drug therapy baricitinib/remdesivir/rhACE2 for the management of COVID-19 infection. *Naunyn Schmiedebergs Arch Pharmacol*. 2022;395(1):99-104.
64. Remdesivir and Covid-19. Accessed April 22, 2022. <https://clinicaltrials.gov/ct2/results?term=remdesivir%2Band%2Bcovid-19>
65. Molnupiravir and Covid-19. Accessed April 22, 2022. <https://clinicaltrials.gov/ct2/results?term=molnupiravir%2Band%2Bcovid-19>
66. PF-07321332 and Covid-19. Accessed April 22, 2022. <https://clinicaltrials.gov/ct2/results?term=PF-07321332%2Band%2Bcovid-19%20>
67. COVID-19 treatment guidelines. Accessed April 22, 2022. <https://www.covid19treatmentguidelines.nih.gov/tables/mab-data/>
68. Therapeutic management of hospitalized adults with COVID-19. Accessed April 22, 2022. <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults-therapeutic-management/>
69. Rahman FI, Ether SA, Islam MR. The "Delta Plus" COVID-19 variant has evolved to become the next potential variant of concern: mutation history and measures of prevention. *J Basic Clin Physiol Pharmacol*. 2021;33:109-112. doi:10.1515/jbcpp-2021-0251
70. Daria S, Bhuiyan MA, Islam MR. Detection of highly muted coronavirus variant Omicron (B.1.1.529) is triggering the alarm for South Asian countries: associated risk factors and preventive actions. *J Med Virol*. 2021;94:1267-1268. doi:10.1002/jmv.27503
71. Islam MR, Hossain MJ. Detection of Omicron (B.1.1.529) variant has created panic among the people across the world: what should we do right now? *J Med Virol*. 2021;94:1768-1769. doi:10.1002/jmv.27546
72. Daria S, Islam MR. The SARS-CoV-2 omicron wave is indicating the end of the pandemic phase but the COVID-19 will continue. *J Med Virol*. 2022;94:2343-2345. doi:10.1002/jmv.27635
73. Mohapatra RK, Tiwari R, Sarangi AK, Islam MR, Chakraborty C, Dhama K. Omicron (B.1.1.529) variant of SARS-CoV-2: concerns, challenges, and recent updates. *J Med Virol*. 2022;94:2336-2342. doi:10.1002/jmv.2763
74. Islam S, Islam T, Islam MR. New coronavirus variants are creating more challenges to global healthcare system: a briefreport on the current knowledge. *Clin Pathol*. 2022;15. doi:10.1177/2632010X221075584
75. Daria S, Islam MR. Indiscriminate use of antibiotics for COVID-19 treatment in South Asian countries is a threat for future pandemics Due to Antibiotic Resistance. *Clin Pathol*. 2022;15. doi:10.1177/2632010X221099889

How to cite this article: Islam T, Hasan M, Rahman MS, Islam MR. Comparative evaluation of authorized drugs for treating Covid-19 patients. *Health Sci Rep*. 2022;5:e671. doi:10.1002/hsr2.671