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Review Article

PROPOSAL TREATMENT PROTOCOL OF SARS-COV-2 (COVID19) USING CHLOROQUINE, AN ANTIPROTEASE, ATP INHIBITOR WITH ANTIBIOTIC DRUG

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ABSTRACT

Because of this contemporary pandemic of Coronavirus-19 and several essays to cure or prevent this illness by chemical products or body self-immunity. Several drugs and medications were described to halt or decrease the impact of this Virus, this review is a study on the best protocols to helps health community. No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2. Viruses are not affected with antibiotics but they help to prevent an opportunist microorganism like bacteria and protozoa. Other antiviral drugs are not efficacy against this virus because of the way and the resistance in fresh air. The best-known medication is Chloroquine/Hydroxychloroquine which is an antimalarial or anti plasmodium drug used to control the intracellular charge of the protozoan *Plasmodium sp.* Another protocol proposed here is, the using of an antiviral drug using generally proteases inhibitor as Lopinavir/Ritonavir or Darunavir with Remdesivir that increase the charge of any other antiviral drug by the inhibition of the Cytochrome P450 enzymes. A good antibiotic to prevent the accompanied illnesses by other microorganisms is also suitable (Rifabutin).

KEY WORDS: Chloroquine; Remdesivir**;** Lopinavir; Ritonavir; Darunavir/Cobicistat ; CytP450; antibiotics (Rifabutin), SARS-CoV-2; Coronavirus; COVID-19; Prezcobix.

INTRODUCTION

Coronaviruses are a group of viruses that cause diseases in mammals and birds. In humans, coronaviruses cause respiratory tract infections that can be mild, such as some cases of the common cold (among other possible causes, predominantly rhinoviruses), and others that can be lethal, such as SARS, MERS, and COVID-19. Coronaviruses constitute the subfamily *Orthocoronavirinae*, in the family *Coronaviridae*, order *Nidovirales*, and realm *Riboviria* (ICTV, 2020). They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry. The genome size of coronaviruses ranges from approximately 27 to 34 kilobases, the largest among known RNA viruses (Sexton et al., 2016). The name *coronavirus* is derived from the Latin *corona*, meaning "crown" or "halo", which refers to the characteristic appearance reminiscent of a crown or a solar corona around the virions (virus particles) when viewed under two-dimensional transmission electron microscopy, due to the surface being covered in club-shaped protein spikes (fig. 1)

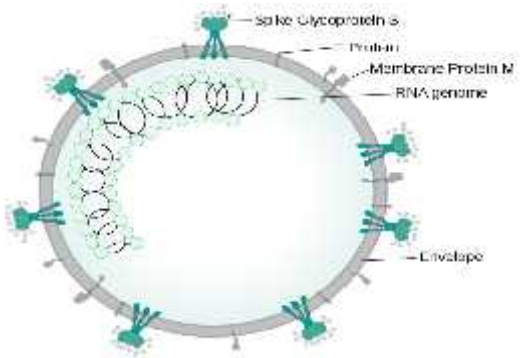


Figure 1. Illustration of Corona Virus (Wikipedia/coronavirus).

Seven strains of human coronaviruses are known, of which four produce the generally mild symptoms of the common cold (OC43 (HCoV-OC43); HKU1; NL63 (HCoV-NL63); 229E (HCoV-229E)). and three with symptoms that are potentially severe: (MERS-CoV; SARS-CoV; SARS-CoV-2), (Corman et al., 2018; WHO, 2020).

There have been 2 self-limiting SARS outbreaks, which resulted in a highly contagious and potentially life-threatening form of pneumonia. Both happened between 2002 and 2004. Since 2004, there have not been any known cases of SARS reported anywhere in the world. The World Health Organization (WHO) continues to monitor countries throughout the world for any unusual disease activity. If there was another SARS outbreak, it should be possible to limit the spread of infection (WHO, 2020). Began in December 2019 in china (Wuhan), a new pandemic virus was spread and caused an international outbreaking respiratory system illness named COVID-19 with ranged symptoms from simple to severe progressive pneumonia, many organs failure and finally the death (Huang et al., 2020; Chen et al., 2020). The ongoing Covid-19 pandemic highlights the critical need for rapid development of vaccines and antiviral treatments to reduce the number of hospitalizations and deaths caused by this dangerous new coronavirus, SARS-CoV-2. The biopharmaceutical industry has quickly responded and at least 80 candidates are already in development. With good luck, we will eventually have some of the tools we need to fight this new global threat (NHS, 2019). Many tests and experiments were carried out from many scientists to reduce the symptoms of this virus, from anti-HIV drugs (Bin Cao et al., 2020) to antimalarial drugs based on the study of (Vincent et al., 2005).

Possible protocols

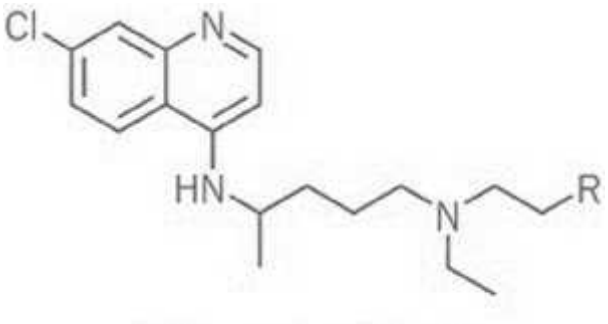
To treat or halt the virus multiplication or cellular infections it must focused on some targets involved in the virus contamination cycle:

1. Vaccine or antibody to one of virus constitutions (S, E, M or N).
2. virus/receptor fusion inhibitors.
3. Receptors blockage.
4. Protease inhibitors blocking polyprotein processing
5. Assembly of polymerase complex inhibition.
6. Transcription/replication
7. Budding
8. Exocytosis
9. New viruses

The best targets are in the receptor's blockage or Protease inhibitors, the vaccine must focused on the virus constituents.

CHLOROQUINE

An antimalarial medication used for many years to control plasmodium spread by the blockage of hemozoin (Hz) from the heme released by the digestion of hemoglobin (Hb). The free heme then lyses membranes and leads to parasite death. **Chloroquine** resistance is due to a decreased accumulation of **chloroquine** in the food vacuole (Foley and Tilley, 1998). The exact contributions of these three postulated mechanisms is not clear, but it is generally accepted that chloroquine exerts it toxic effect by interfering with the conversion of free heme to hemozoin. Large quantities of heme are released as a result of hemoglobin digestion in the food vacuole. The free heme can lyse membranes, lead to the generation of reactive oxygen intermediates, and inhibit many other processes and thus is quite toxic. Heme is detoxified in the food vacuole via a biocrystallization process in which the heme is sequestered into large insoluble crystals called hemozoin or the malarial pigment. The exact mechanism by which chloroquine inhibits hemozoin formation is not known, but chloroquine can bind heme and this binding may prevent the heme from being incorporated into the hemozin crystal. Parasite killing is therefore a result of the accumulation of metabolic wastes (heme) associated with the digestion of hemoglobin.



Chloroquine, R = H
Hydroxychloroquine, R = OH

Figure 2. structure of chloroquine (Cross, 2020)

Other quinoline containing anti-malarials, such as mefloquine and quinine, also appear to affect the food vacuole. However, it is not clear whether these drugs bind heme or affect the formation of hemozoin. Furthermore, these drugs are weaker bases than choroquine and may not exhibit the same degree of ion trapping within the food vacuole.

The food vacuole provides many potential drug targets. In addition to the inhibition of hemozoin formation discussed above, specific inhibitors of the proteases involved in hemoglobin digestion are also being investigated as potential antimalarials. [See more detailed discussion of food vacuole proteases.] The specialized functions of hemoglobin digestion and hemozoin formation are unique to the parasite and not found within the host. Furthermore, both functions--generation of amino acids from hemoglobin and detoxification of heme--are very important for the parasite (Fig. 3).

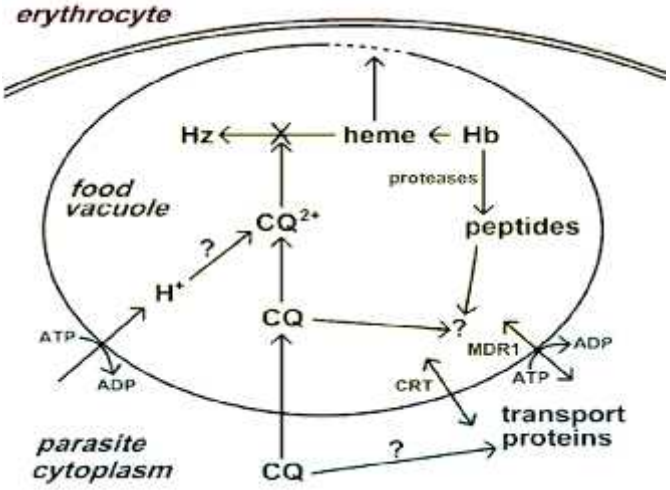


Figure 3. Chloroquine mechanism of action (Foley and Tilley, 1998).

Another chloroquine mechanism of action was described in the work of O'Brien et al., (1966), the synthetic antimalarial chloroquine forms the complexes with DNA and interact with the double helix by ionic attraction which conducted to the stabilization of the DNA, and the inhibition of the nucleic acid. Other findings were shown that chloroquine inhibits the DNA and RNA polymerase reaction.

Chloroquine inhibits DNA/RNA polymerase
Chloroquine stabilize DNA helix (inhibits replication

The causative agent of severe acute respiratory syndrome (SARS) has been identified as a novel coronavirus, SARS-CoV. The main proteinase of SARS-CoV, $3CL^{pro}$, is an attractive target for therapeutics against SARS owing to its fundamental role in viral replication. We sought to identify novel inhibitors of $3CL^{pro}$ to advance the development of appropriate therapies in the treatment of SARS. $3CL^{pro}$ was cloned, expressed, and purified from the Tor2 isolate. A quenched fluorescence resonance energy transfer assay was

developed for $3CL^{pro}$ to screen the proteinase against 50,000 drug-like small molecules on a fully automated system. The primary screen identified 572 hits; through a series of virtual and experimental filters, this number was reduced to five novel small molecules that show potent inhibitory activity (*IC50* = 0.5–7 µM) toward SARS-CoV $3CL^{pro}$ (Blanchard et al., 2004). We will tray to find the best antiprotease for COVID-19.

LOPINAVIR/RITONAVIR

The second medication is the anti-HIV drugs, Lopinavir/ritonavir which inhibits the HIV protease enzyme by forming an inhibitor-enzyme complex thereby preventing cleavage of the gag-pol polyproteins. Immature, non- infectious viral particles are subsequently produced. Lopinavir is 98- 99% protein bound to alpha-1-acid glycoprotein and albumin. Lopinavir undergoes rapid first-pass metabolism in the liver by CYP3A4 and CYP3A5. Ritonavir inhibits the CYP3A4 isoenzyme in the human liver microsomes and results in increased concentrations of lopinavir when the two drugs are coadministered (Kumar et al., 1999). Lopinavir/ritonavir is primarily eliminated by the fecal route with urinary excretion accounting for <2% of the eliminated drug (Kumar et al., 2004).

Lopinavir inhibits another sites of virus Protease

DARUNAVIR/COBICISTAT

This is an antiretroviral drug destined to inhibit the HIV protease, it is generally recommended for use with other antiretrovirals. It is often used with low doses of ritonavir or cobicistat to increase darunavir levels. It may be used for prevention after a needlestick injury or other potential exposure. It is taken by mouth once to twice a day (ASHSP, 2016).

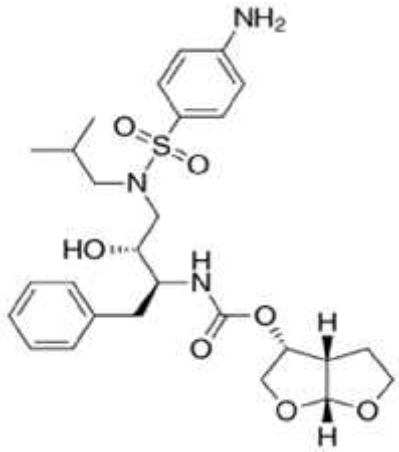


Figure 4. structure of antiretroviral Darunavir (ASHSP, 2016).

Darunavir affects the protease

The question is: is the HIV protease inhibitors take effects on SARS protease?

Many trials are ongoing on this way and the results are contradictory from researcher to other even for the same substance so we go toward other antiviral substance **REMDESIVIR.**

Remdesivir

Is a nucleotide analog inhibitor of RNA-dependent RNA polymerases, it blocks RNA replication by its incorporation and the modification of 3D structure, that be strange to the RNA polymerase and it can not add more subunits (Gordon et al., 2020). Remdesivir is an analog of nucleotide inhibitor of RNA-dependent RNA polymerase (RdRp), Remdesivir-TP competes with its natural counterpart ATP. This suggests that it is more efficiently incorporated than ATP and two other nucleotide analogues. Once incorporated at position i, the inhibitor caused RNA synthesis arrest at position i+3. Hence, the likely mechanism of action is delayed RNA chain termination. The additional three nucleotides may protect the inhibitor from excision by the viral 3'–5' exonuclease activity. Together, these results help to explain the high potency of Remdesivir against RNA viruses in cell-based assays (Gordon et al., 2020).

It is a promoted medication started to evaluated from February 25th, 2020 on patients suffered from SARS-CoV-2.

The accompanied or opportunist illnesses are the most causes of mortality because of the surcharge on immunity system, these are struggled by the antibiotics but the most of them are antiretroviral drugs inhibitors.

Remdesivir affects the energetic and the RNA replication

Rifabutin

Rifabutin is an antibiotic used to treat tuberculosis and prevent and treat Mycobacterium avium complex. It is typically only used in those who cannot tolerate rifampin such as people with HIV/AIDS on antiretrovirals. For active tuberculosis it is used with other antimycobacterial medications. In spite of its side-effects including Nausea, Rash, Headache, low blood neutrophil levels, muscle pains and uveitis (ASHSP, 2016). The most character is the blocking of RNA production in the bacteria (Rockwood et al., 2019).

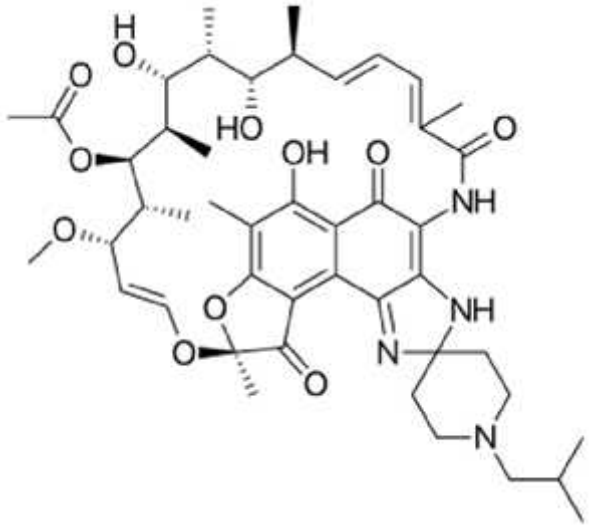


Figure 5. Structure of Rifabutin (Rockwood et al., 2019)

Rifabutin is focused in this review as the best accompanied drug to the proposed COVID-19 treatment

Rifabutin blocks RNA and inhibits opportunist illnesses without affecting ARV drugs

Conclusion

There are no specific therapeutics approved by the Food and Drug Administration (FDA) to treat people with COVID-19, the disease caused by the newly emergent SARS-CoV-2 virus (formerly known as 2019-nCoV). This study and review focused on the best protocol to treat the new SARS-CoV illness, by well illustrating the possible treatment targets (protease, RNA, ATP) and the best combination is:

An antiviral with anti RNA polymerase with protection by a favorable antibiotic with a studied dose from bibliographic data as follow:

Chloroquine: 500=(250x2) mg/day for 6 days. Per Os
Darunavir/Cobicistat (Prezcobix): 500/200mg. Per Os.
Remdesivir: 150mg/day I.V.
Rifabutin: 300 = (150x2) mg/day Per Os.

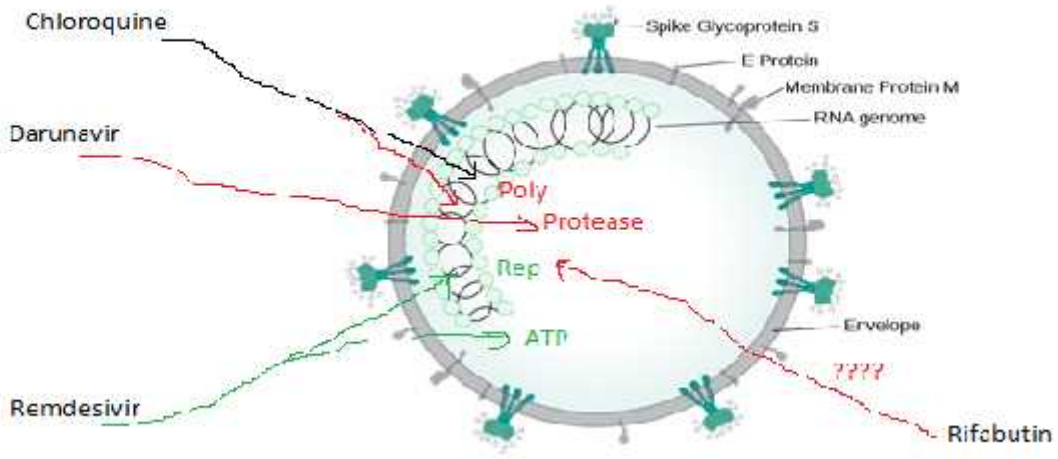


Figure 6. Proposed medication targets.

So, the treatment of SARS-CoV-2 consists of (morning and evening: chloroquine + Rifabutin) and Prezcobix and Remdesivir in the mid-day for 6 days.

Note that this study needs to be confirmed with clinical experiments from health services in hospitals.

Authors contribution statement

RR conceived and designed research, wrote the manuscript. All authors read and approved the manuscript.

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Compliance with ethical standards

This is a proposal/review works according to the universal standards.

Conflict of interest

There is no conflict of interest

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