Molecular Science

AIMS Molecular Science, 7(3): 269–280.
DOI: 10.3934/molsci.2020012
Received: 30 May 2020
Accepted: 13 July 2020
Published: 16 July 2020

http://www.aimspress.com/journal/Molecular

Mini review

Familiar fixes for a modern malady: a discussion on the possible cures of COVID-19

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Abstract: The SARS-CoV-2 virus emerged in December 2019 in Wuhan, China and then spread rapidly all over the world. Scientists are intensifying their research efforts in order to find antivirals specific to the virus and vaccines to treat or prevent COVID-19. Now, for a medicative cure for COVID-19, several drugs such as chloroquine, hydroxychloroquine, lopinavir, ritonavir, remdesivir and favipiravir are currently undergoing clinical studies. Convalescent plasma therapy and high dose of intravenous (IV) vitamin C have also been used to treat SARS-CoV-2 infections. This article outlines aspects related to several antiviral drugs and therapies which may be potentially effective against SARS-CoV-2.

Keywords: COVID-19; SARS-CoV-2; chloroquine; hydroxychloroquine; lopinavir; ritonavir; remdesivir; favipiravir; vitamin C; convalescent plasma

1. Introduction

"Death leaves a heartache that no one can heal."
---Anonymous

The first half of the year 2020 has seen the loss of many a loved one from the lives of people across the globe. It is often the case that a person fails to feel the pain of a neighbour unless he is subjected to it himself. The change in situation before and after the pandemic is so vast that it seems as though we had fallen asleep in one world and have woken up in another. We have suddenly

realised that religion, caste, beauty and money have no control over nature. Human beings are now imprisoned in an environment where uncertainty, unknown fear and misbelief pervade the air. With the surge of COVID-19 (**Co**rona **Vi**rus **D**isease - 2019) in countries throughout the world, experts are putting their minds together to develop new techniques to understand the mechanism of infection, virulence, pharmacology and evaluate potential therapeutics and vaccines to combat coronavirus. Researchers across the globe are relentlessly working to find a potential cure for coronavirus. In this article, a few important antiviral drugs and treatments will be discussed as possible cures for SARS-CoV-2. However, none of them can be accepted as unquestionable remedies for the disease to date. In controlling the COVID-19, most of the drugs tested by the doctors so far are totally based on the information for similar kinds of infections that occurred in the past and treatment is completely oriented towards the 'management' of symptoms.

2. COVID-19 pathophysiology

Coronaviruses (Corona: Crown like shape) generally belong to a family of enveloped viruses with single-stranded, positive-sense RNA genomes infecting humans and animal species [1]. Graphical representation of the structure of corona virus (SARS-CoV-2) has been given in Figure 1 and the representative structure (electron micrograph of infectious bronchitis virus) of coronaviruses (crown-like shape) has been given in Figure 2 [2]. Study reveals that coronaviruses are zoonotic. That means these viruses are mostly present in animals and then are transmitted from animals to human beings. In this family of coronavirus members, those viruses which are responsible for the common cold are known as severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome-related coronavirus (MERS) [3]. However, the one that has recently emerged is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the etiological agent of COVID-19. It was provisionally named as 2019-nCoV (a new coronavirus that was not identified in humans previously). Subsequently, International Committee on Taxonomy of Viruses chose a systemic nomenclature based on an analysis of the new coronavirus' evolutionary history and the pathogen that causes SARS. On 11th of February 2020, they introduced the name as SARS-CoV-2. The World Health Organization (WHO) declared the COVID-19 outbreak as the sixth public health emergency of international concern. Others are H1N1 (2009), Polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of Congo (2019) [3].

General symptoms of COVID-19 disease at the onset of illness are general myalgia, fever and cough. Often the symptoms are extended to production of sputum, headache and diarrhea [4,5]. SARS-CoV-2, like other coronaviruses, mainly infects the respiratory and gastrointestinal tract. Its main target is the multitude of epithelial cells in the respiratory tract eventually leading to diffuse alveolar damage. Apart from causing indirect injury to certain organs, the disease directly infects and affects the functioning of many organs/cell types in the course of the illness. These include mucosal cells of the intestines, tubular epithelial cells of the kidneys, neurons of the brain, and several types of immune cells [6,7]. Modern research indicates that binding of cell through viral S protein to the host receptor angiotensin-converting enzyme 2 (ACE2) is obligatory for the infection to occur [8,9]. After entering the cell, gradually the virus complex is translocated to the endosome. Endosomal acid proteases present in endosome then cleaves the S protein. The viral genome is then released and gets translated into the viral replicase polyproteins PP1a and PP1ab. Viral proteases are responsible for

the breaking down of such polyproteins into functional proteins. Through discontinuous transcription, subgenomic templates for mRNA synthesis and translation of the viral structural proteins take place [10,11]. Viral replication complex mediates viral genome replication and it includes an exonuclease, RNA-dependent RNA polymerase (RdRp), helicase and other accessory proteins. Viral nucleocapsids from the packaged viral genomes and translated viral structural proteins assemble at the endoplasmic reticulum-Golgi intermediate compartment. Subsequently, there is the release of infectious virions from the cell through exocytosis.

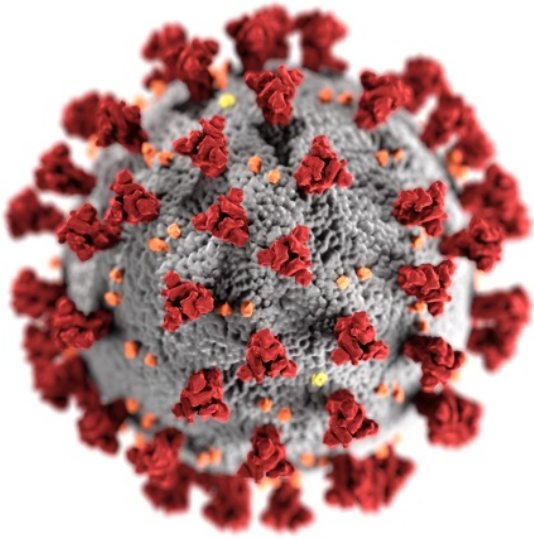

Figure 1. A graphical representation of structure of corona virus (SARS-CoV-2). Source: Centers for Disease Control and Prevention, Public Health Image Library. Credit: Alissa Eckert, MS, Dan Higgins, MAM.

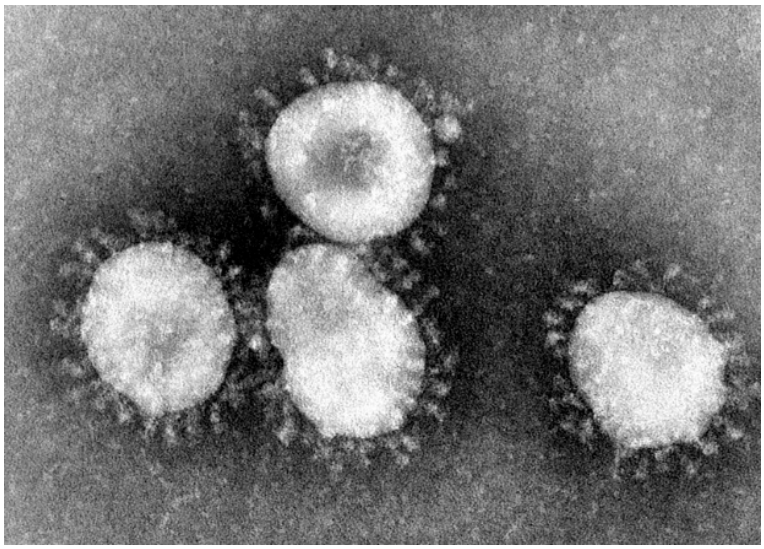

Figure 2. Representative structure (electron micrograph of infectious bronchitis virus) of coronaviruses (crown-like shape). Source: Wikipedia/CDC Credit: CDC/Dr. Fred Murphy.

SARS-CoV-2 being a new disease does not have any clinically proven therapeutics. However, for the treatment of related viruses like SARS and MERS, a substantial preclinical research was reported. It is worthwhile to mention that for the treatment of SARS and MERS, no therapeutic or vaccine designing schedules were completed as these outbreaks did not persist. Consequently, the concepts of drug repositioning and repurposing have received a substantial amount of consideration [10]. In this regard, chloroquine, hydroxychloroquine, lopinavir, ritonavir, remdesivir and favipiravir, have entered clinical trials to address the current SARS-CoV-2 pandemic (Figure 3).

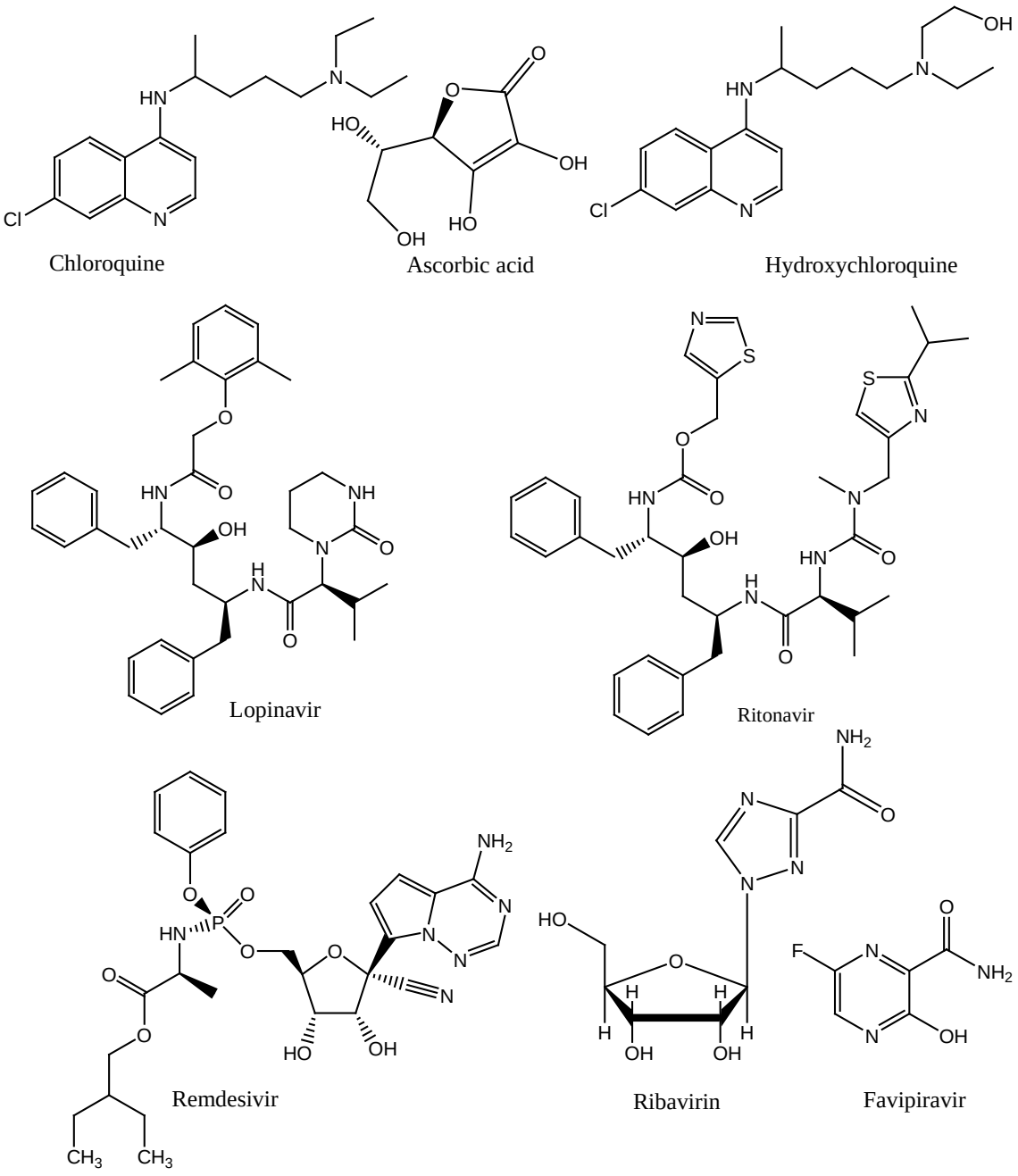

Figure 3. Representative structures of chloroquine, hydroxychloroquine, lopinavir, ritonavir remdesivir, ribavirin and favipiravir.

3. Chloroquine and hydroxychloroquine as possible remedies for COVID-19

While scientists all over the globe were persistent in finding an antidote to the deadly disease caused by this microorganism, certain experts have zeroed down on chloroquine and hydroxychloroquine as possible remedies for this. Chloroquine is not a new name in the world of medicines. It is widely used as an anti-malarial drug with immunomodulatory effects, as a potential curative drug in the treatment of malaria and amebiasis. Chloroquine was found to inhibit the growth of SARS-CoV-2 in an *in vitro* study [10,12]. Its sister compound, hydroxychloroquine, however, is a more suitable option for the treatment of malaria and autoimmune conditions because though it shares the same mechanism of action as chloroquine, the intensity of its toxicity is far lower than that of its sister [12]. Hydroxychloroquine was reported to have anti-SARS-CoV-2 activity in vitro in the previous SARS outbreak. It can therefore be surmised that hydroxychloroquine is a reliable pharmacological agent for the treatment of COVID-19 infection [12]. Unfortunately, to date there is no quantifiable proof to establish the veracity of chloroquine and hydroxychloroquine as treatment for SARS-CoV-2 infection. However, according to new research, both chloroquine and hydroxychloroquine have the potential to impede the growth of coronavirus through a series of steps [13,14]. The changing of the pH at the surface of the cell membrane is the first effect that the drug has on the cell. It can subsequently inhibit viral entry, transport and post-entry events. In addition to this, the compounds have the capacity to control replication of nucleic acid, virus assembly, new virus particle transport, glycosylation of viral proteins, virus release and other processes to achieve their antiviral effects. Inhibition of inflammation and autoimmune reactions can be facilitated with the help of their interactions with cells. They bind to DNA and RNA intercalating between base pairs, thereby stabilizing nucleotides and inhibiting the prepolymerization and transcription necessary for cellular replication and normal protein synthesis. They also accumulate in lysosomes, stabilizing them and thereby interfering with chemotaxis, phagocytosis, autophagy and digestion [15,16].

On conducting a trial with 100 adults suffering from COVID-19 in China, it was found that chloroquine significantly reduced the duration of COVID-19 symptoms, with very mild side effects. Inspired by this study, the National Health Commission of the People's Republic of China made a recommendation for including chloroquine in the upcoming version of the guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19 [14,17]. Gautret *et al*., in Marseille, France, found that hydroxychloroquine had a significant anti-SARS-CoV effect *in vitro*. Since the toxicity level of hydroxychloroquine is quite low, it was considered a safer remedy as compared to Chloroquine [18–20].

4. Lopinavir/ritonavir as potential treatment

In 2003, after the emergence of SARS, screening of several drugs was performed. Researchers observed after meticulous screening lopinavir, a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, as having *in vitro* inhibitory activity against SARS-CoV [21]. Lopinavir is formulated in combination with another protease inhibitor, ritonavir. Ritonavir, when combined with lopinavir, increases its plasma half-life and this takes place through the inhibition of cytochrome P-450. Research indicated that the addition of lopinavir–ritonavir to ribavirin (an antiviral medication used to treat RSV infection, hepatitis C and some viral hemorrhagic fevers)

reduced the risk of acute respiratory distress syndrome [ARDS] [21,22]. This combinatorial medication was also capable of reducing viral load among patients with SARS. Again, lopinavir found its application both *in vitro* and in an animal model, against MERS-CoV [22,23]. Reports suggested that the combination of lopinavir/ritonavir (LPVr) with ribavirin and interferon alfa resulted in virologic clearance and survival. Currently, researchers are trying the oral dose of LPVr for SARS-CoV-2 infection. SARS-CoV-2 virus, single-stranded RNA beta-coronavirus, enter host cells and replicate, producing strands that contain multiple copies of the viral genetic material (RNA) [22,24]. The strands of genetic material, accumulate at the periphery of the cell, ready to be cleaved, packaged and prepared for release from the host cell. The enzyme 3-chymotrypsin-like protease ($3CL^{pro}$) plays a crucial role in processing the viral RNA. As LPVr is a protease inhibitor, it may inhibit the action of $3CL^{pro}$, thereby disrupting the process of viral replication and release from host cells [21,23,24].

When the epidemic was at its peak, an open-label RCT was conducted by Cao *et al.* at a single hospital in Wuhan, China [25]. A total of 199 hospitalised adults with COVID-19 pneumonia and oxygen saturations ≤94% on ambient air were taken in for the test and were randomised to receive different drugs after being divided into two groups. The first group included 99 patients and the second had 100. The patients in the first group were given LPVr 400 mg/100 mg twice daily for a fortnight while the second group received standard medical care. It was observed that both the groups exhibited similar baseline characteristics. The median age was 58 years (interquartile range [IQR] 49–68). Most of the adults under trial were found to be suffering badly and needed immediate medical care. After four weeks, ITT (Intention to Treat) analysis was executed and the results showed that there had been zero alteration in the primary outcome of time to clinical improvement between the two arms (16 days in both groups; hazard ratio 1.31; 95% CI: 0.95 to 1.85; $P = 0.09$). When the analysis was limited to patients registered within 12 days of symptom onset, the results remained unchanged. On execution of modified ITT analysis (excluding three patients who were not treated with LPVr and died within 24 hours of randomization), a minor reduction in the time of clinical improvement was found with LPVr (median of 15 days versus 16 days, respectively; hazard ratio 1.39 [95% CI: 1.00 to 1.91]).

5. Remdesivir as a potential treatment

Remdesivir, is made by Gilead Sciences in collaboration with the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The development of remdesivir was a part of an antiviral development project of Gilead Sciences in 2015 which was initially effective against Ebola virus (EBOV) [11]. Though remdesivir was not developed for the treatment COVID-19, now it is used to treat COVID-19 as among the candidate therapies. Remdesivir has demonstrated efficacy in both *in vitro* and *in vivo* models against coronaviruses [11,26].

Remdesivir a prodrug that is metabolized within cells and then converts into an alanine metabolite. This, on further processing, gets converted into the monophosphate derivative and eventually becomes an active nucleoside triphosphate derivative, which can be utilized by the viral RNA-dependent polymerases for genome replication. Thereafter, viral RNA-dependent RNA polymerase (RdRP) enzyme can misintegrate nucleoside triphosphate into viral RNA and the action goes on [11,27].

Amongst various drugs that were being tested for effectivity against Covid-19 with the disease raging across the globe, Remdesivir was considered a potential cure by certain scientists in China. The first registered trial was made at Capital Medical University on February 5, 2020 and was categorised as a phase 3 randomized, quadruple-blind, placebo-controlled clinical one. The trial was made to test the effectiveness of the drug in patients with mild to moderate SARS-CoV-2 infection alongside testing to see whether it had any harmful effects on the human body [28]. Within another 24 hours, the second registered test made at the same place, Capital Medical University, targeted patients suffering from an advanced stage of COVID-19 respiratory disease [29]. The objective of each of these two tests was to track the duration of time required in clinical improvement. This included normalization of fever, oxygen saturation and respiratory rate and alleviation of cough which was sustained for 72 h. In both the tests, a 200 mg loading dose of remdesivir was used on the first day and that was followed up with 9 subsequent days of maintenance dosing at 100 mg [30].

6. Favipiravir as a potential candidate

Favipiravir is another drug that has received significant attention as it is undergoing clinical trials in treating COVID-19 as of late. In cells, it gets converted into an active phosphoribosylated form, favipiravir-RTP (Favipiravir ribofuranosyl-5'-triphosphate). Consequently, it is recognized as a substrate by viral RNA polymerase therefore inhibiting the RNA polymerase activity. Favipiravir, a potential RdRp inhibitor of RNA viruses which is also capable of inhibiting the 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 [31]. In this way, SARS-CoV-2 being an RNA virus, experiences the potential antiviral action of favipiravir. Clinical trials for the treatment of COVID-19 have shown favipiravir to have more potent antiviral action than that of LPVr and adverse effects are also much lesser compared to LPVr [32,33].

Favipiravir showed considerable effectivity for Covid-19 when tested against it for the first time. In China, 80 patients with COVID-19 were made to undergo an open-label non-randomized trial by being treated with favipiravir [34]. The test recorded a substantial decrease in the time taken for the clearance of SARS-CoV-2 in patients treated with favipiravir in comparison to historical controls treated with lopinavir/ritonavir. Those with mild or moderate COVID-19 were admitted by the end of the seventh day from the inception of the disease; those patients who were above 75 years old, with severe or critical disease, chronic liver disease or end-stage renal disease were left out. An oral dosage of favipiravir 1600 mg was given to patients in the intervention arm twice daily on day 1 followed by 600 mg orally twice daily on days 2–14. A co-treatment of both arms was made by inhaled IFN-α1b 60 μg twice daily and therapy was continued until viral clearance, up to a maximum of a fortnight's duration. While favipiravir was given to 35 patients, 45 patients were treated with lopinavir/ritonavir. These patients had the median age of 47 years (IQR = 35.8–61). Among them, 13.7% were above 65 years of age. It was observed that the median time to viral clearance underwent a marked reduction in patients treated with favipiravir (4 days; IQR = 2.5–9) as opposed to those treated with lopinavir/ritonavir (11 days; IQR = 8–13; $P < 0.001$). Further, by the end of the second week of observation, 91.4% of patients in the favipiravir arm showed radiographic improvement contrasted with 62.2% in the lopinavir/ritonavir arm. A noticeably lower rate of adverse events was observed in patients treated with favipiravir (11.4% versus 55.6%; $P < 0.01$). Considering the

demonstrated in vitro of activity of favipiravir against SARS-CoV-2 and signs of effectiveness in early clinical experience for COVID-19, it is of immediate necessity that further studies be made. There are numerous randomized controlled trials to assess the efficacy of favipiravir for COVID-19 whose results are still awaited. The results obtained from these tests will be able to throw light on the role of favipiravir in the management of the ongoing coronavirus pandemic [34,35].

7. Convalescent plasma as a therapy for COVID-19

In the search for an effective treatment for COVID-19, some researchers and doctors are depending on an old method of fighting infectious diseases: transfusions with convalescent plasma. Convalescent plasma, the plasma from recovered patients, has been used over 100 years to treat a wide array of diseases caused by measles, polio, chickenpox and SARS [36,37]. The notion of using convalescent plasma was initially introduced by physiologist Emil von Behring (Nobel Prize winner in Physiology or Medicine in 1901) and bacteriologist Kitasato Shibasaburou in the late 19th century in order to fight against the bacterial infection caused by diptheria. Since then, researchers and doctors have used passive antibody therapy, on and off, in order to treat or prevent both bacterial and viral infections.

Antibodies are found in plasma, a liquid component of blood. The blood of people who have recovered from COVID-19, contains antibodies which have been produced by their bodies to fight against the coronavirus. Most importantly, antibodies are the molecules that have learned to recognize and fight against the pathogens, such as viruses. In the present situation, doctors can separate antibody-containing plasma from a patient recovered from COVID-19 and administer it by transfusion to a patient who is suffering from COVID-19. In this way, the donor antibodies help the immune systems of the patient to reject the pathogen more efficiently and to fight the disease, in all possibility, by shortening the span and / or reducing the severity of the disease [38].

It is true that convalescent plasma treatment has been used for many years with varying success though the effectiveness for treating COVID-19 is not well known. These methods are known to have some success in China and many other countries but their reliability becomes questionable due to absence of randomized and controlled studies. Moreover, the optimum time at which the plasma should be infused is also beyond the knowledge of researchers and doctors [39].

A randomized test was conducted with 103 patients with median age, 70 years and 60 (58.3%) of them were male [40]. From the entire lot, 52 patients were given convalescent plasma besides standard treatment and 51 patients were given standard treatment alone (control). Out of 103, 101 (98.1%) completed the trial. Significant improvement was observed within four weeks in 51.9% (27/52) of the convalescent plasma group as opposed to 43.1% (22/51) in the control group (difference, 8.8% [95% CI, −10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79–2.49]; $P = 0.26$). In some of the patients who suffered from acute disease, the primary outcome was recorded in 91.3% (21/23) of the convalescent plasma group contrasted with 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07–4.32]; $P = 0.03$) [40].

8. High-dose vitamin C to treat patients with COVID-19

As COVID-19 is now spreading across the world, researchers are seeking new ways through which people can be protected from the virus or at least are trying to find a medicine that can lessen

its effects. One such trial is to test a high-dose of vitamin C in patients with COVID-19 as COVID-19 pneumonia seems to be a lung injury caused by the hyperactivation immune effector cells. Research reports have indicated that a few patients in China suffering from COVID-19 have been treated with high dose of intravenous (IV) vitamin C anticipating speedy recovery since a high-dose vitamin C may result in immunosuppression at the level of these effectors [41].

The idea of using high dose intravenous (IV) vitamin C is not at all new. Linus Pauling, the famous Nobel Prize-winning chemist, considered vitamin C almost as a panacea. Pauling had such a high regard for vitamin C that he considered that vitamin C can combat a series of illnesses including flu, cancer and many other diseases. Vitamin C, an essential enzymatic co-factor for synthesis of collagen, used in boosting immunity and for hormone production can also be considered as a significant anti-oxidant. In order to have vitamin C, the human body should rely on dietary sources as humans are not able to synthesise vitamin C. The sodium-vitamin C co-transporters SVCT1 and SVCT2 transport the reduced form of vitamin C, ascorbic acid, across cellular membranes. Besides this, vitamin C gets oxidised to biologically inactive dehydroascorbate both intracellularly and extracellularly which is quite unstable as it undergoes hydrolysis in an irreversible manner at physiological pH [42,43].

GSH (glutathione), thioredoxin, and NADPH (reduced nicotinamide adenine dinucleotide phosphate) can reduce dehydroascorbate to vitamin C. As a result of this, reactive oxygen species (ROS) scavenging systems involving redox couples such as NADPH/$NADP^+$ and GSH/GSSG (glutathione disulfide) decrease. Consequently generation of ROS increases inside the activated immune cells. Hence, a high-dose of vitamin C, unlike the general assumption, acts as a pro-oxidant [44,45].

Sepsis is a life-threatening organ dysfunction syndrome, characterized by systemic inflammation, increased oxidative stress, insulin resistance and peripheral hypoxia. Rolipram, a novel drug treatment for sepsis, can inhibit TNFα production in activated macrophages as it is a selective phosphodiesterase-4 inhibitor, thereby restraining acute inflammatory response. Similarly, a high-dose of vitamin C in sepsis treatment is most probably due to its immunosuppressive effects. Lung epithelial cells use mitochondrial oxidative phosphorylation procedure to produce ATP whereas, immune effector cells are dependent on glycolysis for their bioenergetic functions. This is responsible for the fact that high-doses of vitamin C treatment acts as a prooxidant for immune cells whereas at the same time antioxidant for lung epithelial cells. Hence, intravenous high-doses of vitamin C could be a safe and beneficial choice of treatment in the early stages of COVID-19 as beside the abovementioned functioning, vitamin C treatment also might protect innate immunity of ATII through the inhibition of the lactate secretion [44–46].

Several reports have been received stating the benefits of high-dose of intravenous vitamin C for the possible cure of COVID-19 patients. According to one such report, in China, almost 50 COVID-19 patients were treated with high-dose of intravenous vitamin C which was given at varying doses from 2 g to 10 g each day for a period of 8 to 10 hours. The oxygenation index improved gradually and finally all the patients were cured and eventually discharged [47,48]. Another report from Hemila and Chalker suggested that various high-dose intravenous vitamin C infusions resulted in a reduction in time of the patient's stay at the intensive care unit (ICU) by 97.8%. It also facilitated a significant reduction in the mortality rate [49]. According to a recent NIH expert panel document, it is clearly stated that a range of 0.2 g/kg to 1.5 g/kg body weight can be considered safe without any side effects [50].

9. Conclusion

As thousands of people have succumbed to COVID-19, doctors, scientists and governments are on the lookout for safe and effective treatments to help those who are infected. However, there is no reliable medicine that can treat or cure COVID-19. Randomized controlled trials are needed to elucidate which therapies can be life-saving for patients suffering with COVID-19.

Acknowledgements

The author is extremely thankful to Mrs. Sayantani Mitra (Teacher, Department of English, Sushila Birla Girls' School, Kolkata, India), for her constant support in reviewing the manuscript.

Conflict of interest

The author declares no conflict of interest in this manuscript.

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