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OPINION REVIEW

Rifampicin for COVID-19

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Abstract

Vaccinations for coronavirus disease-2019 (COVID-19) have begun more than a year before, yet without specific treatments available. Rifampicin, critically important for human medicine (World Health Organization's list of essential medicines), may prove pharmacologically effective for treatment and chemoprophylaxis of healthcare personnel and those at higher risk. It has been known since 1969 that rifampicin has a direct selective antiviral effect on viruses which have their own RNA polymerase (severe acute respiratory syndrome coronavirus 2), like the main mechanism of action of remdesivir. This involves inhibition of late viral protein synthesis, the virion assembly, and the viral polymerase itself. This antiviral effect is dependent on the administration route, with local application resulting in higher drug concentrations at the site of viral replication. This would suggest also trying lung administration of rifampicin by nebulization to increase the drug's concentration at infection sites while minimizing systemic side effects. Recent *in silico* studies with a computer-aided approach, found rifampicin among the most promising existing drugs that could be repurposed for the treatment of COVID-19.

Key Words: COVID-19; SARS-CoV-2; Rifampicin; Antiviral activity; RNA polymerase

Core Tip: Rifampicin may prove pharmacologically effective, supplying a possible and cost-effective solution to the global battle against severe acute respiratory syndrome coronavirus 2, not only for treatment but also for chemoprophylaxis of those at higher risk. It is also possible to administer rifampicin by nebulization. The publications describing the *in vitro* mechanisms and providing proof of clinical efficacy of rifampicin against RNA viruses with their own RNA polymerase have emerged since 1969-1971. Recent *in silico* studies using a computer-aided approach, found rifampicin among the most promising existing drugs that can be repurposed for the treatment of coronavirus disease-2019.

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INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic presents a puzzling challenge without specific treatment yet[1], and while vaccinations have been initiated more than a year before[2], there is still a long way to go before herd immunity can be achieved, even in the developed countries[3]. In the critically ill patients, plasma transfusions from recovered patients have been tried[4] and specific severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) memory T cells could also treat moderate/severe cases of COVID-19[5]. When and with which pharmacological cocktail to intervene is under rigorous investigation worldwide[6]. Chemoprophylaxis of exposed healthcare personnel[7], along with those at higher risk for severe illness, is also equally exigent, at least until sizable worldwide immunization will be achieved[8]. And even if vaccination campaigns do make progress in the Western world, this process may take much longer in the developing countries. Even then, the possible emergence of SARS-CoV-2 new mutated strains could substantially impact the protection of currently available vaccines or the physical immunity acquired from previous illness from the previous SARS-CoV-2 variants[9] (https://theconversation.com/the-lambda-variant-is-it-more-infectious-and-can-it-escape-vaccines-a-virologist-explains-164156).

Rifampicin, discovered in 1965, was marketed in Italy in 1968, and approved in the United States in 1971. It is on the World Health Organization's (WHO) list of essential medicines, classified by the WHO as critically important for human medicine. Made by the soil bacterium *Amycolatopsis rifamycinica*, rifampicin is widely available as a generic medication with an extremely low cost compared to any other modern antiviral medication. It belongs to the *Rifamycins*, characterized as antiviral drugs which inhibit transformation of cells by viruses[10]. While in the fourth wave of this pandemic, without specific medications available yet, along with the ongoing computational analysis of potential drugs[11], it becomes clearer that - at least for now and beyond active immunization - we still need to rely on one hand on the enhancement of our immune system and on the other hand on the known anti-inflammatory and immunomodulatory effects of some antibacterials and the emerging antiviral effects of old but precious drugs, such as rifampicin. For the first task, which is to strengthen our immunity, adding zinc sulphate increased patients' discharges, decreasing the need for ventilation, intensive care unit admissions, and mortality[12]. Increased intracellular zinc concentrations seem to inhibit RNA-dependent polymerases, helping to support robust immune responses and modulating immune cell activity. For that task, researchers have tried high doses of vitamin C[13]. And last but not least, proper supplementation[14,15] or even adjunctive therapy with vitamin-D[16], to capitalize on its extra-skeletal immunomodulatory properties, may also prove valuable, playing a crucial role in enhancing and coordinating the immune system's response to SARS-CoV-2 infection[17,18]. For that purpose, personalized immunotherapy approaches with agents/monoclonal antibodies that block receptors for interleukin-1/6 have been initiated, aiming to control the macrophage activation syndrome which has been suggested as a major mechanism of lung impairment in COVID-19[19]. Monoclonal antibodies have shown promising results, with prompt administration though being a key issue to exert their benefit[20]. Bamlanivimab, a neutralizing monoclonal antibody against SARS-CoV-2, reduced the incidence of COVID-19[21].

Herein, we discuss the possibility of repurposing rifampicin for COVID-19, and we call for immediate coordinated - international if possible - collaboration[22] in *in vitro* studies, open-label pilot trials, and definitive phase 3 clinical trials.

ANTIVIRAL PROPERTIES OF RIFAMPICIN: MECHANISMS AND FACTS

Careful analysis of the COVID-19 clinical characteristics and computed tomography scans indicates that the pulmonary nontuberculous mycobacterial disease, in which azithromycin and rifampicin are among

first line treatment options, seems to share a striking analogy with SARS-CoV-2 pneumonia[23]. Going back to 1969, a conventional antibacterial of proved pharmacological acceptability in man, rifampicin (or rifampin: https://www.accessdata.fda.gov/drugsatfda_docs/Label/2018/050420s077,050627s020Lbl.pdf), was found to have a direct antiviral effect in some mammalian viruses as poxviruses including the causative agent of smallpox and mainly on viruses which have their own RNA polymerase[24], which is the case for SARS-CoV-2 and the main mechanism of action of remdesivir. Initially developed against Ebola, remdesivir raised hope, as it incorporates into nascent viral RNA chains and results in premature termination of viral replication. Remdesivir showed higher recovery and hospital discharge rates, but no significant reduction in mean time to clinical improvement or mortality[25].

Regarding large DNA viruses, the antiviral activity of rifampicin arises from its binding to the F-ring, highly conserved across mammalian poxviruses, which cannot mutate in response to rifampicin inhibition and thus provide a potential base for the development of broad-spectrum inhibitors against infectious poxviruses species in animals and humans[26]. However, the efficacy of rifampicin against viruses with their own RNA polymerase shares the same mechanism with its antibacterial activity against microbial RNA polymerases. The inhibitory mechanism of rifampicin on the RNA polymerases is a simple steric block of transcription elongation due to its ability to bind tightly to non-conserved parts of the structure, disrupting a critical RNA polymerase function[27]. The rifampicin molecule is a condensation product of 3-formyl rifamycin SV and 1-amino 4-methyl piperazine with the antiviral activity existing in the rifamycin part of the molecule. Its antiviral effect is reversible as removal of the drug late in the virus cycle leads to a mature and infectious virus even within 1 h. This would mean that careful monitoring of rifampicin levels may assure effectiveness. The selective antiviral effect of rifampicin involves inhibition of late viral protein synthesis[28], virion assembly[29], and the viral polymerase itself[30].

Table 1 summarizes the studies on the possible antiviral properties of rifampicin against SARS-CoV-2 presenting their main findings.

ADMINISTRATION ROUTE AND POTENTIALS

Studies in volunteers have also shown a dependence of rifampicin's antiviral effect on administration route, with local application resulting in higher concentrations of the drug at the site of viral replication [31]. This would suggest trying lung administration of rifampicin by nebulization[32], increasing the drug's concentration at infection sites while minimizing systemic side effects. This approach, using aerosolized rifampicin-loaded polymeric microspheres, reduced most measures of tuberculosis infection in experimental animals[33]. However, since the major cell entry receptor for SARS-CoV-2 is the metallocarboxyl peptidase angiotensin receptor 2[34], whose expression is very low in the lung, the approach of lung administration may not exhibit the expected systemic antiviral effects of rifampicin and requires further investigation.

An effective intracellular concentration of rifampicin without serious toxicity seems possible and probable, given its pharmacokinetic profile, suitable also for chemoprophylaxis (https://pubchem.ncbi.nlm.nih.gov/compound/Rifampicin#section=Drug-Classes). Current studies have evaluated intravenous rifampicin 20 mg/kg for 2 wk followed by high dose oral formulation (35 mg/kg for 6-8 wk) for improved survival from adult tuberculous meningitis[35]. Data concerning intracellular rifampicin concentrations to exhibit effective antiviral activity against influenza virus A[36], African swine fever virus[37], and cytomegalovirus[38] have been already available.

IN SILICO STUDIES INDICATE POSSIBLE EFFECTIVENESS OF RIFAMPICIN

The above finding may have just been verified by a recent *in silico* study using a computer-aided drug designing approach: Rifampicin was the most promising existing drug that could be repurposed for the treatment of COVID-19[39]. Moreover, using a comprehensive drug repurposing and molecular docking approach, prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 revealed that rifabutin could be an effective drug for COVID-19, having the lowest binding energy compared to the positive control remdesivir[40]. Rifabutin, however, belongs to the rifamycins (rifampicin, rifapentine, and rifabutin), but with rifampicin being the most used[41]. *In silico* virtual screening within the United States Food and Drug Administration (FDA)-approved drugs targeting the RNA-dependent RNA polymerase, which is the critical enzyme for coronavirus replication, also placed rifampicin among the five most potent potential anti-SARS-CoV-2 therapeutics[42]. Virtual screening of FDA-approved drugs targeting not only the main protease of SARS-CoV-2 but also TNF-α, IL-6, and IL-1β, which are the key molecules involved in the 'cytokine storm' occurring in COVID-19, indicated rifampicin as one of the most promising drugs for the treatment of COVID-19, together with letermovir [43]. These were systematic docking studies, further confirmed by molecular dynamics simulations and molecular calculations; however, such studies are prone to the high probability of artifacts needing experimental verification.

Table 1 Studies on the possible antiviral properties of rifampicin against severe acute respiratory syndrome coronavirus 2

Ref.	Year	Findings
Becker[10]	1976	Rifampicin belongs to the *rifamycins*, characterized as antiviral drugs which inhibit transformation of cells by viruses
[24]	1969	Rifampicin has a direct antiviral effect in mammalian viruses as poxviruses including the causative agent of smallpox and on viruses which have their own RNA polymerase
Campbell *et al*[27]	2001	The inhibition mechanism of rifampicin to the RNA polymerases is a simple steric block of transcription elongation due to its ability to bind tightly to non-conserved parts of the structure, disrupting a critical RNA polymerase function
Ben-Ishai *et al*[28], Moss *et al*[29], McAuslan *et al*[30]	1969	Rifampicin inhibits the late viral protein synthesis, the virion assembly, and the viral polymerase itself
Moshkowitz *et al*[31]	1971	Rifampicin's antiviral effect is dependent on the administration route, with local application resulting in higher concentrations at the site of viral replication
Tewes *et al*[32]	2008	Administration of rifampicin by nebulization is possible using aerosolized rifampicin-loaded polymeric microspheres
And *et al*[36]	1980	Intracellular rifampicin concentrations exhibit effective antiviral activity against: Influenza virus A, African swine fever virus and cytomegalovirus
Dardiri *et al*[37]	1971	
Halsted *et al*[38]	1972	

The SARS-CoV-2 RNA-dependent RNA polymerase (nsp12) catalyzes the replication of RNA from RNA templates. Changes in the virus life cycle are exhibited by the fixation of specific ligands in the active site of this crucial enzyme. A recent study found the highly conserved nsp12 motifs (A-G), and discovered the interactions with rifabutin and rifampicin, among other ligands. Both of them interacted with at least two nsp12 motifs, indicating that they could be both used as inhibitors of SARS-CoV-2 nsp12 protein[44]. Another *in silico* docking approach also found that rifampicin has good binding affinity with the COVID-19 protease[45], proposing its use as therapeutic treatment as well as prophylaxis.

Of course, all the above findings require further validation by *in vitro* studies and clinical trials. Table 2 summarizes the *in silico* studies indicating effectiveness of rifampicin against SARS-CoV-2.

DRUG MONITORING AND INTERACTIONS

Experience from coadministration of antitubercular use of rifampicin with antiretroviral therapy may, however, be complicated by drug-to-drug interactions concerning drug metabolism and transport[46], which warrants caution in clinical trials designed to test the efficacy of rifampicin against SARS-CoV-2 in case of co-administration with other drugs that are also metabolized in the liver. A plan is needed to treat COVID-19 in the special group of patients with advanced liver disease[47], as rifampicin is an agonist of the nuclear pregnane nuclear receptor that regulates CYP3A4[48,49], a part of cytochrome P450 enzymes that metabolizes 60% of prescribed drugs. Thus, rifampicin can cause serious drug-to-drug interactions in combination with other medications for COVID-19 treatment. Also, it should be noted that concerning rifampicin, therapeutic drug monitoring is needed when extracorporeal membrane oxygenation is to be used as a life-saving system for critically ill patients with cardiac and/or respiratory failure[50]. The co-administration of plant-derived compounds such as gallic acid and tannic acid, which are effective potentiators resulting in a 4-fold increase in the potency of rifampicin, warrants further study[51]. A known infrequent occurrence, with few cases reported in the literature, of rifampicin-induced pneumonitis mimicking acute respiratory distress syndrome and requiring SARS-CoV-2 testing[52], merits caution. Because of an uncommon immuno-allergic reaction, following intermittent rifampin administration, with disseminated intravascular coagulation including fever, hypotension, abdominal pain, and vomiting within hours of ingestion[53], awareness is warranted for COVID-19 patients suffering from the life-threatening cytokine storm syndrome[54]. Hence, even in the latter case, as in an allergic reaction to rifampicin, apart from targeted anti-cytokine therapy[55], broadly immunosuppressive glucocorticoids would be of value.

SAFETY AND ADVANTAGES OF RIFAMPICIN

Rifampicin is not the only antibiotic that could be repurposed for COVID-19. Quinupristin, for example, is an antibiotic in clinical use for two decades now with minor side effects and has also proven *in silico*

Table 2 *In silico* studies indicating rifampicin's possible effectiveness against coronavirus disease-2019

Ref.	Year	Findings
Mishra *et al*[39]	2020	Using a computer-aided drug designing approach, rifampicin was the most promising existing drug that could be repurposed for the treatment of COVID-19
Parvez *et al*[40]	2020	Using a comprehensive drug repurposing and molecular docking approach, prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 revealed that rifabutin could be an effective drug for COVID-19, having the lowest binding energy compared to the positive control remdesivir
Forrest *et al*[41]	2010	Rifabutin belongs to the rifamycins (rifampicin, rifapentine and rifabutin); rifampicin is the most used
Pokhrel *et al*[42]	2020	In silico virtual screen within the United States Food and Drug Administration-approved drugs targeting the RNA-dependent RNA polymerase, which is the critical enzyme for coronavirus replication, placed rifampicin among the five most potent potential anti-SARS-CoV-2 therapeutics
Pathak *et al*[43]	2021	A similar approach, by targeting the main protease of SARS-CoV-2 but also TNF-α, IL-6, IL-1β, revealed rifampicin as one of the most promising drugs
Elkarhat *et al*[44]	2020	The SARS-CoV-2 RNA dependent RNA polymerase (nsp12) catalyzes the replication of RNA from RNA templates. Changes in the virus life cycle are exhibited by the fixation of specific ligands in the active site of this crucial enzyme. A recent study found the highly conserved nsp12 motifs, and discovered the interactions with rifabutin and rifampicin, concluding that both could function as inhibitors of the SARS-CoV-2 nsp12 protein
Soni *et al* [45]	2020	An *in silico* docking approach also found that rifampicin has good binding affinity with the COVID-19 protease, proposing its use as therapeutic treatment as well as prophylaxis

COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

potentially effective against SARS-CoV-2[42]. However, the knowledge and clinical experience as well as the safety profile of rifampicin even in neonates, infants[56], and pregnant woman[57] make a compelling case where alternative therapeutic options are limited. Last, but not least in this instance, the particularly low cost and the potential for worldwide availability of rifampicin as a generic medication may prove a worthy solution, for early intervention protocols against SARS-CoV-2.

RIFAMPICIN IN COVID-19 IN CLINICAL PRACTICE

A recent case report described the favorable outcome under treatment with chloroquine and rifampin of an unusual association of COVID-19, pulmonary tuberculosis, and human immunodeficiency virus infection[58], attributed either to rifampicin inhibiting the formation of mRNA of SARS-CoV-2 and/or the possible synergistic effect of chloroquine and rifampin, despite that anti-tubercular drugs such as rifampicin are powerful enzyme inducers that can reduce the effectiveness of chloroquine. Up to now, there are no clinical studies available on the treatment of COVID-19 patients with rifampicin. Anecdotally, experienced pediatricians have also successfully treated neonates and infants[59] found positive for SARS-CoV-2 with rifampicin, clearly aiming for their protection with their parents suffering overt COVID-19 with an eventful clinical course.

CONCLUSION

Timely administration, though, is important for all current regimens on trial: It must not be too late when treatment starts. Specifically, rifampicin interferes with the viral replication, and thus, early administration after diagnosis of COVID-19 could make a significant difference to its presumed effectiveness against SARS-CoV-2 infection. Similarly, for rifampicin's use for postexposure prophylaxis to people exposed to index cases of invasive meningococcal infection, pre-exposure together with post-exposure prophylaxis could also be a potential strategy, at least for unvaccinated people[60]. The WHO proposed a similar approach for people at elevated risk for infection, before or after exposure, during the influenza pandemic.

Call for studies

Facing this unprecedented global emergency and given the experience, safety, and knowledge behind rifampicin, we call for international collaboration proposing *in vitro* studies, open-label pilot trials, and definite phase 3 clinical trials for testing treatment and chemoprophylaxis efficacy of rifampicin against COVID-19. With all the above compelling evidence, rifampicin merits evaluation against COVID-19.

FOOTNOTES

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