Adverse Drug Reactions and Mechanism of Action of Paxlovid and Remdesivir in COVID-19 Therapy: A Comprehensive Review

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Abstract

Corona virus Disease 2019 (COVID-19), caused by SARS-CoV-2, is a systemic, hyper inflammatory vasculitis with a wide clinical spectrum ranging from mild symptoms to severe respiratory failure. Since the declaration of COVID-19 as a global pandemic by the WHO in March 2020, various therapeutic strategies have been explored, including the repurposing of drugs such as Azithromycin, Hydroxychloroquine, and Lopinavir/Ritonavir. Two major antiviral agents—**Paxlovid** (nirmatrelvir/ritonavir) and **Remdesivir**—have shown efficacy in treating COVID-19 and received emergency use authorization. SARS-CoV-2 enters host cells primarily via ACE2 and TMPRSS2-mediated pathways, but emerging evidence indicates alternative ACE2-independent entry routes. The infection progresses through distinct stages: an early viral replication phase, a pulmonary phase, and a severe systemic inflammatory phase associated with ARDS, cytokine storm, coagulopathy, and multi organ dysfunction.

Adverse drug reactions (ADRs) have been documented for both antivirals. Paxlovid is associated with gastrointestinal symptoms, dysgeusia, and rare drug interactions, particularly in transplant recipients and pregnant women. Remdesivir has shown elevated liver enzymes, gastrointestinal disturbances, and potential hepatotoxicity, though generally with favorable renal and cardiovascular safety profiles. Despite known ADRs, both drugs have demonstrated significant reductions in COVID-19 morbidity and mortality. Special populations, such as pregnant women and immunocompromised individuals, require careful assessment due to altered pharmacodynamics and increased susceptibility to ADRs. Understanding COVID-

19’s pathophysiology and the pharmacological mechanisms of these antivirals is critical to optimizing treatment outcomes while minimizing risk.

Introduction:

The SARS-CoV2 virus causes coronavirus disease 2019 (COVID-19), a systemic thrombo hyper inflammatory vasculitis with symptoms ranging from a simple cold to a serious acute respiratory infection. The World Health Organization (WHO) designated COVID-19 a pandemic on March 11, 2020; since then, 51.7 lakh deaths and 25.9 crore infections have been reported globally. To date, 4.67 lakh deaths and 3.45 crore infections have been reported in India [1].About 15% of infected individuals experience severe pneumonia, and a further 5% suffer critical disease with acute respiratory distress syndrome that necessitates ventilator support, despite the fact thatthe majority of COVID-19 infections are self-limited. Since there were no approved medicines for COVID-19 patients at first, Azithromycin, Hydroxychloroquine, and lopinavir/ritonavir were repurposed and their potential as therapeutics was examined [2]. The novel coronavirus, now known as SARS-CoV-2, initially appeared in the world in Wuhan, China. Since it caused severe respiratory illnesses and spread over the world at a never-before-seen rate, the coronavirus disease 2019 (COVID-19) was declared a pandemic. Globally, as of June 15th, 2021, the World Health Organization [WHO] reported 1.76 billion COVID-19 cases and almost 38 million deaths[3].Adverse drug reactions (ADRs) associated with pharmaceutical therapies for the novel disease during the 2020 coronavirus disease 2019 (COVID-19) pandemic[4].

The new antiviral medication "Paxlovid" from Pfizer demonstrated good efficacy against COVID-19. The drug is marketed under the name Paxlovid™ and is composed of two generic drugs, ritonavir and nirmatrelvir [5].The Malaysian National Pharmaceutical Regulatory Agency received 1001 complaints of 1714 Paxlovid®-related adverse events at the beginning of October 2022. Bitter taste (562 instances), diarrhea (247 cases), dysgeusia (134 cases), vomiting (70 cases), and nausea (69 cases) were the most frequently reported adr [6].The first antiviral medication licensed by the US FDA to treat COVID-19 is Remdesivir (DB14761). The US FDA authorized its emergency usage for those over 12 and weighing more than 40 kg in October 2020 [7]..Headaches, hypokalemia, and nausea are the most often reported adverse effects.15. Additionally, 1% of patients in the 5-day care group, 2% in the 10-day care group, and 2% in the routine care group experienced mortality on day 28.15[8].

Pathophysiology of covid-19:

Interactions and entry of the SARS-CoV-2 into the cell:

The main source of new infections is asymptomatic carriers and confirmed COVID-19 patients [9]. Infection through the fecal-oral pathway has been hypothesized in addition to respiratory droplets and contact with contaminated surfaces [10]. Pneumocytes, bronchial epithelial cells, and nasal cells are among the host cells that SARS-CoV-2 enters through the binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor during the initial infection of humans [11].

The rapid spread of this pandemic may be explained by the S protein of SARS-CoV-2's 10–20 times greater binding affinity for ACE2 than SARS-CoV [12]. Type 2 transmembrane serine protease (TMPRSS2), a cellular protease that is specifically found in alveolar epithelial type II cells, further primes S protein to facilitate coronavirus entrance and viral uptake. Many tissue cells, such as those in the airways, cornea, esophagus, ileum, colon, liver, gallbladder, heart, kidney, and testis, typically express the ACE2 receptor. The much wider spread of TMPRSS2 expression suggests that ACE2, not TMPRSS2, may be a primary and limiting determinant for viral entry in the early stages of infection [13, 14].

Notably, SARS-CoV-2 invasion and transmission in host cells can be inhibited by pharmacological intervention targeting ACE2 and TMPRSS2 [15, 16]. The binding of the S protein to ACE2 in the viral entry process entails multiple steps, which helps to clarify the mechanism of viral entry into host cells: Attachment: The SARS-CoV-2 S protein attaches itself to the host cell's ACE2 receptor.

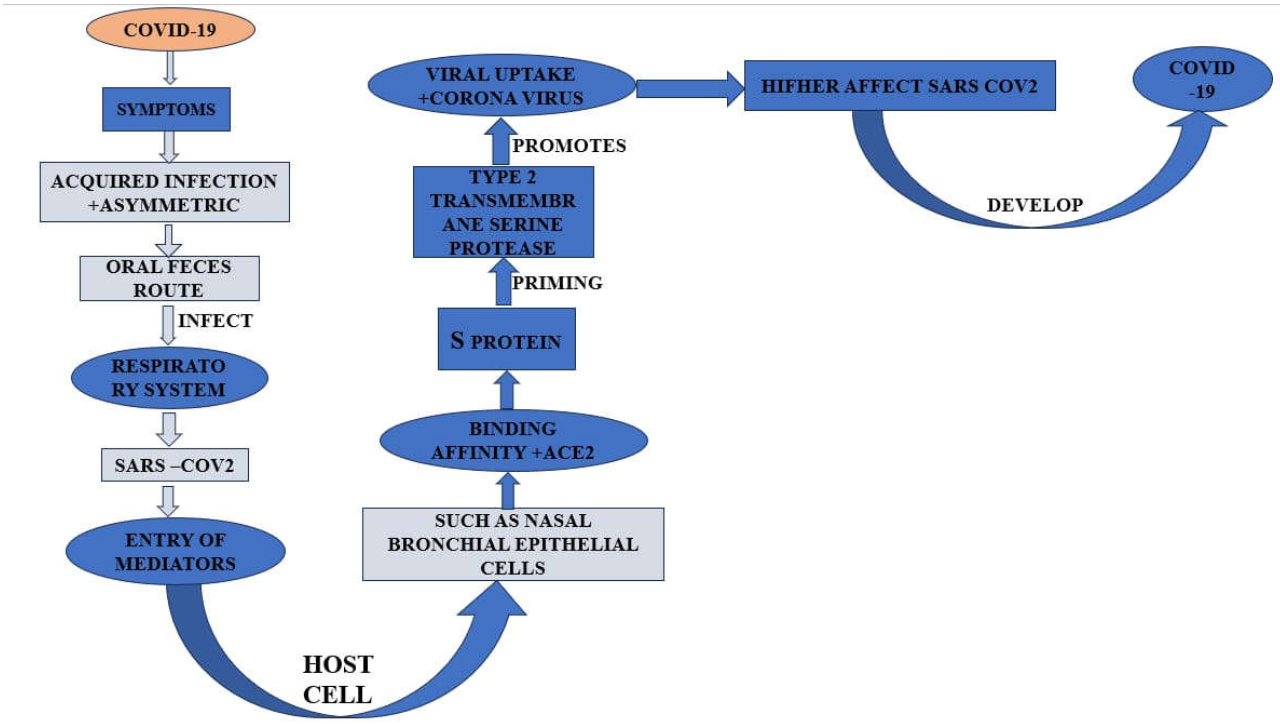
Priming: A host protease enzyme known as TMPRSS2 subsequently cleaves the S protein. The S protein's shape changes as a result of this cleavage, revealing a fusion peptide that makes it easier for the viral and host cell membranes to fuse. Fusion: The viral genetic material (RNA) can enter the host cell when the viral membrane merges with the host cell membrane.

Replication: The viral RNA serves as a template for the production of additional viral proteins and RNA once it has entered the host cell. The freshly generated viral proteins and RNA come together to form new viral particles, which are subsequently expelled from the host cell to infect further cells. All things considered, the SARSCoV-2 S protein's attachment

to the host cell's ACE2 receptor is essential to the virus's entrance and the subsequent generation of COVID-19. To effectively prevent and cure COVID-19, it is essential to comprehend the molecular mechanisms underlying this process [17,18].

More recent data suggests that SARS-CoV-2 enters cells, particularly immune cells, independently of ACE2 [19].

It is unclear what pathogenic effects ACE2-independent SARS-CoV-2 entrance into host cells will have. Furthermore, it is still unknown if the extrapulmonary symptoms, like multi-organ failure, are a direct result of the virus infecting those tissues or if the host's inflammatory response is to blame.



Interaction And Entry Of SARS-COV-2

Early stage of infection:

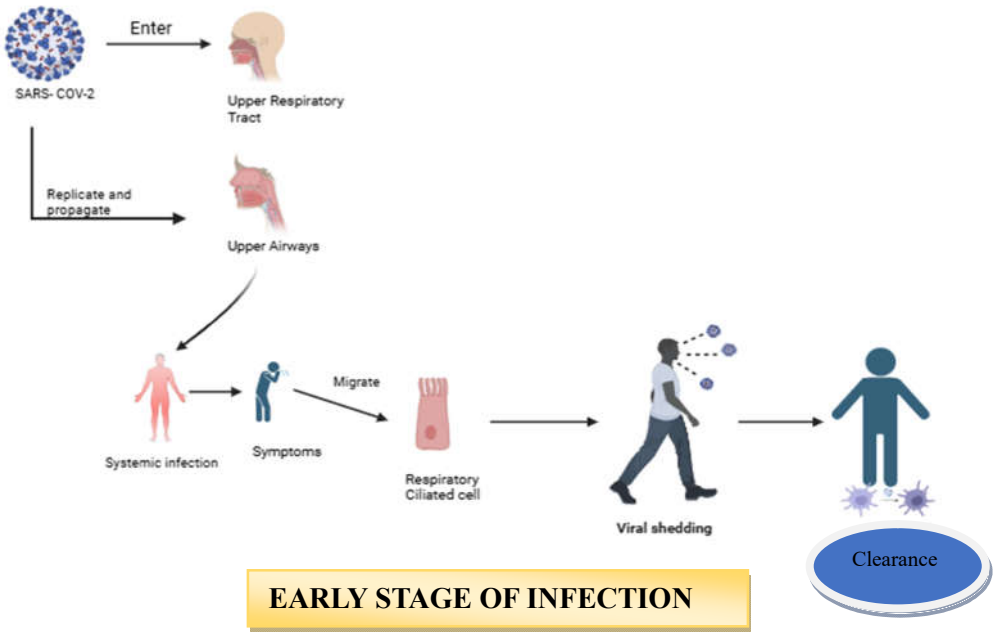
SARS-CoV2 begins to multiply and spread in the nose and upper airways after entering cells in the upper respiratory tract. The high viral load of infected people, which peaks around the start of symptoms, makes them extremely contagious even if they may not exhibit any symptoms at this point [20, 21].

The virus may then move through the ciliated cells in the conducting airways from the nasal epithelium to the upper respiratory tract [22, 23].

In addition to coughing or sneezing, infected people might also release virus particles while they converse, eat, or even exhale during daily activities. According to many studies conducted on various populations, pre-symptomatic transmission is thought to be a major factor in viral transmission, accounting for 9.1% to 62% of positive cases [24,25,26]. Additionally, the virus spreads during the course of the illness and may even persist after the symptoms have subsided [27].

Early on, those who are infected show signs of fever, lethargy, coughing, and sputum production. The adaptive immune response is started by the host mounting an innate response that is mediated by cytokines and antiviral interferons. At this point, the host may be able to regulate viral replication and reduce the severity of the disease if they can generate a robust interferon-mediated response, as is the case in adults and children [28, 29, 30].

Although the exact mechanisms of early viral clearance are still unclear, interferons play a crucial role in viral elimination due to their strong antiviral activity and strong over expression in patients with moderate illness [31].



Last Stage Of Infection:

COVID-19 symptoms, which can vary in intensity and length, are a sign of the clinical phase or later stage of the infection, which can occur in subjects who are unable to eradicate the virus in its early stages [32].

A fifth of infected patients are thought to develop severe symptoms like acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and pulmonary embolism as their infection spreads to the lower respiratory tract, where it affects the alveolar epithelial type II cells.

Three separate phases can be distinguished in the clinical phase of SARS-CoV-2: the lethal/recovery phase, the viremia phase, and the acute or pneumonia phase. Imaging indications of ground-glass opacity or consolidation in the lung, along with pulmonary symptoms such coughing, sputum production, and dyspnea, are what define the acute phase of pulmonary illness. The development of ARDS in COVID-19 is characterized by hyaline membrane formation, desquamation of pneumocytes, and diffuse alveolar injury [33].The deadly illness is exacerbated by the pulmonary vasculature's increased permeability, which hinders oxygen diffusion. One of the many multifactorial factors that contribute to lung permeability during COVID-19 is the direct cytopathic effects of the coronavirus in infected endothelium, which can lead to extensive endothelialitis [34]. The kallikreinbradykinin pathway, which increases vascular permeability, is indirectly enhanced by SARS-CoV-2's

decrease of ACE2 activity and the ensuing rise in angiotensin [35]. Immune cells like activated neutrophils release vasoactive mediators and inflammatory cytokines that cause endothelial cells to contract and weaken their tight connections. Fluid retention is encouraged by the breakdown of glycocalyx and the deposition of hyaluronic acid in the extracellular matrix [36].

Reduced blood oxygenation, a sign of the severity of the disease, is a result of compromised lung function brought on by increased lung vascular permeability. When the virus infiltrates the peripheral circulation, the viremic phase starts. Although little is known about the molecular mechanisms behind COVID-19 viremia, it has been demonstrated that the virus's ACE2-independent entrance into peripheral monocytes increases pyroptotic cell death and the severity of the illness [37]. Multiple systemic inflammation and multiorgan failure are caused by the viremia and the host reaction that follows.

It is challenging to identify the precise mediator of the inflammatory response during severe COVID-19 because the inflammatory response is mediated by a simultaneous increase in multiple inflammatory cytokines, including TNF-a, interferons (IFN-b, IFN-l), MCP-1, MIP-1 a, IL-1a, IL-1b, IL-6, IL-8, IL-12, and IL17 [38]. The significance of cytokines in COVID-19 is further complicated by the possibility that the early inflammatory response aids the host in limiting viral multiplication. It should come as no surprise that treatments that targeted particular cytokines, like TNF-a or IL-6, produced inconsistent outcomes [39,40].

A chronic illness that presents both locally and systemically mediates the fatal phase. Severe patients had a markedly higher inflammatory response, as evidenced by cytokine storm and coagulation factors, than non-severe patients [41,42]. The lung tissue sequesters neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells during this phase [43].

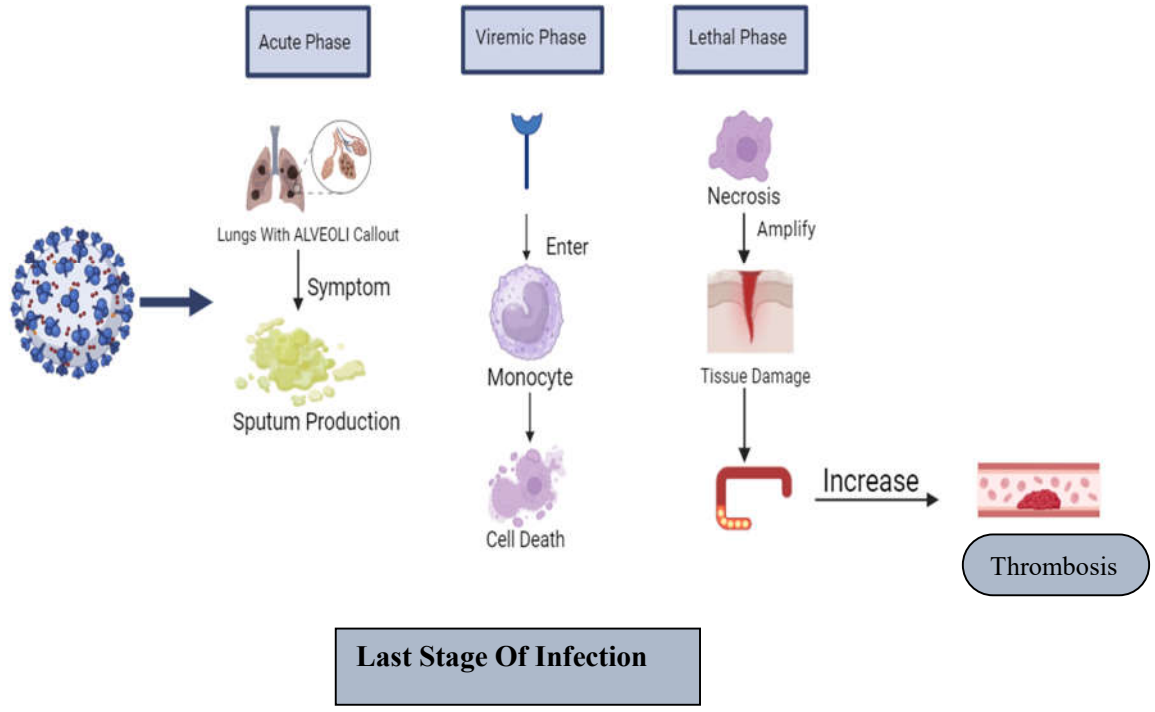
The tissue damage may be exacerbated by the host cells' ongoing apoptosis, necrosis, or pyroptosis. Furthermore, the inflammatory environment increases the activation of the coagulation cascade in the lungs by inducing the production of activated tissue factor on neutrophils, macrophages, and endothelial cells [44]. At this point, coagulation pathway markers such Ddimer overexpression are readily apparent. Wichmann et al. showed in an autopsy research that pulmonary embolism (PE) was directly responsible for one-third of the deaths and that 58% of COVID-19 patients had concurrent DVT [45].

SARS-CoV-2-related vasculitis may be the cause of ischemia symptoms in several organs, as evidenced by the possible involvement of thrombosis in pulmonary veins distal to the

alveolar capillary bed, which ought to serve as clot filters [46].

Because of this, severe COVID-19 is a multisystem illness that affects more than just the respiratory system. It can cause cardiac damage, arrhythmia, acute coronary syndrome, and venous thromboembolism, among other cardiovascular symptoms. These symptoms are directly linked to the severity of the illness and its development into a fatal condition [47].

Given all of these characteristics, immunomodulatory drugs and anticoagulant therapy are most likely required to reduce the prothrombotic and hyperinflammatory states [48].



ADR Reporting:

Paxlovid

Pregnant women and other high-risk populations are more likely to experience negative consequences from an acute COVID-19 infection [49,50]. In their research of a cohort of 91,412 women, including 8207 pregnant women, Ellington et al. discovered that being pregnant was linked to a significantly greater risk of hospitalization (relative risk, 0.9; 95% confidence interval 0.5–1.5) [51].

According to Troiano et al.'s narrative evaluation of 15 research, women's lower vaccination acceptance rate may further increase the risk among pregnant women [52]. Nonetheless, it is thought to be rare for SARS-COV-2 to spread through breast milk [53]. Due to adverse

effects and contraindications, some women who are pregnant or nursing may not be able to receive vaccinations [54].

Thirty percent of patients had three or more negative effects, and eighty-five percent reported at least one. Most effects appeared 1-2 hours after taking Paxlovid and went away 24 hours after quitting the drug. In a meta-analysis of 13 studies, Zheng et al. also concluded that the usage of Paxlovid was safe and effective for the approved population [55].

Seven pregnant patients who got nirmatrelvir/ritonavir medication and had a remission of their symptoms without any immediate negative effects were the subject of a retrospective descriptive study by Loza et al. There were no negative effects on the fetus or newborn [56].
In comparison to control, they found that COVID-19 patients receiving nirmatrelvir/ritonavir had a significantly lower death rate and a lower chance of developing a severe illness; additionally, the effects were more noticeable in cases of immunosuppression and neurological or cardiovascular comorbidities. Their results support the idea that nirmatrelvir and ritonavir can change the disease's progression and mortality rate [57].
In order to investigate the use of nirmatrelvir/ritonavir in pregnant women, Loza et al. conducted a brief follow-up on seven pregnant women with non-severe COVID-19 who were prescribed nirmatrelvir/ritonavir at varying gestational ages [58]. Prikis and Cameron recently reported that acute renal impairment and an abruptly elevated tacrolimus level in a kidney transplant patient undergoing nirmatrelvir/ritonavir medication necessitated stopping treatment. According to their findings, nirmatrelvir/ritonavir's inhibition of tacrolimus' metabolism may result in adverse effects, such as acute renal damage, from elevated concentrations of tacrolimus and its metabolites. For this reason, alternative immunosuppressive medications or a reduction in the daily dosage of tacrolimus should be taken into consideration during the course of COVID-19 treatment [59].

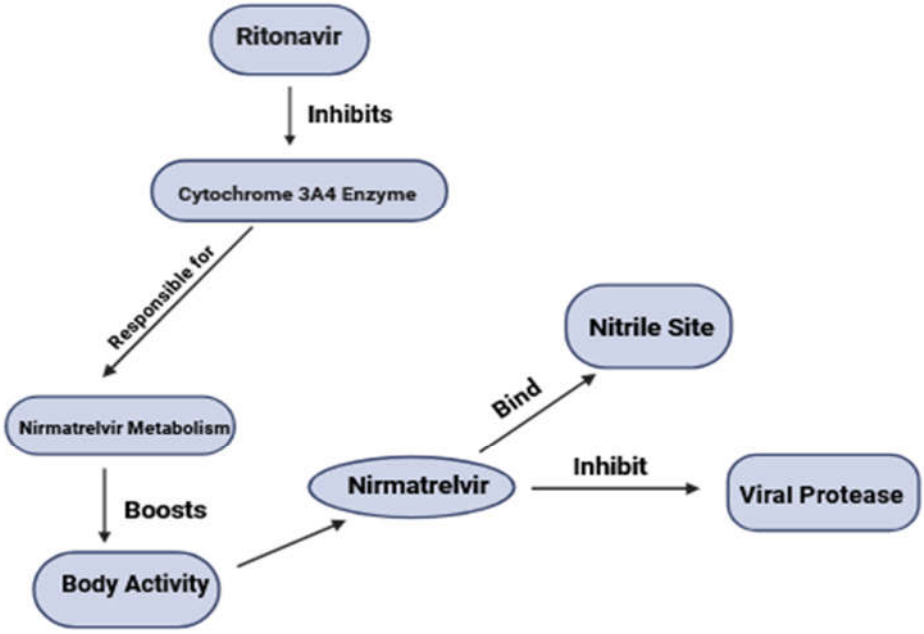
Yet, according to certain research, nirmatrelvir/ritonavir may cause typical adverse effects such headache, nausea, loose stool, and a distorted sensation of taste. Elevated blood pressure and muscle pains were also observed seldom [60]. The Malaysian National Pharmaceutical Regulatory Agency received 1001 complaints of 1714 Paxlovid®-related adverse events at the beginning of October 2022. Bitter taste (562 instances), diarrhea (247 cases), dysgeusia (134 cases), vomiting (70 cases), and nausea (69 cases) were the most frequently reported side effects [61]. Early identification of ADRs linked to Paxlovid® may improve patient outcomes and lessen the financial strain on the healthcare system.Pharmacists routinely

monitor unusual ADRs, such as anaphylaxis and hypersensitivity responses, in addition to frequent ADRs [62].

Mechanism of Action:

Nirmatrelvir's presence in the body is prolonged and its activity is increased when Ritonavir inhibits cytochrome P450 3A4, the enzyme that is in charge of Nirmatrelvir metabolism [63]. Nirmatrelvir, which binds from its nitrile site to the cited dyad of Mpro, is an oral protease inhibitor that was found in 2021 while trying to create medicines that block SARS-CoV-2 3CLpro [64]. Ritonavir is a tripeptide that binds to the functional location of HIV protease to block it [65].

Furthermore, all seven human coronavirus types—including betacoronaviruses (MERS-CoV, SARS-CoV-1, SARS-CoV-2, HCoV-OC43, and HCoV-HKU1) and alphacoronaviruses (HCoV-NL63 and HCoV-229E)—can have their Mpro proteolytic activity strongly inhibited by nirmatrelvir [66]. Molnupiravir works by attaching itself to the RNA-dependent RNA-polymerase, which results in a series of mistakes that eventually cause "lethal mutagenesis" and stop the virus from replicating [67]. The viral protease Mpro, which is necessary for viral replication, is inhibited by nimmatrelvir [68]. It is a CYP3A4 inhibitor and is given with ritonavir to improve pharmacokinetics [69].



Remdesivir:

Recent publications on adverse medication reactions are based on preliminary data. Hypersensitivity, anaphylaxis and infusion-related events (rare), transaminase elevation (very common), nausea (common), headache (common), rash (common), and renal impairment (precaution) are among the known possible risks [70]. Even in individuals with impairment, remdesivir did not significantly alter glomerular filtration rate or liver enzymes, according to a team of researchers studying renal, cardiac, and hepatic safety. Even with significant cardiovascular system (CVS) comorbidity, they saw a decrease in heart rate but no damage to the CVS [71].

With a 23% frequency, elevated liver enzymes were the most frequent adverse event in this trial. Furthermore, the increased liver aminotransferase was the reason for one of the four patients to stop receiving medication [72]. But according to the same study, grade 1–2 hypoalbuminemia (15:13%) and grade 1–2 elevated bilirubin (9:10%) were the most frequent liver side events, the latter of which also resulted in medication cessation (1%) [73]. In two further case reports, patients who had previously received lopinavir/ritonavir treatment and were taking remdesivir with or without HCQ showed evidence of hepatic enzyme increase [74].

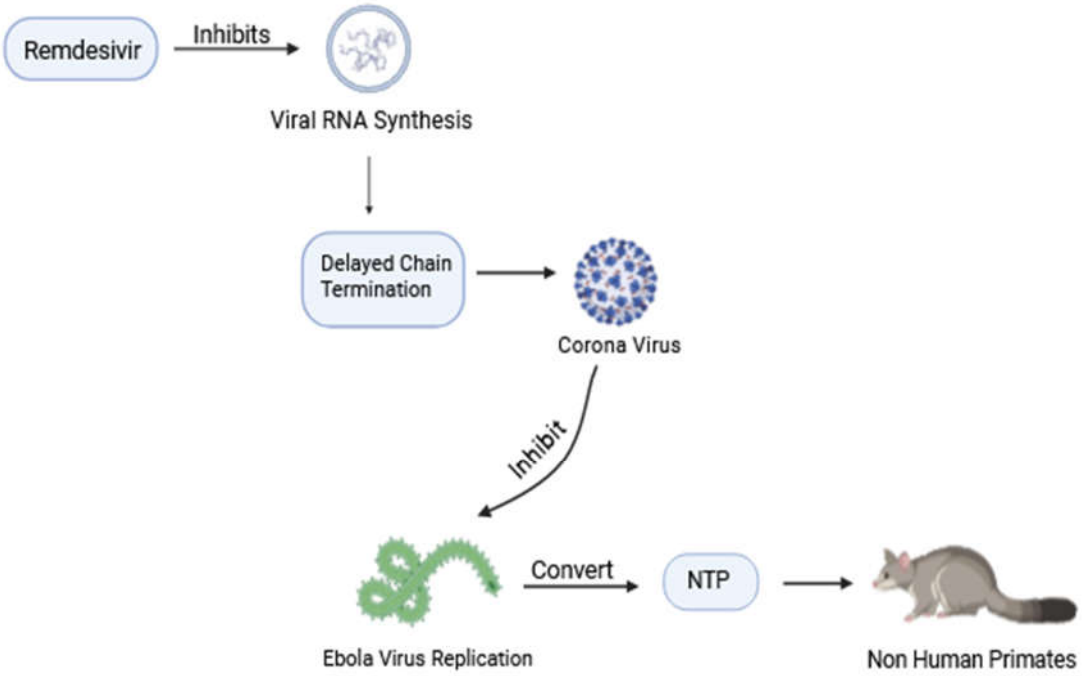
In terms of event type, cardiac events, renal/urinary tract diseases, and hepatic/hepatobiliary disorders accounted for the majority of recorded adverse events. In this regard, the remdesivir clinical research program has already reported hepatotoxicity, with certain cases in both healthy volunteers and COVID-19 patients raising concerns about possible hepatobiliary problems linked to its use [75]. In their investigation on the compassionate use of remdesivir for the treatment of COVID-19, Grein et al. found that patients experienced hematuria (4%), acute kidney injury (6%), and renal impairments (8%) [76]. Furthermore, as stated in the SmPC, evaluations of liver function and estimated glomerular filtration rate (eGRF) must be performed both prior to and during antiviral medication [77]. Remdesivir use may be linked to a higher chance of reporting bradycardia.Specifically, the authors discovered that 302 out of 2.603 ICSRs in VigiBase were suggestive of a cardiac adverse event associated with the usage of remdesivir. Bradycardia accounted for 94 of these cardiac complaints; the majority were severe, with some of them being fatal (17%) [78].

Mechanism of Action:

Remdesivir is an analog of a nucleotide [79]. Many viral RNA-dependent RNA polymerase (RdRp) complexes use the triphosphate form of RDV, or RDV-TP, as a substrate. It has been shown to inhibit viral RNA synthesis for all three coronaviruses (MERS-CoV, SARS-CoV, and SARS-CoV-2) RdRp through a particular mechanism of delayed chain termination [80].

Viral RNA-dependent RNA-polymerases (RdRp) are anticipated to be inhibited by the intracellular anabolism of the active triphosphate metabolite (NTP), which is necessary for the mechanism of action of Nuc [81].

By targeting the Ebola virus's RdRp and preventing viral RNA synthesis after an effective intracellular conversion to NTP in non-human primates, GS-5734 specifically prevents the virus from replicating. Although this chemical was inert against alphaviruses or retroviruses, it exhibited a wide range of antiviral activity against numerous RNA viruses, such as the respiratory syncytial virus (RSV), Junín virus, Lassa fever virus, and Middle East respiratory syndrome virus [82].



Conclusion:

The SARS-CoV2 virus causes coronavirus disease 2019 (COVID-19), a systemic thrombohyperinflammatory vasculitis with symptoms ranging from a simple cold to a serious acute respiratory infection.The World Health Organization (WHO) designated COVID-19 a pandemic on March 11, 2020; since then, 51.7 lakh deaths and 25.9 crore infections have been reported globally. To date, 4.67 lakh deaths and 3.45 crore infections have been reported in India. Yet, according to certain research, nirmatrelvir/ritonavir may cause typical adverse effects such headache, nausea, loose stool, and a distorted sensation of taste. Elevated blood pressure and muscle pains were also observed seldom. Nirmatrelvir's presence in the body is prolonged and its activity is increased when Ritonavir inhibits cytochrome P450 3A4, the enzyme that is in charge of Nirmatrelvir metabolism. The viral protease Mpro, which is necessary for viral replication, is inhibited by nimmatrelvir. Use of remdesivir for the treatment of COVID-19, Grein et al. found that patients experienced hematuria (4%), acute kidney injury (6%), and renal impairments (8%). Cardiac adverse event associated with the usage of remdesivir. Remdesivir is an analog of a nucleotide.

Discussion

Acknowledgment

Diksha Devi gives an idea about manuscript and Sidhant Sharma write the manuscript. Devanshi, Poonam and kiran analyze the data. There is no fund provide for this study.

Conflict of Interest

The author(s) declare that there is no conflict of interest regarding the publication of this paper.

References

1. BintiHamzah FA, Lau CH, Nazri H, Ligot DC, Lee G, Tan CL, et al. Corona Tracker: worldwide COVID-19 outbreak data analysis and prediction. Bull World Health Organ 2020;1:1-3.

2. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebocontrolled, multicentre trial. Lancet 2020;395:1569-78. doi: 10.1016/ S0140-6736(20)31022-9, PMID 32423584.

3. World Health Organization. WHO COVID-19 dashboard. covid19. who.int. 2021. Accessed June 2021. https://covid19.who.int/.

4. World Health Organization. Descriptive analysis of COVID-19-related spontaneous reports from VigiBase: interim results. 2020. https://www.who.int/medicines/regulation/medicines-safety/ COVID19-PV-update4.pdf?ua=1. Accessed 1 June 2020.

5. JMei CS. Nirmatrelvir/Ritonavir (PAXLOVID): risk of anaphylaxis and hypersensitivity reactions. 2022.

6. Mei CS. Nirmatrelvir/Ritonavir (PAXLOVID): risk of anaphylaxis and hypersensitivity reactions. 2022.

7. https://www.npra.gov.my/index.php/en/health-professionals/recent-updates/435-english/safety-alerts-main/ safety-alerts-2022/ 1527403-nirmatrelvir-ritonavir-paxlovidtm-risk-of anaphylaxis-and-hypersensitivity.html. Accessed 11 Oct 2022.

8. 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.

9. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. J Am Med Assoc. 2020;324 (11):1048–1057. doi:10.1001/jama.2020.16349.

10. Hoehl S, Rabenau H, Berger A, Kortenbusch M, Cinatl J, Bojkova D, et al. Evidence of SARS-coV-2 infection in returning travelers from wuhan, China. N Engl J Med (2020) 382(13):1278–80. doi: 10.1056/NEJMc2001899.

11. National Health Commission OfThe People's Republic Of China. Protocol for prevention and control of COVID-19 (Trial edition 6). Available at: http:// wwwnhcgovcn/yzygj/s7653p/202203/b74ade1ba4494583805a3d2e40093d88shtml.

12. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-coV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell (2020) 181(2):271–80 e8. doi: 10.1016/ j.cell.2020.02.052.

13. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. CryoEM structure of the 2019-nCoV spike in the prefusion conformation. bioRxiv (2020). doi: 10.1101/2020.02.11.944462.

14. Sungnak W, Huang N, Becavin C, Berg M, Queen R, Litvinukova M, et al. SARSCoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med (2020) 26(5):681–87. doi: 10.1038/s41591-020-0868-6.

15. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med (2020) 14(2):185–92. doi: 10.1007/ s11684-020-0754-0.

16. Chen R, Fu J, Hu J, Li C, Zhao Y, Qu H, et al. Identification of the immunodominant neutralizing regions in the spike glycoprotein of porcine deltacoronavirus. Virus Res (2020) 276:197834. doi: 10.1016/j.virusres.2019.197834.

17. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-coV-2. Am J Respir Crit Care Med (2020) 202 (5):756–59. doi: 10.1164/rccm.202001-0179LE.

18. Klein J, Wood J, Jaycox J, Lu P, Dhodapkar RM, Gehlhausen JR, et al. Distinguishing features of Long COVID identified through immune profiling. medRxiv (2022). doi: 10.1101/2022.08.09.22278592.

19. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-coV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell (2020) 181(2):271–80 e8. doi: 10.1016/ j.cell.2020.02.052.

20. Sefik E, Qu R, Junqueira C, Kaffe E, Mirza H, Zhao J, et al. Inflammasome activation in infected macrophages drives COVID-19 pathology. Nature (2022) 606 (7914):585–93. doi: 10.1038/s41586-022-04802-1.

21. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med (2020) 26(5):672–75. doi: 10.1038/s41591-020-0869-5.

22. Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J (2021) 97(1147):312–20. doi: 10.1136/ postgradmedj-2020-138577.

23. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-coV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell (2020) 181(2):271–80 e8. doi: 10.1016/ j.cell.2020.02.052.

24. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol (2020) 94(7). doi: 10.1128/JVI.00127-20.

25. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med (2020) 26(5):672–75. doi: 10.1038/s41591-020-0869-5.

26. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA (2020) 323(14):1406–07. doi: 10.1001/jama.2020.2565.

27. Zhang J, Tian S, Lou J, Chen Y. Familial cluster of COVID-19 infection from an asymptomatic. Crit Care (2020) 24(1):119. doi: 10.1186/s13054-020-2817-7.

28. Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. Euro Surveill (2020) 25(17). doi: 10.2807/1560-7917.ES.2020.25.17.2000257.

29. Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J (2021) 97(1147):312–20. doi: 10.1136/ postgradmedj-2020-138577.

30. Anka AU, Tahir MI, Abubakar SD, Alsabbagh M, Zian Z, Hamedifar H, et al. Coronavirus disease 2019 (COVID-19): An overview of the immunopathology, serological diagnosis and management. Scand J Immunol (2021) 93(4):e12998. doi: 10.1111/sji.12998.

31. Yoshida M, Worlock KB, Huang N, Huang N, Lindeboom RGH, Butler CR, Kumasaka N, et al. Local and systemic responses to SARS-CoV-2 infection in children and adults. Nature (2022) 602(7896):321–27. doi: 10.1038/s41586-021-04345-x.

32. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science (2020) 369(6504):718–24. doi: 10.1126/science.abc6027.

33. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA (2020) 324(8):782–93. doi: 10.1001/jama.2020.12839.

34. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med (2020) 46(6):1105–08. doi: 10.1007/s00134-020-06059-6.

35. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med (2020) 8(4):420–22. doi: 10.1016/S2213-2600(20)30076-X.

36. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Bruggemann RJ, et al. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. Elife (2020) 9. doi: 10.7554/eLife.57555.

37. Singh SP, Pritam M, Pandey B, Yadav TP. Microstructure, pathophysiology, and potential therapeutics of COVID-19: A comprehensive review. J Med Virol (2021) 93 (1):275–99. doi: 10.1002/jmv.26254.

38. Sefik E, Qu R, Junqueira C, Kaffe E, Mirza H, Zhao J, et al. Inflammasome activation in infected macrophages drives COVID-19 pathology. Nature (2022) 606 (7914):585–93. doi: 10.1038/s41586-022-04802.

39. Fu Y, Cheng Y, Wu Y. Understanding SARS-coV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin (2020) 35(3):266– 71. doi: 10.1007/s12250-020-00207-4.

40. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet (2020) 395(10234):1407–09. doi: 10.1016/S0140-6736(20)30858-8.

41. Garbers C, Rose-John S. Genetic IL-6R variants and therapeutic inhibition of IL6 receptor signalling in COVID-19. Lancet Rheumatol (2021) 3(2):e96–7. doi: 10.1016/ S2665-9913(20)30416-1.

42. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet (2020) 395(10235):1517–20. doi: 10.1016/S0140-6736(20)30920-X. .Ochani R,

43. Asad A, Yasmin F, Shaikh S, Khalid H, Batra S, et al. COVID-19 pandemic: from origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management. Infez Med (2021) 29(1):20–36.

44. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). Treasure Island (FL: StatPearls (2022).

45. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med (2020) 46(6):1089–98. doi: 10.1007/s00134-020-06062-x.

46. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: A prospective cohort study. Ann Intern Med (2020) 173(4):268–77. doi: 10.7326/M20-2003.

47. McGonagle D, Bridgewood C, Ramanan AV, Meaney JFM, Watad A. COVID19 vasculitis and novel vasculitis mimics. Lancet Rheumatol (2021) 3(3):e224–e33. doi: 10.1016/S2665-9913(20)30420.

48. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol (2020) 17 (9):543–58. doi: 10.1038/s41569-020-0413-9.

49. Bonaventura A, Vecchie A, Dagna L, Martinod K, Dixon DL, Van Tassell BW, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID19. Nat Rev Immunol (2021) 21(5):319–29. doi: 10.1038/s41577-021-00536-9.

50. Phosphor, W.N.; Khaliq, O.P. Is pregnancy a risk factor of COVID-19? *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2020**, *252*, 605–609.[CrossRef].

51. Wastnedge, E.A.N.; Reynolds, R.M.; van Boeckel, S.R.; Stock, S.J.; Denison, F.C.; Maybin, J.A.; Critchley, H.O.D. Pregnancy andCOVID-19. *Physiol. Rev.* **2021**, *101*, 303–318. [CrossRef] [PubMed].

52. Ellington, S.; Strid, P.; Tong, V.T.; Woodworth, K.; Galang, R.R.; Zambrano, L.D.; Nahabedian, J.; Anderson, K.; Gilboa, S.M.Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status—United States, January 22–June 7, 2020. *MMWR Morb. Mortal Wkly. Rep.* **2020**, *69*, 769–775.

53. Troiano, G.; Nardi, A. Vaccine hesitancy in the era of COVID-19. *Public Health* **2021**, *194*, 245–251.

54. Spaatz, D.L.; Davanzo, R.; Müller, J.A.; Powell, R.; Rigourd, V.; Yates, A.; Geddes, D.T.; van Goudoever, J.B.; Bode, L. Promotingand Protecting Human Milk and Breastfeeding in a COVID-19 World. *Front. Pediatric.* **2020**, *8*, 633700. [CrossRef].

55. Clinical Guidance for COVID-19 Vaccination | CDC. Available online: https://www.cdc.gov/vaccines/covid-19/clinicalconsiderations/interim-considerations-us.html#contraindications (accessed on 19 August 2022).

56. Zheng, Q.; Ma, P.; Wang, M.; Cheng, Y.; Zhou, M.; Ye, L.; Feng, Z.; Zhang, C. Efficacy and safety of Paxlovid for COVID-19:a meta-analysis. *J. Infect.* **2022**. [CrossRef].

57. Loza, A.; Farias, R.; Gavin, N.; Wagner, R.; Hammer, E.; Shields, A. Short-term Pregnancy Outcomes After Nirmatrelvir-ritonavir Treatment for Mild-to-Moderate Coronavirus Disease 2019 (COVID-19). *Obstet. Gynecol.* **2022**, *140*, 447–449. [CrossRef].

58. R. Najjar-Debbiny, N. Gronich, G. Weber, J. Khoury, M. Amar, N. Stein, et al., Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients, Clin. Infect. Dis. (2022).

59. A. Loza, R. Farias, N. Gavin, R. Wagner, E. Hammer, A. Shields, Short-term pregnancy outcomes after nirmatrelvir-ritonavir treatment for mild-to-moderate coronavirus disease 2019 (COVID-19), Obstet. Gynecol. 140 (3) (2022) 447–449.

60. M. Prikis, A. Cameron, Paxlovid (Nirmatelvir/Ritonavir) and tacrolimus drug-drug interaction in a kidney transplant patient with SARS-2-CoV infection: a case report, Transpl. Proc. 54 (6) (2022) 1557–1560.

61. E. Duffy, Treat. COVID-19 Paxlovid Prim. care (2022).70. Mei CS. Nirmatrelvir/Ritonavir (PAXLOVID): risk of anaphylaxis and hypersensitivity reactions. 2022.https://www.npra.gov.my/index.php/en/health-professionals/recent-updates/435-english/safety-alerts-main/safety-alerts-2022/1527403-nirmatrelvir-ritonavir-paxlovidtm-risk-ofanaphylaxis-and-hypersensitivity.html. Accessed 11 Oct 2022.

62. European medicines Agency. Paxlovid for the treatment of Covid-19. 2021. p. 131. https://www.ema.europa.eu/en/documents/referral/paxlovid-pf-07321332-ritonavir-covid-19-article-53-procedure-assessmentreport_en.pdf. Accessed 8 Sept 2022.

63. JA OS. EUA 105 Pfizer Paxlovid LOA (12222021). In: Administration USFaD, editor. 2021.

64. D.R. Owen, C.M.N. Allerton, A.S. Anderson, L. Aschenbrenner, M. Avery, S. Berritt, etal., An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19, Science 374 (6575) (2021) 1586–1593.

65. H. Eng, A.L. Dantonio, E.P. Kadar, R.S. Obach, L. Di, J. Lin, et al., Disposition of nirmatrelvir, an orally bioavailable inhibitor of SARS-CoV-2 3C-Like Protease,across Animals and Humans, Drug Metab. Dispos. 50 (5) (2022) 576–590.

66. A. Zarei, S.T. Fardood, F. Moradnia, A. Ramazani, A review on coronavirus family persistency and considerations of novel type, COVID-19 features, Eurasia Chem. Commun. (2020) 798–811.

67. Malone, B.; Campbell, E.A. Molnupiravir: Coding for catastrophe. *Nat. Struct. Mol. Biol.* **2021**, *28*, 706–708. [CrossRef].

68. Hilgenfeld, R. From SARS to MERS: Crystallographic studies on coronaviral proteases enable antiviral drug design. *FEBS J.* **2014**, *281*, 4085–4096. [CrossRef].

69. Owen, D.R.; Allerton, C.M.N.; Anderson, A.S.; Aschenbrenner, L.; Avery, M.; Berritt, S.; Boras, B.; Cardin, R.D.; Carlo, A.; Coffman, K.J.; et al. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. *Science* **2021**, *374*, 1586–1593. [CrossRef].

70. European Medicines Agency. Summary of product characteristics for Veklury. 2020. https://www.ema.europa.eu/en/documents/other/veklury-product-information-approvedchmp-25-june-2020-pending-endorsement-european-commission_en.pdf. Accessed 21Sept 2020.

71. 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.

72. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med.* (2020) 382:2327–36. doi: 10.1056/NEJMoa2007016.

73. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet (London, England).* (2020) 395:1569–78. doi: 10.1016/S0140-6736(20)31022-9.

74. Lee C, Ahn MY, Byeon K, Choi J-P, Hahm C, Kim H, et al. Clinical experience with use of remdesivir in the treatment of severe acute respiratory syndrome Coronavirus 2: a case series. *Infection & Chemotherapy.* (2020) 52:369–80. doi: 10.3947/ic.2020.52.3.369.

75. Goldman, J.D.; Lye, D.C.B.; Hui, D.S.; Marks, K.M.; Bruno, R.; Montejano, R.; Spinner, C.D.; Galli, M.; Ahn, M.-Y.; Nahass, R.G.; et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N. Engl. J. Med. **2020**, 383, 1827–1837. [Google Scholar] [CrossRef].

76. J.; Ohmagari, N.; Shin, D.; Diaz, G.; Asperges, E.; Castagna, A.; Feldt, T.; Green, G.; Green, M.L.; Lescure, F.-X.; et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N. Engl. J. Med. **2020**, 382, 2327–2336. [Google Scholar] [CrossRef] [PubMed].

77. EMA—Veklury-Summary of Product Characteristics. Available online: https://www.ema.europa.eu/en/documents/other/veklury-product-information-approved-chmp-25-june-2020-pending-endorsement-european-commission_en.pdf (accessed on 14 April 2021).

78. Touafchia, A.; Bagheri, H.; Carrié, D.; Durrieu, G.; Sommet, A.; Chouchana, L.; Montastruc, F. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): A new safety concerns. Clin. Microbiol. Infect. **2021**. [Google Scholar] [CrossRef].

79. T.K. Warren, D. Siegel, H.C. Hui, *et al.*Discovery and Synthesis of GS-5734, a Phosphoramidate Prodrug of a Pyrrolo [2, 1 f][triazin 4 amino] Adenine C-Nucleoside (GS 5734) for the Treatment of Ebola and Emerging VirusesUSAMRIID Ft Detrick United States (2017).

80. C.J. Gordon, E.P. Tchesnokov, E. Woolner, *et al.*Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potencyJ Biol Chem (2020), 10.1074/jbc.RA120.013679[Epub ahead of print.

81. A. Cho, O.L. Saunders, T. Butler, L. Zhang, J. Xu, L.E. Vela, J.Y. Feng, A.S. Ray, C.U. Kim Synthesis and antiviral activity of a series of 10-substituted4-aza-7,9-dideazaadenosine C-nucleosidesBioorg. Med. Chem. Lett., 22 (2012), pp. 2705-2707, 10.1016/j.bmcl.2012.02.105.

82. T.K. Warren, R. Jordan, M.K. Lo, A.S. Ray, R.L. Mackman, V. Soloveva, *et al.*Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeysNature, 531 (2016), pp. 381-385, 10.1038/nature17180.