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Overview on life saving drug in Covid 19: Remdisivir

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ABSRACT :

The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-cov-2) has created an urgent need for effective antivirals Drug. Remdesivir (formerly GS-5734) is a nucleoside analogue pro-drug Used in COVID-19 clinical trials. Itshaveing unique structural features with high concentrations of the active triphosphate metabolite to be delivered intracellularly and it Result reading to successfully inhibit viral RNA synthesis. In pre-clinical models, remdesivir has demonstrated potent antiviral activity against diverse human and zoonotic β-coronaviruses, including SARS-cov-2. In this article, we critically review available data on remdesivir with an emphasis on biochemistry, pharmacology, pharmacokinetics, Mode of action and in vitro activity against coronaviruses as well as clinical experience and current progress in COVID-19 clinical trials.

The search for effective therapies has become a worldwide priority. The antiviral agent remdesivir has become a viable option and is now available in the United States for I.P.D patients through an emergency use authorization. This article describes remdesivir's historical background, pharmacology, key trials, adverse events,MOA, and issues regarding accessibility.

An inhibitor of the viral RNA-dependent, RNA polymerase with in vitro inhibitory activity against SARS-cov-1 and the Middle East respiratory syndrome (MERS-cov).

KEYWORDS : Remdesivir , COVID-19, SARS-CoV-2, coronavirus, severe acute respiratory syndrome.

I. INTRODUCTION :

Current situation tells us that the world is seviourlyAffected by covid-19 pandemic; Dec 2019 corona virusCame into existence and changes our life completely. PrimeMoto is to take the safety precautions like wearing masks,Using sanitizers, staying indoors and maintaining social lDistancingand strengthen the immunity.(2)This Disease isCommunicated by a Novel corona virus which is also knownAs acute respiratory syndrome corona virus 2 i.e. Sars-cov2. This virus belong to seventh corona virus familyWhich is responsible for infecting the human beings.(3)(4)TheMajor reason fast spread of this disease is due to closeContact with infected person through droplets eighterfromSneezingor coughing.(5)This disease id having lots ofSymptoms and the symptoms are mild to severe. MajorityOf patient shows the fever followed by cough, myalgiaAndfatique. Sputum production and headache is also seen.Sometimes virus directly attacks the alveolar epithelial cellWhich may lead to respiratory failure which may be fetal toPatient.(6)

This small virus affects the drug to that large extendBecause of lack of drugs medicines and vaccines as wellSo to beat this condition one can follow all the rules andRegulations regarding covid-19 and boost immunity.(2)

Ayurveda and some traditional Chinese medicinesFromvedic period 1600-500 BCE, giving world thePotential medicines to boost the immunity and cure againstIllness caused by micro-organism.(7)Drugs from Ayurveda Having wide range of effectiveness against various microorganisms without showing any side effect. By takingHerbal drugs or medicines which are having active chemicalConstituent which may be having therapeutic effect like antiinflammatory, antiviral, etc.(8)Curcuma longa widely usedAsayurvedic drug because of its effects like anti-oxidants,Anti-inflammatory, anti mutagenic, anticancer, antimicrobialEffects.(9)(10)

The drugs containing active constituents like Flavanoids, proanthocyanidins, saponins, monoterpenoids,Triterpenoids, glucosides, sesquiterpenes, and alkaloids Shows activity against viral infections.(11)Ashvagandha,Giloe, tulasi, cardamom, cinnamon, cinchona, turmeric, Amla, black pepper, fennel, garlic are some commonExamples of drugs used from the ancient times to cureMultiple diseases. In india generally

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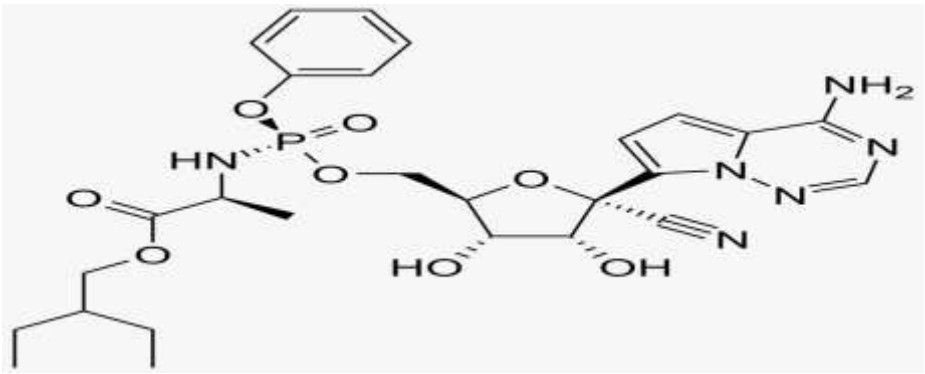
all this herbs are usedIn the day to day activities and some of the herbs are Integral part of the Indian kitchen. Almost all the drugsHavingimmunomodulatory activities. All this drugs areVery common Indian day to day life. Every Indian no matterWhat religion, financial conditions, Geographical state,Community they belong one of the above mentioned drugIs used daily. All the drugs potentially proven for their

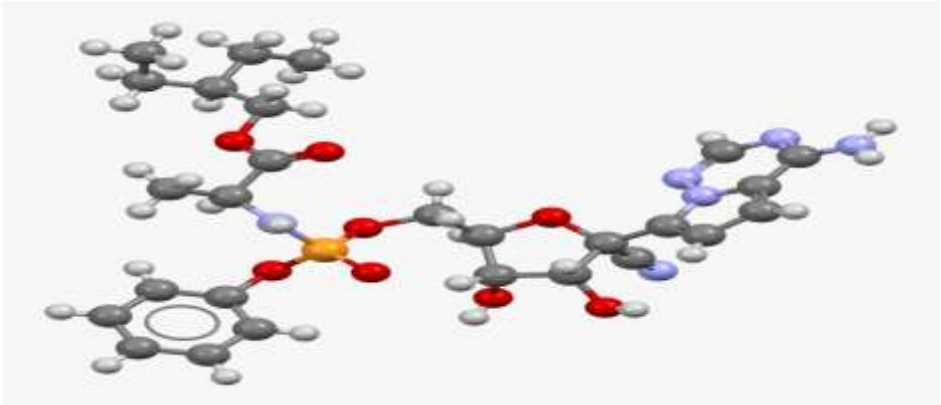
Immune modulatory, anti-oxidant and anti inflammatoryProperties. Because of that only the death rate in indiaisLower than others.(12)GlycyrhizaGlabra roots are used in treatment ofBronchitis and gastritis from ancient times. It is also havingAnti-oxidant and anti-inflammatory property.

Citrus Limon (Lemon)-Lemon is rich in vitamin C andIt is also used to relieve cough and used as expectorantIn bronchitis. It is also used as anti-inflammatory for soreThroat.(13)

GingiberOfficinalis (Ginger)-Many preclinical studiesReports analgesics, expectorant, anti-pyretic and antiinflammatory effect. It is also effective in common cold andCough, asthma.(14)(15)The dictoction of ginger, colve and piper nigrumProvides humeral and cell mediated response to healthy asWell as covid-19 infected person. It also reduces the nasalCongestion. The drug like Tulsi is present in every homeGarden also having wide range of effects like anti-microbialAromatic etc.(16)(18)

Remdesivir, sold under the brand name Veklury,(19)(20) is a broad-spectrum antiviral medication developed by the biopharmaceutical company Gilead Sciences.(21)It is administered via injection into a vein.(22)(23) During the COVID‑ 19 pandemic, remdesivir was approved or authorized for emergency use to treat COVID‑ 19 in numerous countries.(24)Remdesivir was originally developed to treat hepatitis C,(25) and was subsequently investigated for Ebola virus disease and Marburg virus infections(26) before being studied as a post-infection treatment for COVID‑ 19.(27)(28). The most common side effect in healthy volunteers is raised blood levels of liver enzymes.(19)The most common side effect in people with COVID‑ 19 is nausea.(19) Side effects may include liver inflammation and an infusion-related reaction with nausea, low blood pressure, and sweating.(29)





Moleculer Structure of Remdesivir

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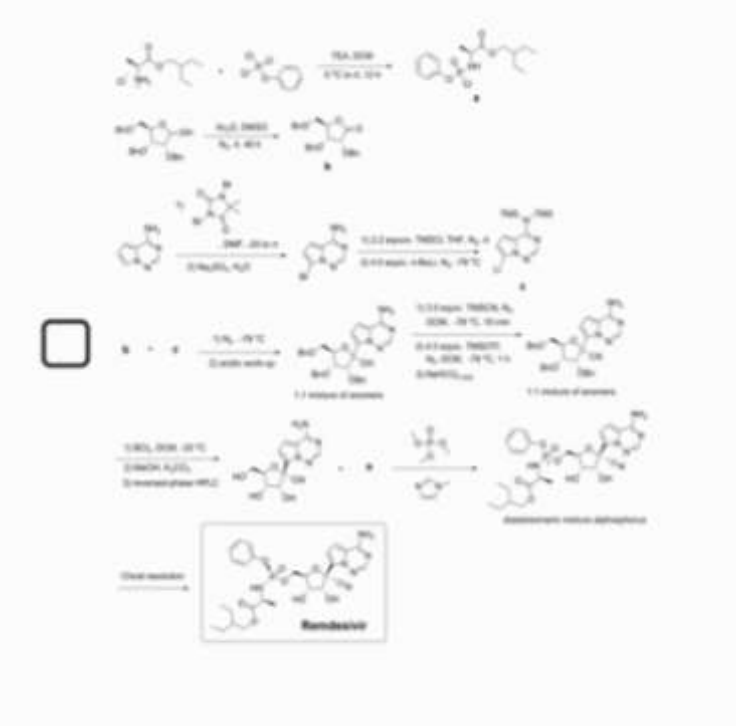
Synthesis



Remdesivir can be synthesized in multiple steps from ribose derivatives. The figure to the right is one of the synthesis routes of remdesivir invented by Chun and coauthors from Gilead Sciences. (30)(31) In this method, intermediate a is firstly prepared from L-alanine and phenyl phosphorodichloridate in presence of triethylamine and dichloromethane; triple benzylprotected ribose is oxidized by dimethyl sulfoxide with acetic anhydride and give the lactone intermediate b; pyrrolo[2,1-f] [1,2,4]triazin-4- amine is brominated, and the amine group is protected by excess trimethylsilyl chloride. N-butyllithiumundergoes a halogen-lithium exchange reaction with the bromide at −78 °C (−108 °F) to yield the intermediate c. The intermediate b is then added to a solution containing intermediate c dropwise. After quenching the reaction in a weakly acidic aqueous solution, a mixture of 1:1 anomers was obtained. It was then reacted with an excess of trimethylsilyl cyanide in dichloromethane at −78 °C (−108 °F) for 10 minutes. Trimethylsilyltriflate was added and reacts for one additional hour, and Resistance Interactions Synthesis the mixture was quenched in an aqueous sodium hydrogen carbonate. A nitrile intermediate was obtained. The protective group, benzyl, was then removed with boron trichloride in dichloromethane at −20 °C (−4 °F). The excess of boron trichloride was quenched in a mixture of potassium carbonate and methanol. A benzyl-free intermediate was obtained. The isomers were then separated via reversed-phase HPLC. The optically pure compound and intermediate a are reacted with trimethyl phosphate and methylimidazole to obtain a diastereomer mixture of remdesivir. In the end, optically pure remdesivir can be obtained through chiral resolution methods.

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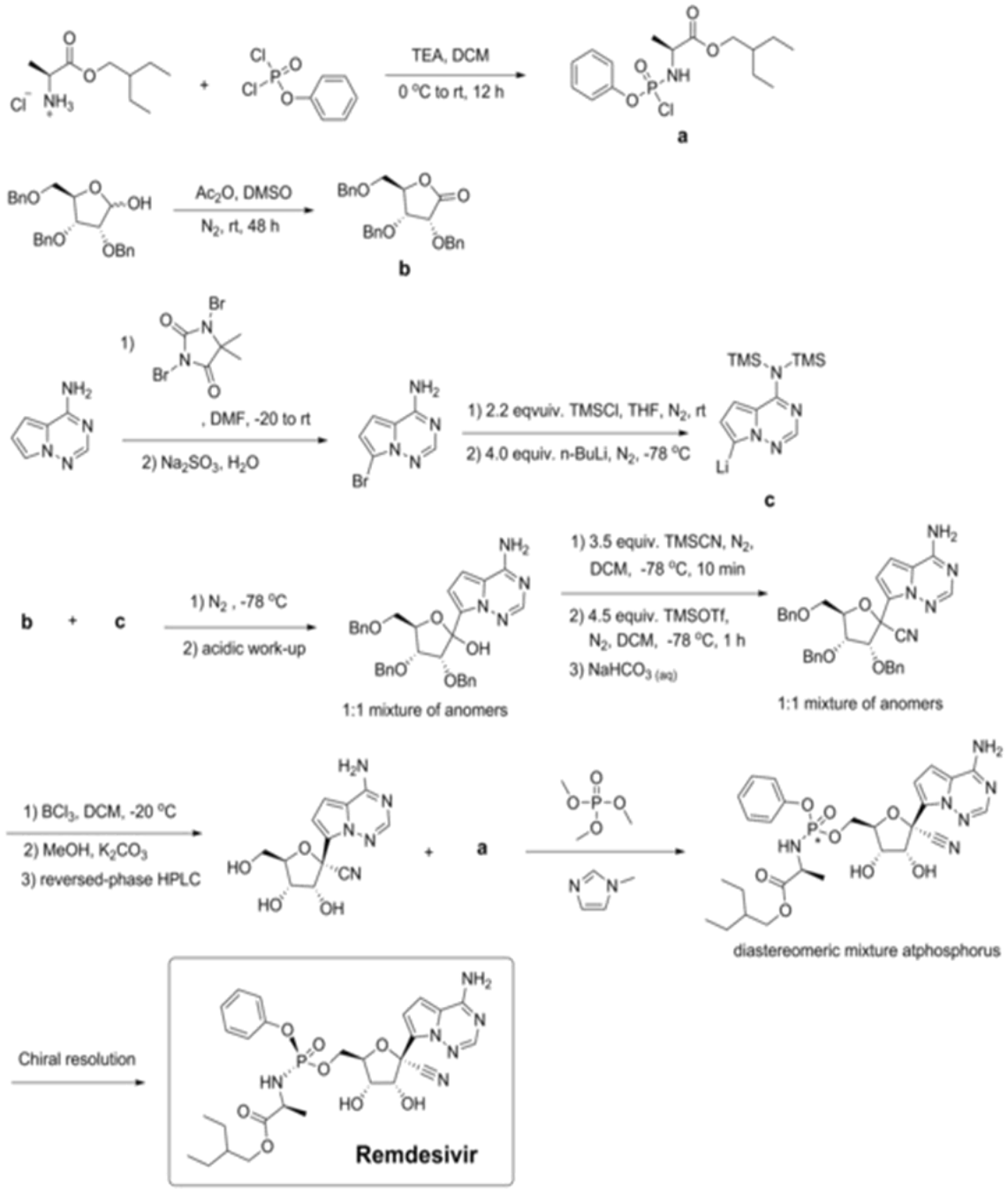

Synthesis of Remdesivir

- **Probable molecular mechanism of Remdisivir against SARS-CoV- 2:**

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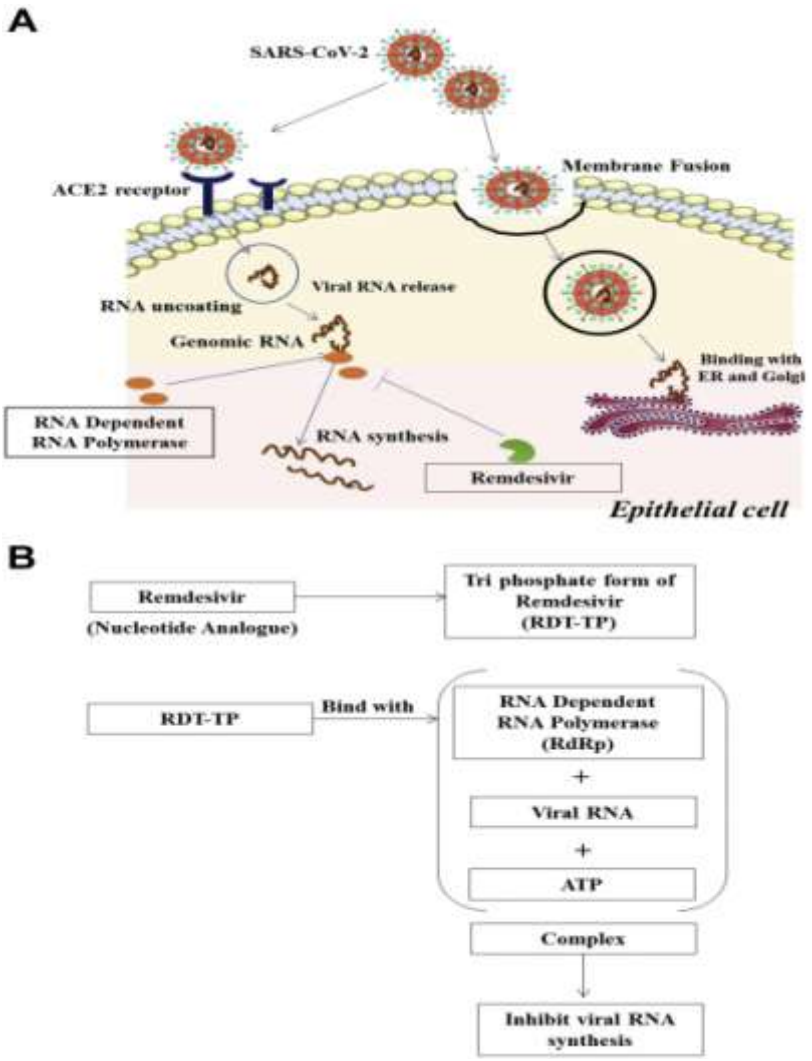

a) Thematic diagram shows the SARS-CoV-2 viral entry and its RNA synthesis which can be block by Remdisivir.(32)

b) Detail molecular mechanism of Remdisivir to inhibit the synthesis of viral RNA.(32)

c) MODE OF ACTION:

a) Remdesivir is a broad-spectrum antiviral agent that has previously demonstrated antiviral activity against filoviruses (Ebola viruses, Marburg virus), coronaviruses (SARS-CoV, MERS-Co-V, SARS-CoV-2), paramyxoviruses (parainfluenza type III virus, Nipah virus, Hendra virus, measles, and mumps virus), and Pnemoviridae.

b) Remdesivir enters cells before being cleaved to its monophosphate form through the action of either carboxylesterase 1 or cathepsin A; it is subsequently phosphorylated by undescribed kinases to yield its active triphosphate form remdesivirtriphosphate.

CHEMISTRY AND PHARMACOLOGY :

d) Remdesivir (formerly GS-5734) is a phosphoramidate pro-drug of a 1′-cyano-substituted nucleoside analogue (GS-441524). It inhibits viral replication by competing with endogenous nucleotides for incorporation into replicating viral RNA via RNA dependent RNA polymerase (rdrp). .(34)

e) The rdrp non-structural protein (nsp12) is highly conserved across coronaviruses making it an attractive target for broad-spectrum antiviral drugs. Once inside cells, remdesivir undergoes rapid metabolic conversion by intracellular kinases to its active nucleoside triphosphate metabolite (GS-443902). In general, the rate-limiting step for activation of

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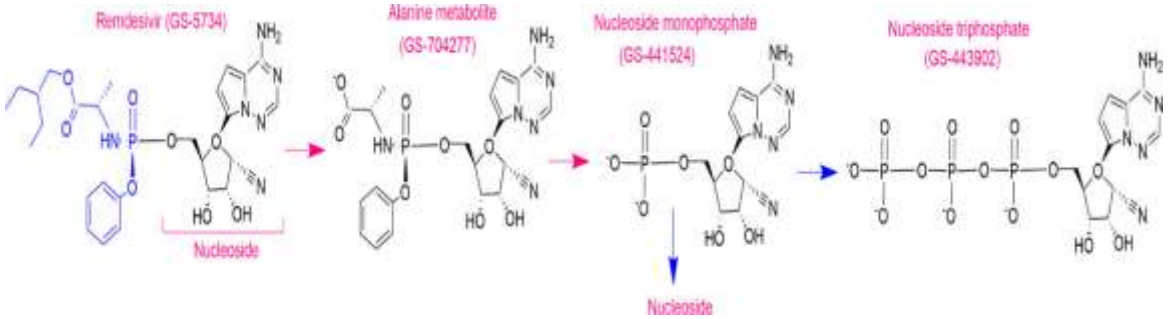
nucleoside analogues is the generation of the nucleoside monophosphate.(34)

f) Nucleoside phosphoramidates, like remdesivir (and GS-441524), are bioisosteres of monophosphates and are thereby able to bypass this rate-limiting step.(34)

Nucleoside phosphoramidates, however, must be administered as pro-drugs to mask the charged phosphonate group and allow faster cell entry. In the case of remdesivir, the negative charge is masked by the 2-ethylbutyl and L-alanine groups, which are rapidly removed by intracellular esterases. In addition, the 1′-CN group on remdesivir and its metabolites confers high selectivity for rdrpcompared to human polymerases.



PHARMACOKINETICS :

g) As described in the chemistry and pharmacology section, remdesivir is a pro-drug; concentrations decline rapidly after IV administration (plasma half-life, T½ ~1 hr), followed by the sequential appearance of the intermediate alanine metabolite GS-704277 and the nucleoside monophosphate metabolite GS-441524 (plasma T½ 24.5 hrs) . Inside cells, GS-441524 is rapidly converted to the pharmacologically active triphosphate analogue, GS-443902, which has a prolonged intracellular T ½ (peripheral blood mononuclear cell, PBMC T½ ~ 40 hrs). Both remdesivir and GS-441524 exhibit linear PK following single doses between 3 mg and 225 mg and no remdesivir accumulation was observed following once daily dosing for up to 5 days. By contrast, GS-441524 reaches steady state around day 4 and accumulates by ~2-fold after multiple once daily dosing.(35)

h) The remdesivir dosing regimen being evaluated in clinical trials (200 mg IV on day 1, then 100 mg IV on days 2 through 5 or 10) was substantiated by in vitro data and bridging the PK with the rhesus monkey experience to human.(36) (37)

summarizes pertinent PK parameters of remdesivir and metabolite GS-441524, which were derived from single- and multiple-dose studies in healthy human adult volunteers.(38)As shown, remdesivirC_{max} values are many fold above concentrations required in vitro to inhibit SARS-cov-2 replication by 50% and 90% (EC_{50} 0.137–0.77 μmol/L, EC_{90} 1.76 μmol/L, see microbiology section).(38)(39)

MEDICAL USES :

In the European Union, remdesivir is indicatedfor the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged twelve years and older with body weight at least 40 kilograms (88 lb)) with pneumonia requiring supplemental oxygen and for adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.(40)(19)

In the United States, remdesivir is indicated for use in adults and adolescents (aged twelve years and older with body weight at least 40 kilograms (88 lb)) for the treatment of COVID-19 requiring hospitalization.(41) In January 2022, the FDA expanded the indication for remdesivir to include its use in non-hospitalized adults and adolescents with positive results of direct SARS-cov-2 viral testing, and who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.(42)(43) In April 2022, the approval was expanded to include children 28 days of age and older weighing at least 3 kilograms (6.6 lb) with positive results of direct SARS-cov-2 viral testing.(44) In November 2020, the FDA issued an emergency use authorization (EUA) for the combination of baricitinib with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized

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people two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).(45) In Australia, it is approved for those aged four weeks of age and older with a body weight at least 3 kilograms (6.6 lb) with pneumonia requiring supplemental oxygen or those aged four weeks of age and older with body weight at least 40 kilograms (88 lb) who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

SIDE EFFECT :

The most common adverse effects in people treated with remdesivir were respiratory failure and blood biomarkers of organ impairment, including low albumin, low potassium, low count of red blood cells, low count of thrombocytes, and elevated bilirubin (jaundice). Other reported adverse effects include gastrointestinal distress, elevated transaminase levels in the blood (liver enzymes), infusion site reactions, and electrocardiogram abnormalities.(36)Remdesivir may cause infusion-related reactions, including low blood pressure, nausea, vomiting, sweating or shivering.

Other possible side effects of remdesivir include:

Infusion-related reactions. Infusion-related reactions have been seen during a remdesivir infusion or around the time remdesivir was given.(47) Signs and symptoms of infusion-related reactions may include: low blood pressure, nausea, vomiting, sweating, and shivering(47)

Increases in levels of liver enzymes, seen in abnormal liver blood tests.(47)Increases in levels of liver enzymes have been seen in people who have received remdesivir, which may be a sign of inflammation or damage to cells in the liver

II. CONCLUSION :

At this time there are no therapies that have been scientifically proven to improve mortality in COVID-19. Current management is largely focused on supportive care and prevention of complications.(48)(49)Efficacious and safe antiviral agents are therefore urgently needed to relieve the burden on health-care systems. As detailed in this review, remdesivir is a nucleoside analogue pro-drug with unique structural features that allow high concentrations of the active triphosphate metabolite to be delivered intracellularly.(34) It evades proofreading to successfully inhibit viral RNA synthesis and has demonstrated potent antiviral activity against β-coronaviruses, including SARS-cov-2 both in vitro and in animal models. (36)(50)(29)(51)(52) These data, coupled with early safety data from clinical experience in Ebola virus infection,(53) provide strong rationale for prioritizing testing of remdesivir in COVID-19 clinical trials. The unpredictable nature of a pandemic however poses many challenges to researchers attempting to conduct clinical trials.(54)As of April 30, 2020, more than 2000 patients with COVID-19 have received remdesivir through compassionate use or expandedaccess programs.(55)It is impossible to know if these patients benefited or were harmed but we do know these programs do little toadvance science. When patient enrollment in clinical trials is not available, many clinicians face intense pressure to offer unproven therapies based on compelling pre-clinical data. Efforts must focus on ensuring the necessary infrastructure is in place to expand patient access to pragmatic clinical trials and make it simple for clinicians to enroll them. This could obviate the need for compassionate use programs.

Although the first randomized controlled trial evaluating remdesivir for COVID-19 was conducted a multiple sites in the initial outbreak epicenter, it failed to meet its target sample size due to slow enrollment after the surge in cases diminished and produced inconclusive results. It did however provide data on the use of remdesivir gathered in a rigorous manner. ACTT-1 represents a remarkable global effort with a total of 60 study sites in 10 countries enrolling more than 1000 patients over approximately 2 months.(56) Remdesivirtreatment resulted in an accelerated time to recovery by 4 days which represents meaningful progress for patients and healthcare systems. The stubbornly high mortality rates and apparent absence of benefit among the most critically ill patients however suggests the need for more effective and / or adjunctive therapies. With at least 6 remdesivir randomized-controlled trials currently underway worldwide with and without adjunctive immunomodulatory agents, there is reason to be optimistic that we will accumulate good data to more precisely define remdesivir's therapeutic niche in COVID-19.

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CONFLICT OF INTERST:
The authors whose names are listed immediately below certify that they have NO affiliations with or involvement inany organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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