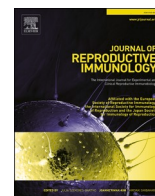Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Review article

Covid-19 pandemic: Perspectives on management

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ABSTRACT

The pandemic COVID-19 presents a major challenge to identify effective drugs for treatment. Clinicians need evidence based on randomized trials regarding effective medical treatments for this infection. Currently no effective therapies exist for the progression of the mild forms to severe disease. Knowledge however is rapidly expanding. Remdesivir, an anti- retroviral agent has in vitro activity against this virus and has shown to decrease the duration of ICU care in patients with severe disease, while low dose dexamethasone also showed a decrease in the duration of stay in cases of severe disease requiring assisted ventilation. At the time of writing this article, two mRNA-based vaccines have shown an approximate 95 % efficacy in preventing infection in large clinical trials. At least one of these drugs has regulatory permission for vaccination in high-income countries. Low and middle-income countries may have difficulties in initiating vaccine programs on large scales because of availability, costs, refrigeration and dissemination. Adequately powered randomized trials are required for drugs with in vitro activity against the virus. Supportive care should be provided for stable, hypoxia and pneumonia free patients on imaging. Vaccines are of obvious benefit and given the preliminary evidence of the efficacy of over 95 %, Low and middle-income countries must develop links with the WHO COVAX program to ensure global distribution of vaccines.

1. Introduction

The first episode of Covid-19 (2019-nCoV) began in December 2019 in the city of Wuhan, China (Al-Mandhari et al., 2020; Chen et al., 2020). The WHO reported that this novel coronavirus 2019-nCoV causes a mild to moderate respiratory illness and most recover without specific treatment (World Health Organization, 2020a). However, the elderly and those with underlying medical conditions such as cardiovascular disease, diabetes, chronic respiratory illnesses and cancer are more likely to develop serious illnesses which may be fatal (World Health Organization, 2020b). Furthermore, the WHO advised that hygienic measures such as frequent hand washing with water and soap or an alcohol-based solution, to avoid touching the face wear a mask and avoid going into crowded places' is likely to prevent human-to-human spread of this virus. (World Health Organization, 2020c). On 11 March, the WHO called the outbreak of Covid-19 a pandemic because it had spread to more than 114 countries, infected more than 118 000 individuals and caused the death of more than 4291 people (World Health Organization, 2020d).

2. The coronaviruses

The coronaviruses are the largest viruses, known to date (Channappanavar and Perlman, 2017). The genome is about 30 Kb, have an envelope and are positive sense RNA viruses (Channappanavar and Perlman, 2017). Huang et al. (2020), described the clinical features of 41 Chinese individuals who had contacted 2019-nCoV (Huang et al., 2020). These authors found that <50 % had underlying diseases such as diabetes, hypertension and other cardiovascular diseases; that the most common symptoms at the onset of the disease were fever, cough, myalgia or fatigue whilst sputum production, haemoptysis and diarrhoea were less common symptoms (Huang et al., 2020). In addition, > 50 % had dyspnoea, 22 (30 %) had acute respiratory distress syndrome (ARDS) and 16 had to be admitted to intensive care units (ICU) (Huang et al., 2020). Rodriguez-Morales et al. (2020) conducted a systematic review with meta-analysis of all articles published on SARS-CoV-2 (Rodriguez-Morales et al., 2020). They further reported that those who had contacted the coronavirus had a mean age of 51.8 years and that in most patients (n = 656), the Coronavirus causes mild respiratory illnesses, affecting mostly the upper-airways. In addition, 20.3 %

required admissions into ICU, presenting with ARDS, acute cardiac injury, acute kidney injury, shock and fatal outcomes in 13.9 % (Rodriguez-Morales et al., 2020). In those with chest x-rays, the predominant findings were bilateral pneumonia and radiological imaging showed ground-glass opacities (Rodriguez-Morales et al., 2020; Channappanavar and Perlman, 2017). However, in the elderly and in those presenting with co-morbid conditions such as diabetes, obesity, cardiac conditions such as heart failure and hypertension, renal failure and cancer experience severe symptoms such as acute respiratory and gastrointestinal problems (Cossarizza et al., 2020).

3. Binding of SARS-CoV-2 virus with membrane receptors and propagation of SARS-CoV-2

The spike (S) protein occurs on the outer surface of the coronavirus virion, and it facilitates the entry of the virus into target cells (Hoffmann et al., 2020; Yan et al., 2020). SARS-CoV-2 recognizes its receptor, angiotensin converting enzyme 2 (ACE-2), a transmembrane receptor, on human host cells (Zhang et al., 2020). SARS-CoV-2 has two spike glycoproteins on its outer surface, called S1 and S2 domains, which mediate receptor recognition and membrane fusion respectively (Zhang et al., 2020; Yan et al., 2020). Therefore, during an infection the S protein on the virus surface is cleaved into S1 and S2 subunits (Yan et al., 2020; Zhang et al., 2020). The S1 subunit has the receptor-binding domain (RBD) which binds the virus to the peptidase domain (PD) of ACE-2 receptors. The S2 subunit of the viral membrane not only fuses with the ACE-2 membrane but also uses it to gain entry into the cell (Yan et al., 2020; Zhang et al., 2020; Cao et al., 2020b). Once inside the cell, the virus exposes its RNA, translates its RNA replicase-transcriptase complex then forms an RNA negative strand and later forms into an RNA structural protein and the viruses leave the cell by exocytosis to infect other cells (Cao et al., 2020b). The ACE-2 receptor occurs on the surface of biological membranes and are found in abundance in the lungs, heart, gastrointestinal tract (GIT), arteries, veins and renal tissue (Cao et al., 2020b). The presence of SARS-CoV-2 virus in the faeces in some of infected individuals may explain the GIT being a target for this virus (Cao et al., 2020b).

4. Normal function of ACE-2 receptors

Even prior to the presence of SARS-CoV infection of 2002–2003 which showed the virus uses the ACE-2 receptors to gain entry into some or many cells of the body, scientists showed interest in the mechanisms that operate in the body to modulate ANG II, which is one of the main causes of hypertension. There has to be a normal function of ACE-2 for individuals to seek its production sites. For example, ACE is produced by ACE receptors found especially in endothelial cells of the somatic system but especially in the pulmonary circulation whereby ACE coverts ANG I to ANG II. This is required for maintenance of the normal blood pressure. It is also known that ANG II is a powerful vasoconstrictor and that it can lead to hypertension in some individuals.

The pharmacological drugs, called angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), are used in individuals with hypertension to maintain normal blood pressure levels. In addition, to systemically produced ANG II, local RAS also operates in certain tissues, e.g. cardiac myocytes and cardiac fibroblasts. Therefore, in the heart tissues, excess ANG II can cause cardiac hypertrophy and fibrosis during cardiac failure and the use of ACEi can reverse such situations. In addition, several other vasoactive products related to ANG II and I occur, such as ANG-(1–9), ANG-(1–7), ANG III and ANG IV. However, the receptor site/s and mechanism of production were unknown. Therefore, the search of cells that produce these had to be identified. One or more studies were undertaken to discover the cells responsible for such production. Therefore independent studies by Donoghue et al. (2000) and Tipnis et al. (2000) identified these cells whilst the former called these cells ACE-2 the latter called the same cells

ACEH. In addition, both research groups have declared that both ACE-2 and ACEH share a common homology with ACE (Donoghue et al., 2000; Tipnis et al., 2000). Both research groups have identified that ACE-2 or ACEH are found in the heart, kidney and testes including the endothelial cells in these organs (Donoghue et al., 2000; Tipnis et al., 2000). However, Tipnis et al. (2000) also found that moderate levels of ACEH are also produced in the ileum, colon and the ovary (Tipnis et al., 2000).

Angiotensin converting enzyme-2 (ACE-2) or ACEH is able to convert ANG I to ANG-(1–9) but ACE is required for conversion of ANG-(1–9) to the active form of ANG-(1–7) which causes vasodilation (Tipnis et al., 2000; Donoghue et al., 2000). However, ACE-2 or ACEH is able to directly convert ANG II to ANG-(1–7) which has vasodilatory and has anti-proliferative effects but its receptors are not yet known (Tipnis et al., 2000). Furthermore, subsequent to the emergence to SARS-CoV, Hamming et al. (2004) immunolocalised ACE2 receptors in other tissues, in addition to earlier reporting on localization sites of ACE-2 being in the heart, kidney, testes and the blood vessels in these tissues (Fig. 1) (Hamming et al., 2004). The first findings was that ACE-2 receptors occurred in endothelial cells of small and large arteries and veins in almost all structures (Hamming et al., 2004). These workers also reported seeing ACE-2 receptors in the arterial smooth muscle cells, in myo-fibroblasts and in membranes of fat cells on the various structures, they investigated (Hamming et al., 2004). They also reported a marked immunostaining of ACE-2 receptors in types I and II alveolar epithelial cells in the normal lungs, and type II alveolar epithelial cells of fibrotic lungs (Hamming et al., 2004). Furthermore, they also found ACE-2 immunostaining in bronchial epithelial cells, in the basal layer of non-keratinizing epithelial cells of nasal and mucosal cells and in the nasopharynx (Hamming et al., 2004). In addition, these researchers also localised ACE-2 immunostaining in smooth muscle cells of the muscularis mucosae and in the muscularis propria and endothelial cells in the stomach, small and large intestines and in the enterocytes of the small intestine and the cells, which were in contact with the external environment (Hamming et al., 2004). ACE-2 receptors are also found in other tissues, especially in the lung where it ultimately causes hyaline membrane disease, which on radiography gives "ground glass" appearance. However, we are of the view that ACE2 receptors is/was high-jacked by coronaviruses to gain entry into the cell but the main function of ACE2 is for maturation of angiotensin I (ANG)I and ANG II for the control of blood pressure (Yan et al., 2020).

5. Immune response to COVI9-19 infection

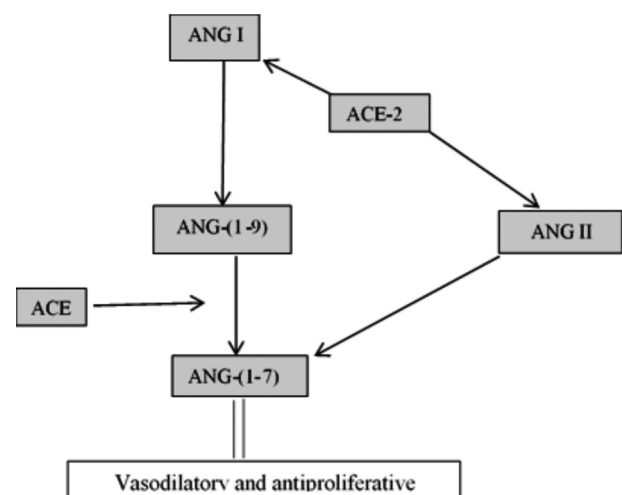Blood IL-6 levels together with other cytokines (such as IL-1A, IL-1B,

Fig. 1. Action of ACE-2 and ACE on the formation of ANG-(1-7) from ANG I and ANG II (Adopted from (Aronson and Ferner, 2020).

IL-2, IL-17 Interferon-γ and the TNF's) are raised during a cytokine storm that occurs in patients with severe COVID-19 (Bizzarri et al., 2020; Cao et al., 2020b). The CD4-T lymphocytes are rapidly activated to become T helper-1 cells, which subsequently leashe out a cytokine storm in the lung interstitium and elevates the levels of IL-6 and other cytokines in COVID-19 patients (Mehta et al., 2020; Bizzarri et al., 2020). Oxygen exchange is infiltrated by a large number of inflammatory cells (Bizzarri et al., 2020; Mehta et al., 2020). It is the opinion of some physicians that patients with such a disorder should be given drugs that inhibit IL-6 such as tocilizumab (Bizzarri et al., 2020; Mehta et al., 2020) or down regulate the action of IL-6 by the use of myo-inositol (Bizzarri et al., 2020). It is further known that rheumatoid flare up is also associated with COVID-19 disorders through the cytokine storm in which there is a rise in IL-6 and it is also known therefore giving such patients either myo-inositol or tocilizumab may be helpful (Georgiev, 2020). Cao et al. (2020a,b) have suggested to inhibit IL-17 with the IL-17 inhibitor, *secukinwmab*, but extensive investigations first need to be done (Cao et al., 2020b). We doubt there being any success because a whole list of cytokines are involved in SARS-CoV-2 infection.

6. Use of anti-viral agents for the management of COVID-19

Agrawal et al. (2020) suggested that the use of certain antiviral agents to be beneficial for COVID-19 infections (Agrawal et al., 2020). One of these is neuraminidase inhibitors, which work prophylactically against influenza, another is protease inhibitors used to treat HIV infections and the third group is the use of antimalarial compounds (Agrawal et al., 2020).

6.1. Protease inhibitors

Protease inhibitors are used to treat HIV patients. Cao et al. (2020a, b) conducted a clinical trial with Lopinavir-Ritonavir (LP/r) mixture (400 mg-100 mg) twice daily for 14 days with standard care (n = 99) or standard care only (n = 100) (Cao et al., 2020a). The trial found that there was no significant difference between LP/r mixture and standard care. The authors recommended further trial be conducted possibly by adding another antiviral medication. However, in a separate study, Ye et al. (2020) could not verify their findings, because of the small sample size of the control group *vs* the test group, although they observed that the LPV/r group performed better than the control group (Ye et al., 2020).

Another patient was successfully treated against COVID-19 infection with Lopinavir-Ritonavir mixture (400 mg-100 mg) in Korea (Lim et al., 2020). A group of researchers tried a mixture of protease inhibitors, lopinavir/ritonavir (LP/r) with an antiviral agent, arbidol, which is used to treat patients with influenza and LP/r to treat COVID-19 patients (Deng et al., 2020). This group observed that COVID-19 patients did better when arbidol was combined with LP/r than those who received LP/r on its own (Deng et al., 2020). A mixture of protease inhibitors (LP/r) against an antiviral agent (Arbidol) on its own have been used to treat COVID-19 patients (Zhu et al., 2020). It has been found that arbidol given on its own was better than LP/r mixture in COVID-19 patients (Zhu et al., 2020).

6.2. Nucleoside analogues

One such drug is remdesivir (GS5734) and it proved to be an effective treatment for the Ebola virus (Gordon et al., 2020; Cao et al., 2020b). It is an RNA-dependent RNA polymerase (RdRp) inhibitor drug (Cao et al., 2020b; Gordon et al., 2020). Wang et al. (2020a,b), tested both chloroquine and remdesivir for SARS-CoV-2 for their efficacies in an *in vitro* model of SARS-CoV-2 cell lines and they found that both were effective against the replication. These workers therefore suggested their use in the treatment of COVID-19 patients (Wang et al., 2020a,b).

Clinical Trials on the use of Remdesivir were carried out in COVID-19 patients (Cao et al., 2020b; Gordon et al., 2020). In addition, the WHO indicated that remdesivir had a great potential and could be the best drug for COVID-19 patients. Hillaker et al. (2020) got an approval from the hospital where a patient was admitted for COVID-19 to use remdesivir on compassionate grounds (Hillaker et al., 2020). This is because the patient was being maintained with hydroxyquinoline for 5 days without success and remdesivir was begun on day 9 of being hospitalized i.e. 13 days after the onset of symptoms, this patient made a remarkable recovery 60 h later when the patient was extubated (Hillaker et al., 2020). Therefore, late initiation of the use of remdesivir can be useful unlike other drugs (Hillaker et al., 2020). Ko et al. (2020) put forward ideas for approval and use of remdesivir for COVID-19 patients (Ko et al., 2020). Of the 53 patients, data were analysed at baseline, 30 patients received mechanical ventilation and four received extra corporeal mechanical oxygen (EXMO). After completing treatment with remdesivir, there were seven deaths and the rest were discharged (Grein et al., 2020). In a mini review of the use of remdesivir, Li et al. (2020a,b) cautions against the use of remdesivir in COVID-19 patients on the following grounds: its safety in use in COVID-19 patients require high powered, well designed, and robust clinical trials, despite the drug being used on compassionate grounds. In addition; based on the inclusive use of drugs during SARS-CoV and MERS-CoV outbreaks, the use of remdesivir should not be overestimated and finally, further explorations are urgently required on the use of drugs in COVID-19 patients in order to bring SARS-CoV-2 outbreak to rest (Li et al., 2020a,b).

However, the use of remdesivir on compassionate grounds and its use in clinical trials involving small numbers of patients, the WHO on November 2020, recommended against the use remdesivir based on the results of the Solidarity Trial as well as three other randomized controlled trials. In all, an expert panel considered data from over 7000 patients across four trials. This expert panel suggested no important effect on mortality, need for mechanical ventilation, time for clinical improvement and other important outcomes (World Health Organization, 2020e).

7. Anti-malarial compounds

7.1. Chloroquine and hydroxychloroquine

The in vitro models showed that both chloroquine and hydroxychloroquine have antiviral activity (Yao et al., 2020). In these in vitro models, both antimalarial drugs were found to decrease viral replication in a concentration dependent manner (Yao et al., 2020). However, in these in vitro model's hydroxychloroquine was found to be superior to chloroquine (Yao et al., 2020). Therefore, in these in vitro models, compared to chloroquine, hydroxychloroquine showed a better anti-SARS-COV-2 activity (Yao et al., 2020)

Gautret et al. (2020), tried treating COVID-19 patients with hydroxychloroquine and azithromycin in an open label non-randomized clinical trial (Gautret et al., 2020). In this study, the patients were divided into two groups; those receiving hydroxychloroquine (n = 20) and the control (n = 16). Among the hydroxychloroquine patients, six received azithromycin. At the end of this trial, these researchers found that 70 % of those treated with hydroxychloroquine were free of any viruses compared to 12.5 % in the control group. Those who were treated with hydroxychloroquine and azithromycin were 100 % free of COVID-19 infection (Gautret et al., 2020). Comparing those who received only hydroxychloroquine with those who received both hydroxychloroquine and azithromycin 57.5 % vs 100 % (Gautret et al., 2020). This study, in the authors view is NOT a clinical trial as the of number COVID-19 patients seem too small in the experimental and in the control groups to reach any conclusion and being non-randomised adds further to the complexity.

However, reports state that chloroquine and hydroxychloroquine are ineffective in treatment of COVID-19 patients and suggest that a properly powered control trial be conducted to state the benefit prior to

stating that chloroquine and hydroxychloroquine are of benefit in treating COVID-19 patients (Ferner and Aronson, 2020). Recently, a randomised clinical study in Brazil used a high dose and low dose Chloroquine in COVID-19 patients with acute severe respiratory syndrome and all patients also received ceftriaxone and azithromycin (Borba et al., 2020). These researchers found that the usage of high dose chloroquine was toxic and recommended that its usage should be discontinued, however, since all patients were also on azithromycin it became difficult to state whether azithromycin or high dose chloroquine caused the toxicity (Borba et al., 2020). Furthermore, these researchers also commented that this trial did not have a placebo control group and the sample size was too small to reach a conclusion (Borba et al., 2020). In addition, to Fihn et al. (2020) stated : "Science poorly conducted or poorly reported is counter to the public interest"(Fihn et al., 2020) Mehra et al. (2020) reported their findings of a multilateral task team who investigated the use of chloroquine, hydroxychloroquine with or without a macrolide for treatment of COVID-19 patients 48 h following admission (Mehra et al., 2020). These researchers observed that each of the drugs with or without a macrolide used in the trial were associated with increased risk of in-hospital mortality (Mehra et al., 2020). From these observations the authors concluded that these drugs should not be used outside the trial regiment (Mehra et al., 2020).

8. Artemisia annua and anti-malarial compounds

Stebbings et al. (2016), described Artemisia *annua,* as a plant grown in temperate China. The Chinese as traditional medicine have used the extracts, called artemisinin, for more than 2000 years as antimalarial, fever and as anti-inflammatory agents (Stebbings et al., 2016).

According to the Chinese belief, the extracts called artemisinin derived from the plant have anti-inflammatory properties as well, and used artemisinin as a medication for osteoarthritis (Stebbings et al., 2016). In 1985, Artemisia annual was reviewed extensively (Klayman, 1985). According to Klayman (1985), the active ingredient (artemisinin) was extracted in the USA from Artemisia annua. The aerial portions of the plant were used to extract artemisinin (Klayman, 1985). However, no side effects or liver abnormalities have been stated (Klayman, 1985). A few years prior to him, artemisinin (qinghaosu) was compared with mefloquine for their antimalarial properties and it was found that although mefloquine effectively cured malaria in a single dose, qinghaosu had a more rapid action and it also cured the infection (Jiang et al., 1982). However, Mohamed et al., 2020 discussed natural substances e.g. artemisinin and compared its actions against modern medicines, the former have fewer side effects, less costly and affordable and can be used to fight several illnesses (Mohammadi et al., 2020). According to the editorial in the journal Travel Medicine, the Chinese used artemisinin derivatives, which is a plant extract from Artemisia annua.

Since artemisinin has antimalarial properties and it can also be used for COVID-19 patients as perhaps it was used for SARS-CoV and MERS-CoV (Schlagenhauf et al., 2020). Artemisia annua is now being used to make "tea" and this extract is thought to cure COVID-19 patients. However, "WHO urges extreme caution over reports touting the efficacy of such products. As explained in a WHO position statement, there is no scientific evidence based to support the use of non-pharmaceutical forms of *Artemisia* for the prevention or treatment of malaria (Max-- Planck-Gesellschaft., 2020). There is also no evidence to suggest that COVID-19 can be prevented or treated with products made from *Artemisia*-based plant material." However, the Chinese claim that it was used for treatment of SARS-CoV and MERS-CoV (Max-Planck-Gesellschaft., 2020).

9. Bacille Calmette-Guérin (BCG) vaccination and COVID-19 patients

Whilst BCG vaccination protects one from tuberculosis, it also offers other non-specific effects such as protecting an individual from other

infections as well as enhancing immunogenicity of certain other vaccines e.g., influenza (Miller et al., 2020). In many countries of the world it was compulsory to be vaccinated against tuberculosis (TB) infection whilst other countries revoked this requirement (Miller et al., 2020). These phenomena could explain why in some countries the SARS-CoV-2 infection rate and the degree of infection were high whilst in other countries the incidence of SARS-CoV-2 infections was lower (Miller et al., 2020). The BCG vaccination may offer some sort of protection against SARS-CoV-2 infection; since a country such as Italy, which has a high SARS-CoV-2 infection and death rate and never implemented a universal BCG coverage with Japan, which has been implementing a universal BCG vaccination since 1947. Moreover Japan has not been implementing a strict social isolation programme (Miller et al., 2020).

Berg et al. (2020), has also indicated that BCG universal immunization "herd immunity" helped in flattening the curve of SARS-CoV-2 infection (Berg et al., 2020). The growth rate of SARS-CoV-2 infection was slower in countries, which had mandated BCG immunisation policy compared to the countries, which lacked this policy. Furthermore, death rates from contracting the SARS-CoV-2 virus was significantly less in countries that had a mandated BCG policy compared to countries without such policy (Berg et al., 2020). However, trials on the use of BCG vaccines and its role in protection against SARS-CoV-2 infection is presently underway and is being led by the Max Planck institute and Serum Institute of India (Lawton, 2020). In addition, BCG trails have also commenced in Netherlands and Australia (Lawton, 2020). However, the pulmonary pathology seen in SARS-CoV is not caused by SARS-CoV *per se* but it is due, perhaps, by other mechanisms such as cytokines and other mechanisms caused by the viral infection proximal to but not necessarily within the lung tissue itself (Ksiazek et al., 2003).

10. Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: their role in Covid-19 and should individuals prescribed these drugs continue taking them

The renin-angiotensin-aldosterone system plays an important role in cardiovascular and renal physiology and pathophysiology (Abassi et al., 2020). Following the SARS-CoV episode of 2002–2003, it was concluded that Angiotensin II is the chief effector substance with vasoconstrictor, profibrotic and proinflammatory properties. Therefore, ACEi and ARBs play an important role in maintenance of normal blood pressure (Hamming et al., 2007). Abassi et al. (2020) also associated SARS-CoV-2 infections in Italy, United States of America, and China with myocardial abnormalities such as myocarditis, myocardial infarction, and worsening heart failure (Abassi et al., 2020). Although pneumonia is a prominent feature of SARS-CoV-2 infection, it may be related to the cardiovascular abnormalities (Abassi et al., 2020). ACE-2 receptors have a high affinity for ANG II, converting ANG II to ANG-(1–7) which has vasodilatory, natriuretic/diuretic, anti-inflammatory and antifibrotic effects via Mas receptors (Masr). Therefore, overexpression of ACE-2 receptors in cardiac tissue of spontaneously hypertensive rats led to decreased cardiac remodelling by the presence of decreased left ventricular wall thickness and perivascular fibrosis (Abassi et al., 2020). The binding of SARS-CoV-2 virus to ACE-2 receptors causes the cell to internalize both ACE-2 receptors and the virus by cardiomyocyte, and a consequent reduction of ACE-2 receptors in the outer cell membrane of cardiomyocytes (Abassi et al., 2020). The importance of ACE-2 in cardiac physiology was highlighted by Crackower et al. (2002), who found that cardiac function was strengthened in ACE-2 knockout mice, in which ventricular wall thinning rather than hypertrophy occurred (Crackower et al., 2002). Similarly, SARS-CoV-2 viruses spread through the respiratory system including the lungs where it may cause pneumonia and ground glass appearance, the stomach and intestines causing diarrhoea, and the kidneys. Nevertheless, preliminary data from SARS-CoV-2 patients receiving either ACEi or ARBs have severe symptoms and high death rate compared to non-users of the medication (Abassi et al., 2020).

Patients prescribed either angiotensin converting enzymes inhibitors (ACEi) or angiotensin receptors blockers (ARBs) should continue taking these drugs despite contracting COVID-19 (Aronson and Ferner, 2020). The European Society of Cardiology recommends that COVID-19 patients, despite being hypertensive, diabetic or other cardiovascular complications, should continue taking these medications because currently there is no clinical or scientific evidence available to suggest that ACEi or ARBs should be discontinued if inflicted with COVID-19.

The renin-angiotensin-aldosterone system (RAAS) may be involved in COVID-19 patients, angiotensin converting enzyme (ACE) which converts angiotensin 1 to angiotensin 2 is mainly found in the endothelial layer of blood vessels of the pulmonary circulation (Busse et al., 2020). In severe cases of lung injury, which occurs during COVID-19, it is expected that the level of ACE would fall (Busse et al., 2020). This may compromise the patients with very low levels of ACE from functioning, which can thus be an independent factor to mortality (Busse et al., 2020).

The SARS-CoV-2 viruses uses the ACE-2 receptors in the lung parenchyma and in other organs and the cellular protease, transmembrane serine protease 2 (TMPRSS2), to enter a given cell (Busse et al., 2020; Aronson and Ferner, 2020). Thus, ACE-2 and the protease enzyme TMPRSS2 are both essential for the viral entry into a given cell (Aronson and Ferner, 2020). However, there is no direct evidence showing ACE-2 and susceptibility to the degree in COVID-19 patients (Guo et al., 2020).

Since both ACE-2 and ACE are of two types of receptors on the same cell surface in many tissues, especially the lungs, this may mean that if ACEi or ARBs are given to COVID-19 patients, theoretically the level of ACE-2 might increase thus allowing more virus entry into a given cell (Aronson and Ferner, 2020). However, in the presence of increased ACE-2 levels (in COVID-19) more ANG II may be converted to ANG-(1–7) a peptide which leads to vasodilation of blood vessels (Fig. 1) (Aronson and Ferner, 2020). In addition, endogenous ANG II polypeptide prevents SARS-CoV-2 in the following ways: It (ANG II) may bind with ACE2 to form ANG-(1–7) which causes vasodilatation and thus competing with SARS-CoV-2 for ACE-2 receptors. The binding of ANG II to AT1 receptors may cause internalization and down regulation of ACE-2 receptors (Koka et al., 2008) and its destruction through lysosomes.

However, it is also believed that withholding treatment with ACEi and ARBs from individuals with SARS-CoV-2 infection, which causes in some cases hypertension or diabetes for a few weeks may not do harm to the COVID-19 patients and ACEi and ARBs may be replaced with other anti-hypertensive drugs such as calcium channel blockers (Esler and Esler, 2020; Fang et al., 2020). However, both ACEi and ARBs are prescribed medications worldwide and guidance on the use of these drugs in COVID-19 patients is urgently required (Vaduganathan et al., 2020). There is also concern that withdrawal of RAAS inhibitors may be harmful in certain high risk or suspected patients with COVID-19 (Vaduganathan et al., 2020). Recently, a retrospective study of hypertensive patients taking ACEi or ARBs or without taking these drugs had a non-significant difference in the death rate between the two groups (Yang et al., 2020).

11. New variants of SARS-CoV-2 and COVID-19 vaccines

11.1. SARS-CoV-2 variants

A number of SARS-CoV-2 variants are circulating globally (World Health Organization, 2020a,b,c,d,e,f; Center for Disease Control (CDC), 2021). Initially according to WHO, SARS-CoV-2 coronavirus mutated to the variant D614 G in late January – early February 2020 (World Health Organization, 2020a,b,c,d,e). This variant eventually replaced the original SARS-CoV-2 (World Health Organization, 2020a,b,c,d,e,f). Since then the virus D614 G has mutated a few times. Across United Kingdom (UK), as of 26 December 2020, SARS-CoV-2 testing by authorities identified variant B.1.1.7. In the meantime authorities in South

Africa have identified a new variant and labelled the new variant B.1.351 (Tegally et al., 2020; Challen et al., 2021).

11.2. COVID-19 vaccines

Currently there are three types of COVID-19 vaccines viz mRNA vaccines, viral vectors and protein subunit vaccines which have been developed and used in clinical trials (Kaur and Gupta, 2020; Dhama et al., 2020; Wang et al., 2020b).

The Center for disease Control and Prevention (CDC) together with the Federal Drug Agency (FDA) in the USA have recommended three vaccines (Center for Disease Control (CDC), 2021):

- Pfizer-BioNTech is only available for ≥16 years, taken as two doses, three weeks apart.
- Moderna only available for ages ≥18 years taken as two doses, one month apart.
- Johnson & Johnson' Janssen for ages ≥18 years given as a single dose.

There is a considerable amount of data from COVID-19 vaccine trials that these vaccines are safe, effective and well tolerated with no serious safety concerns (Li et al., 2020a,b; Castells and Phillips, 2021). These vaccines have therefore received emergency authorization for vaccination programs world-wide (Li et al., 2020b).

We agree with the WHO that vaccines will help save millions of lives per year of death from COVID-19 disease and the UK has seen a substantial fall in COVID-19 infection rates since the initiation of its vaccine roll out program together with public health measures such as physical distancing, wearing of masks and hand sanitizing (World Health Organization, 2021). The WHO reports that since 18 February 2021, seven vaccines have been rolled out across three countries centres and at least 60 vaccines are undergoing clinical development (World Health Organization, 2021). However, at the time of writing this article, there have been two concerning developments in respect of COVID-19 vaccinations. Firstly. There has been the finding that SARS-CoV-2 has developed the ability to mutate and a number of variants have been found in South Africa (B.1.351), the UK (B.1.1.7), USA (B.1.526, and Brazil (P.1) (Mahase, 2021b). The concern has been whether the current vaccines given emergency authority will be effective against these new variants, which have been reported to be potentially more contagious and may avoid the immune system (Mahase, 2021b). It would seem that the present generation of vaccines (Pfizer, Moderna, Astra-Zeneca, Johnson and Johnson) are probably effective against the mutations found in South Africa and the UK, in preventing severe disease (Mahase, 2021b).

The second new development that is a concern for COVID-19 vaccination programs is the finding of thrombotic effects in participants below the age of 50 years who received the Astra-Zeneca and Johnson and Johnson COVID-19 vaccines. These thrombotic effects only occurred in about 1 in a million individuals (Mahase, 2021a). However, there is a report released in Europe stating that Astra-Zeneca had no association with increased blood clotting (Dyer, 2021). The actual reason this thrombotic side-effect is currently unknown. However, some reports suggest a severe allergic response to a chemical agent called polyethylene glycol which is used in the mRNA vaccines which has not been used in the manufacturing of vaccines previously. The Janssen vaccine which contains polysorbate 80, has raised similar concerns (Dyer, 2021).

Vaccine programs are a major pathway to overcome the COVID-19 program and is highly likely that any temporary pause to the use of Janssen will be re-instated with precautionary measures to ensure that detailed history be taken about allergies (The New York Times, 2021). It is important for the government to take measures to provide full information on the vaccine concerns, so as to overcome "vaccine hesitancy" in the general public (Kim et al., 2021).

12. Conclusion

We are, presently, of the view that it is unknown in whom; SARS-CoV-2 would cause commobilities, such as hypertension, shock or cardiovascular abnormalities, diabetes and renal failure. We believe that withholding any treatment or substituting with alternates should not be done as soon as diagnosis of COVID-19 is made. Perhaps treating with a vaccine may be more ideal than withdrawing a set of drugs such as RAAS inhibitors, which have been proven to work in hypertension, shock, gastrointestinal or renal problems. Finally, there is new reports of three vaccines with efficacy rates of over 90 %. The vaccines, however, will have challenges in LMICs. Not only because of distribution of limited supplies but also because they require two injections, a month apart and at least one of the vaccines needs to be frozen at 70 °C (Pfizer BioNTECH). There are challenges particularly for countries in Sub-Saharan Africa.

Author's contribution

Professor Gathiram contributed to the planning, designing and writing of the review.

Professor Moodley contributed to the structure, writing and editing of the review.

Dr Khaliq contributed to editing, writing and formatting of the review.

Declaration of Competing Interest

The authors report no declarations of interest.

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