Management of SARS-COV-2; The Missing Link?:
A Critical Pharmaco-Immuno-Logical Review

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Abstract

The pandemic of SARS-CoV-2 which started in Wuhan, China has now affected almost every corner of the world. The number of death tolls continues to rise and a large number of countries have been forced to do social distancing and lockdown. Lack of targeted therapy continues to be a problem Till date there have many treatment protocols followed on a trial and error basis. Many human trials on a definitive treatment of this virus is also taking place in different part of the world. SARS-CoV-2 has the ability to bind to human angiotensin-converting enzyme 2 receptors causing deleterious effects. The main aim of this review is to critically assess every pharmacological and its immunological effects in this SARS-CoV-2 pandemic.

Keywords: SARS-CoV-2; COVID-19; Pharmacological Management; Immunological Management

Introduction

The 2019 coronavirus disease outbreak (COVID-19) in Wuhan area, China, has rapidly evolved into a public health crisis and has spread exponentially to other parts of the world. The novel coronavirus is part of a single-stranded RNA virus family known as the Coronaviridae. This virus family is known to be zoonotic or transmitted from animals to humans [1].

The novel coronavirus closely resembles other beta-coronaviruses like SARS-CoV and MERS-CoV [2].

COVID-19 patients typically suffer from clinical signs of fever, dry cough and myalgia. Moreover, less obvious symptoms such as nausea, diarrhea, decreased sense of smell (hyposmia), and abnormal sensation of the taste (dysguesia) were also reported. Additionally, irregular chest X-rays and computed tomographic findings including ground-glass opacities are usually located in the chest. The incubation period of this virus is 3 - 7 days and as reported the virus remains in the body for 14 - 17 days [3].
With many ongoing research projects going on different parts of the world regarding a definitive treatment of the novel coronavirus (SARS-CoV-2), the aim of this review is to critically analyse various treatment experiments and modalities till date and thus find the missing link to the treatment of SARS-CoV-2 [4].

Recent trends of pharmacological management of SARS-CoV-2

Betadine gargles

Povidone-iodine PVP-I, also known as iodopovidone, is an antiseptic used before and after surgery for skin disinfection. It may be used both to disinfect the hands of healthcare providers and the skin of the person they are caring for. It can also be used against minor wounds. It may be applied to the skin as a liquid or a powder.

Povidone-iodine has been found to have the highest virucidal activity profile among several antiseptics such as CHG, benzalkonium chloride (BAC), BEC and alkyl-di-aminoethyl-glycine hydrochloride (AEG).

PVP-I gargle was found to inactivate a panel of viruses using a standardized in vitro approach that included herpes simplex virus, influenza, adenovirus, poliovirus coxsackie virus, mumps, rotavirus, rhinovirus, rubella, measles and human immunodeficiency virus. PVP-I products, which included gargle and throat spray, demonstrated rapid virucidal activity against both highly pathogenic (H5N1) and low pathogenic (H5N3, H7N7 and H9N2) avian influenza strains in a more recent study [5].

While, SARS-CoV-2 viruses are genetically related to SARS-CoV, the viral load in the oropharynx with SARS-CoV-2 infection is as high in asymptomatic patients as those with symptoms [6].

It is known that SARS-CoV-2 can bind receptors that are highly concentrated in salivary glands like human angiotensin-converting enzyme 2; this may be an explanation for the existence of SARS-CoV-2 in secretory saliva. Ather., et al. reported, Povidone iodine gargles had an effect on Subacute respiratory Syndrome (SARS- CoV) and Middle-East Respiratory Syndrome (MERS-CoV) [7].

Eggers., et al. PVP-I 7% gargle/mouthwash showed rapid bactericidal activity and virucidal efficacy in vitro at a concentration of 0.23% PVP-I and may provide a protective oropharyngeal hygiene measure for individuals at high risk of exposure to oral and respiratory pathogens [8].

It was reported that povidone-iodine (PVP-I) products in the form of mouthwashes and throat sprays have a prophylactic effect on SARS-CoV transmission during the outbreaks [9].

According to Mady., et al. [10] the following outlines a stratified approach to treatment:

- Apply nasal and oral PVP-I in patients suspected/confirmed with SARS-CoV-2 infection every 2 - 3h, up to 4 day.
- Has high-risk procedures (e.g. nasal mucosal, dental, pharyngeal, and pulmonary secretions).
- Are from areas of COVID-19 hotspots. Apply nasal and oral PVP-I to health care providers before and after patient contact (with regular contact every 2 - 3 hours, up to 4 day) that:
  - Are active in the treatment of suspected/confirmed SARS-CoV-2 infection patients.
  - Are involved in high-risk patient procedures at COVID-19 hotspots.
  - Lacking adequate PPE (e.g. PAPR, N95).

Possible nasal and oral application of PVP-I in patients and/or health care providers every 2 - 3 hours, up to 4 day in: a. High risk treatments in patients with asymptomatic conditions. b. COVID-19 hotspots.
Hydroxychloroquine (HCQ)

Hydroxychloroquine is said to prevent and treat malaria in areas where malaria remains sensitive to chloroquine. Chloroquine can impact virus infection in many ways, and the antiviral effect partially depends on how many endosomes the virus uses for entry. According to Tipnis., et al. Chloroquine has a positive effect on the ACE-2 responsible for effects Subacute Respiratory syndrome [11].

Moreover, CQ was shown to potently inhibit entry of SARS-CoV into cells by interfering with the glycosylation of its cellular receptor angiotensin converting enzyme 2 receptor (ACE2). SARS-CoV-2 also uses ACE2 as a receptor for cell entry, suggesting a possible similar effect of CQ on SARS-CoV-2 at this step of virus replication [12].

Hydroxychloroquine and chloroquine inhibit SARS-CoV-2 in vitro, and a Chinese commentary, mentioning 15 trials, reported that, “Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia [13].

Singh., et al reported in their study that HCQ and Chloroquine should be considered for the treatment on SARS-CoV-2 in diabetic patients [14].

Gautret., et al. concluded that hydroxychloroquine and azithromycin had been successful in reducing the viral load. Results on Day 3 revealed that 50 per cent of patients treated with hydroxychloroquine had a reduction in viral load with p = 0.005; on Day 4 showed a reduction of 60 per cent with p = 0.04; on Day 5 showed a reduction of 65 per cent with p = 0.006; and on Day 6, 70 per cent showed a reduction in viral load with p = 0.001 [15].

Yao., et al. who proposed the potential for hydroxychloroquine for treating COVID-19 [16].

However due to its effects on health, many countries in the world have stopped the use of Hydroxychloroquine has been stopped for the use of SARS-CoV-2.

Ivermectin

Ivermectin is an FDA-approved broad spectrum anti-parasitic agent that has shown an anti-viral activity in recent years against a wide variety of in vitro viruses. Originally identified as an interaction inhibitor between the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and the importer (IMP) α/β1 heterodimer responsible for IN nuclear production, Ivermectin has since been reported to inhibit IN nuclear production and replication of HIV-1. Other ivermectin actions have been reported but it has been shown that ivermectin inhibits the nuclear import of host and viral proteins, including simian SV large tumor antigen (T-ag) and non-structural protein dengue virus (DENV) [17].

Caly., et al. reported that Ivermectin had a positive response to Coronavirus 2 h post-infection with SARS-CoV-2 that could reduce viral RNA by approximately 5000-fold at a dose of 5 μM at 48h [18].

Yuvaz., et al. stated that clinical trials can be performed with ivermectin and nitazoxanide at low doses [19].

Chaudhary., et al. stated that azithromycin, hydroxychloroquine and ivermectin in the three drug groups seemed potentially countering new coronavirus infections. However, to combat COVID-19 infection, their effectiveness must be studied in detail individually and in combination in vivo [20].

However, Momekov., et al. reported that the available pharmacokinetic data for ivermectin indicate that at the doses routinely used for the management of parasitic diseases the SARS-CoV-2 inhibitory concentrations are practically not attainable which may be considered a drawback for the use of Ivermectin for SARS-CoV-2 [21].
Ribavirin

Ribavirin is an antiviral drug used to treat RSV, hepatitis C and some hemorrhagic viral fevers. It also has been used in SARS-CoV and MERS-CoV [22].

On RNA viruses, the carboxamide group of Ribavirin may, depending on its rotation, make the native nucleoside drug resemble adenosine or guanosine. For this cause, when ribavirin is integrated into RNA, it pairs equally well with either uracil or cytosine as a base analog of either adenine or guanine, causing mutations in RNA-dependent replication in RNA viruses. Such hypermutation can potentially be lethal to RNA viruses [23].

Koren., et al. reported the pharmacological use of Ribavirin for Subacute Respiratory Distress Syndrome [24].

Ribavirin is also widely used in the treatment of SARS and was given to more than 90 percent of Hong Kong patients. This is an equivalent nucleoside that has in vitro action against a variety of DNA and RNA viruses [25].

Ho., et al. reported the extensive use of Ribavirin and Corticosteroids during the outbreak of SARS-CoV [25].

Omrani., et al. in Saudi Arabia, an interventional study of MERS-CoV patients who received oral ribavirin, and weekly s.c. In the treatment group, 180 ug interferon-α2a for 2 weeks (n = 20) versus supportive care alone (n = 24) indicated superior survival and reduced ICU admission rate [10]. In that report, the oral ribavirin dose was maintained for 8-10 days, with dose changes dependent on creatinine clearance calculated. Three dose groups were administered based on creatinine clearance, specified as group 1: > 0.833 mL/sec/m², group 2: 0.333 - 0.833 mL/sec/m², and group 3: 200 mg every 6 hours for 4 days and then 200 mg every 12 hours for 4 - 6 days. It was also concluded that Ribavirin was well tolerated [26].

In China during the outbreak of SARS-CoV-2, Ribavirin was given at a dose of 500 mg iv BID or TID [11,27,28].

Hung., et al. 2020 reported that triple antiviral therapy with interferon beta-1b, lopinavir-ritonavir, and ribavirin were safe and superior to lopinavir-ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19 [29].

Favipiravir

Favipiravir (Avigan™), (T-705), (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), (CAS number: 259793-96-9), is an oral pyrazine carboxamide derivative and guanine analogue developed by Toyama Chemical, Japan that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRP) of RNA viruses and induces lethal RNA transversion mutations, thereby producing a nonviable virus phenotype.

Favipiravir inhibits replication of a large number of RNA viruses, including influenza A virus, flavi, alpha-, filo-, bunya-, arena- and noroviruses as well as West Nile virus, yellow fever virus, foot-and-mouth-disease virus, Ebola virus and Lassa virus [30].

Antivirals will not prove effective or safe for the treatment of COVID-19 unless used in the context of randomized clinical trials. Nearly 30 000 people developed Ebola viral disease in the 2014 outbreak, and numerous therapies have been tested against this virus, including chloroquine, hydroxychloroquine, favipiravir, brincidofovir, monoclonal antibodies, antisense RNA, and convalescent plasma, among many others [31].

Notwithstanding the urgent need for an efficient antiviral treatment for COVID-19 via randomized controlled trials, some agents are used worldwide on the basis of either in vitro or extrapolated evidence or observational studies. The most widely used drugs, including chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir and remdesivir, in Turkey and around the world [19].
Dosage
Day 1: 2X1600 mg, Day 2 - 7 (or 10): 2 × 600 mg/day.

Remdesivir

Remdesivir (also GS-5734) is an adenosine analog monophosphoramidate prodrug that has a wide antiviral range including filoviruses, paramyxoviruses, pneumoviruses, and coronavirus. It was developed by the biopharmaceutical company Gilead Sciences. As of 2020, Remdesivir is being tested as a specific treatment for COVID-19 and has been authorized for emergency use in the U.S. and approved for use in Japan for people with severe symptoms [32].

It has shown antiviral and clinical effects in animal models of SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV infections.

Remdesivir has been superior to a combined interferon beta and lopinavir–ritonavir treatment in a lethal murine form of MERS [33].

Sheahan., et al. stated that LPV/RTV-IFNb therapeutic enhances pulmonary function but does not minimize viral replication or serious lung pathology. So, we have in vivo proof of Remdesivir’s ability to treat MERS-CoV infections [34].

Remdesivir is a potent inhibitor of replication of SARS-CoV-2 in human nasal and bronchial epithelial airway cells [35].

Reina reported that, although all studies have been carried out with SARS-CoV and MERS-CoV, it seems that by virological and functional analogy, Remdesivir is one of the few antiviral drugs with proven efficacy. Martinez reported that Remdesivir can be used positively against SARS-CoV-2 [36]. However, the use of Remdesivir is still under clinical trial stage and extensive studies are needed for its effect.

Plasma therapy

Passive immunization therapy was successfully used until the 1890s to treat infectious diseases. An individual suffering from infectious diseases and recovers has blood drawn and screened for antibodies neutralizing particular microorganism. After identifying those with high titers of neutralizing antibody, convalescent plasma containing these neutralizing antibodies can be administered to reduce symptoms and mortality in individuals with a specified clinical disease.

Plasma therapy has an extremely long history of use in infectious disease treatment. Its use was well known in various periods during the outbreak of many diseases, including Spanish Influenza A (H1N1) infections in 1915-1917 [37].

In this systematic analysis of CPT to CoVid-19 patients, we identified 5 studies that represented about 27 patients, and critically assessed them. All research reported positive outcomes after CPT completion, but all were considered to be at risk of bias due to a combination of non-randomized tests, confounding, predictor classification and inadequate participant selection technique, CPT dose and therapy length [38].

The doses of CPT used in the different studies are varied. A Chinese pilot study showed minimal use of a single dose of 200 mL convalescent plasma, with antibody titers neutralizing > 1:640 [39].

In addition, CP’s therapeutic effect on COVID-19 is determined by the level of an antibody titer neutralizing SARS-CoV-2 (NAT). A research on SARS showed that the specific IgG started to rise after start around week 3 and peaked at week [40].

In China, Shen., et al. confirmed that five critically ill patients with COVID-19 (also with acute respiratory distress syndrome) received SARS-CoV-2 specific IgG transfusion (binding titer > 1:1000; neutralizing titer > 40) 22 days following admission. Their health condition
improved, with three discharges after 55 days of hospitalization. It should be noted that these patients also had mechanical ventilation help and antiviral agents (combinations of lopinavir, ritonavir, interferon α-1b, favipiravir, arbidol, and/or darunavir) and methylprednisolone, a steroid, were also obtained.

In global terms, there is currently no successful post-infection prophylaxis for COVID-19 diagnosis, although some medications are being repurposed [41].

There are also no antibodies for COVID-19 prevention, and it will probably take months before the antibodies emerge from clinical trials. For SARS-1 and MERS, and for COVID-19, CP, a post-infection drug, has demonstrated limited to moderate effectiveness [41,42].

Transfusion-related incidents involving chills, nausea, anaphylactic reactions, transfusion-related acute lung damage, circulatory failure, and hemolysis are the most common adverse reactions of CP therapy [43].

**Herd immunity**

Herd immunity is caused by the effects of scaled human immunity to population level. It refers to the indirect immunity bestowed upon susceptible persons from infection when there is a sufficiently large proportion of resistant persons in a population. As of 4 May 2020, the ongoing SARS-CoV-2 pandemic has caused more than 3.5 million clinically confirmed COVID-19 cases and claimed over 250,000 lives around the world. There are currently several clinical trials underway to test novel vaccine candidates and drug repurposition approaches for the prevention and treatment of SARS-CoV-2 infection. However, it is uncertain if these trials can yield successful vaccines, and it is unclear how long such trials would take to determine effectiveness and safety, although an optimistic estimate is at least 12 - 18 months for any vaccine trial. Within the absence of a vaccine it is potentially possible to build up herd immunity from SARS-CoV-2 via natural infection. There is no straightforward, ethical path to achieving that goal, however, as the social consequences of achieving it are devastating. An estimated R0 of approximately 2.2 was estimated from an initial cohort of 425 confirmed cases in Wuhan, China, meaning that on average each infected person gives rise to 2.2 other infections [43].

More recent estimates also position R0 higher at 5.7, although there are several estimates within this range [44].

These variables is difficult to obtain a herd immunity in this pandemic. On a positive note, induction of herd immunity by vaccination is a tried and tested approach. All places are not equally prone to the spread of infection especially in developing countries. On a positive note, localized herd immunity can help in further impeding the spread of COVID-19 [41,45].

**Live attenuated vaccine**

Ever since the live attenuated vaccine for polio virus had been developed by Salk, there has been considerable research regarding the use of live attenuated vaccines for the purpose of immunization against microbials.

Several SARS-CoV-1 vaccines have been developed and tested in animal models, including recombinant S-protein vaccines, inactivated and whole vaccines, and vector vaccines [46].

Most of these vaccines protect animals from SARS-CoV-1 challenges, though many do not induce immunity from sterilization. In some cases, vaccination with the live virus leads to complications, including damage to the lungs and infiltration of eosinophils in a mouse model and damage to the liver in the furet [47].

Another consideration for effective development of the coronavirus vaccine could be a decline in the antibody response. Human coronavirus infection does not always cause long-lived antibody responses, and after an prolonged period of time, re-infection of an person with the same virus is likely.

CEPI has given funds to many highly creative players in the field and all of them are likely to succeed in producing a SARS-CoV-2 vaccine eventually.

A mRNA-based vaccine, co-developed by Moderna and the National Institutes of Health Vaccine Research Center, which expresses target antigen in vivo in the vaccine after injection of mRNA encapsulated in lipid nanoparticles, is currently the furthest along, and a phase I clinical trial. Johnson and Johnson (J and J) (Johnson and Johnson, 2020), and Sanofi (2020) have recently joined forces to create vaccines for SARS-CoV-2. Nevertheless, J and J uses a vector model for the experimental adenovirus that has not yet resulted in an approved vaccine. Sanofi’s vaccine, to be produced using a method similar to that used for their approved Flublok recombinant influenza virus vaccine [48], is still months, if not years, from being ready for use in humans [49].

Conclusion
All the research till today is on trial and error basis and there is has been 100% definitive treatment in the management of SARS-CoV-2. Till date there has been a missing link for the treatment of SARS-CoV-2 and there has been a constant trail for a definitive treatment to overcome the odds in this crisis situation. There is a hope that someday we shall overcome this obstacle as there is a constant evolution of knowledge and research by us in a try to defeat SARS-CoV-2.

Bibliography


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