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A comprehensive review on rational and effective treatment strategies against an invisible enemy; SARS Cov-2 infection

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ABSTRACT

The year 2020 is began with the declaration of a pandemic of novel coronavirus, which first occurred by the end of 2019 in Wuhan region of China. The novel virus infection is so called as Covid-19 or SARS Cov-2. The infection rapidly spread all over the world and changed the lives of millions. In this extended review, we aimed to discuss current and possible treatment strategies against SARS Cov-2 infection. Treatment options mentioned here include but not limited to chloroquine/hydroxychloroquine, favipiravir, remdesivir, lopinavir/ritonavir, umifenovir, steroids, cepharanthine, convalescent plasma, anticoagulants and monoclonal antibodies. In conclusion, mainstay of the SARS Cov-2 treatment is general measures such as patient isolation and supportive care. However, encouraging developments are being achieved in terms of discovery of an effective treatment and production of a potent vaccine.

Keywords: Covid-19, SARS Cov2, treatment, vaccine.

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Introduction

By the end of 2019, a new pandemic of coronavirus (Covid-19 or namely, SARS Cov-2) arose from China and rapidly spread to the rest of the world. It is not only an important infectious disease but also a concern of public health emergency [1]. Angiotensin-converting enzyme 2 (ACE2) receptors play important role in the infection since surface spike proteins of the virus bind to these receptors and enter the human cells [2]. Type II alveolar cells in the lungs express ACE2 receptors, therefore, devastating effects of the infection mainly occur in the lungs [3]. Heart, kidneys, vascular endothelium and intestinal epithelium also express ACE2 which could be the underlying mechanism of multiorgan dysfunction and micro-thrombi formation that caused by SARS Cov-2 [4,5]. Although the SARS Cov-2 infection could be asymptomatic, about 15% of the patients complicate with the severe course of the disease [6]. The infection could begin with flu-like symptoms. Indeed, nearly 2 or 3 of every 4 subjects that have positive RT-PCR throat swab results remain without symptoms and only in 10% of the symptomatic patients develop dyspnea, interstitial pneumonia, ARDS and/or multiorgan dysfunction [7]. Fever,

headache, myalgia, fatigue, rhinorrhea, cough, mild dyspnea, sore throat and conjunctivitis are common symptoms of the disease [8,9], which all seen in other respiratory conditions as well. Rare presentations of the infection include diarrhea, nausea and vomiting [10]. Determining the mortality rate of SARS Cov-2 infection is difficult since it might be an earlier period of the pandemic, however, Jiang et al reported the mortality rate of the disease was 3% [11]. Although this rate is lower than previous coronavirus infections; severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), which have mortality rate of 10% and 35%, respectively, elderly population and subjects with chronic diseases (i.e. diabetes mellitus, hypertension, heart failure, coronary heart disease) tend to have more serious clinical course and increased risk of death. As of 29th of September in 2020, 33,249,563 people infected with Covid-19 and 1,000,040 of them died in the whole world [12]. More than half of the cases (16,434,186) and deaths (551,313) were reported from North and South America [12]. Unluckily, to date, there is no proven and effective treatment against SARS Cov-2 infection [13]. However, several drugs and attempts to develop a vaccine are on the way.

The purpose of this review is evaluating the current experimental and clinical treatment options of SARS Cov-2 infection, as well as focusing the attempts on developing an effective vaccine for the disease.

Current treatment option of SARS Cov-2

Oxygen supplementation
This is an important step in the management of SARS Cov-2 after obtaining protective measures such as isolation of the patients. A number of subjects with SARS Cov-2 may develop hypoxemia during the course of the infection. Supplemental oxygen is indicated if the oxygen saturation drop below 93% or in cases with evident respiratory distress [10]. Face mask, nasal cannula or non-invasive ventilation are the routes of oxygen therapy [14]. Prone positioning may be useful in oxygen supplementation [15]. Indeed, most of the patients in critical care may respond well to prone positioning [14,16]. Endotracheal intubation is evitable when the oxygen saturation is not reached to target levels.

Chloroquine/hydroxychloroquine
Chloroquine and Hydroxychloroquine are antimalarial drugs which are also used in rheumatologic diseases. They have immunomodulatory effect and were used against SARS and MERS since they reduced viral replication [17,18]. Hydroxychloroquine is useful in the treatment of autoimmune disorders (i.e. rheumatoid arthritis and Sjögren's syndrome) since it decrease the serum levels of inflammatory cytokines [19]. These effects of the drug might be promising in the severe form of SARS Cov-2, which is associated with cytokine storm.

The first human Covid-19 study about the efficacy of chloroquine showed that duration of the symptoms and severity of the pneumonia was reduced in subjects treated with chloroquine [20]. In a following study, authors compared the nasopharyngeal viral clearance on 6th day of the subjects received hydroxychloroquine or hydroxychloroquine plus azithromycin to the controls and reported higher clearance rate in subjects received hydroxychloroquine plus azithromycin (100%) than the patients received hydroxychloroquine alone (57%) and the controls (12.5%) [21]. However, the efficacy of these drugs against SARS Cov-2 infection is controversial. Wang

et al. and Colson et al reported that chloroquine was effectively reduced viral replication in an in vitro study [18,22]. Moreover, antibiotic treatment to prevent bacterial infection is lack of evidence [10].

These drugs' antiviral effects are driven by the immunomodulatory effects, by increased cytoplasmic pH and by glycosylation of cellular receptors of the virus [22]. Glycosylation of cellular receptors may prevent viral binding to ACE2 receptors [23,24]. Both chloroquine and hydroxychloroquine act similarly and prevent the membrane fusion by changing the pH of acidic intracellular organelles (endosome, lysosome) [19]. Therefore, authors believe that these agents could be effective in treatment of SARS and SARS Cov-2 infections [18,25].

Sialic acid, which is a monosaccharide required for ligand recognition and is a part of receptors that used as ligand by coronaviruses and orthomyxoviruses [19]. Chloroquine prevents the synthesis of sialic acid by inhibiting the enzyme quinone reductase-2 [19]. This inhibition could be responsible of the broad antiviral effects of chloroquine [19]. Moreover, chloroquine interferes with the virion budding of SARS Cov-2 via inhibition of MAP-kinase molecular crosstalk [18,22].

In vitro studies showed that hydroxychloroquine is superior to chloroquine in inhibition of SARS Cov-2 infection [26,27]. Beside effectiveness, chloroquine also provides an affordable treatment for the infection, since it is inexpensive. A Chinese consensus report that published in February 2020, declared that chloroquine 500 mg twice daily for ten days was recommended for SARS Cov-2 pneumonia [28]. Netherlands control of disease control also recommended treatment with chloroquine, but only for those that necessitate hospitalization, oxygen supplementation or intensive care support [29]. Moreover, an Italian guide by

Italian Society of Infectious and Tropical disease also suggest treatment with chloroquine or hydroxychloroquine for 10 days for patients with SARS Cov-2 infection [30]. In addition, a Korean task force recommended chloroquine or hydroxychloroquine in treatment of moderate and severe SARS Cov-2 cases [31]. Despite both 500 mg twice daily chloroquine and 200 mg twice daily hydroxychloroquine are suggested as effective treatments for SARS Cov-2 [1,32], optimal therapy requires a loading dose before maintaining dose [33].

Side effects of chloroquine include QT interval prolongation in electrocardiography, hematological disorders (anemia, leukopenia, and thrombocytopenia), elevation in liver enzymes, serum electrolyte disturbances, elevation in renal function tests and visual deterioration. QT prolongation is the most important side effect and this side effect may be potentiated by concomitant use of other drugs that increase QT interval, such as, macrolide antibiotics, antiarrhythmic agents, antidepressants, antipsychotics, ondansetron and quinolones. Therefore, close monitorization of the patients regarding hemogram and ECG is advised.

Favipiravir

Favipiravir is a purine nucleic acid analog that target RNA viruses by potently and competitively inhibiting the RNA-dependent RNA polymerase [34].

Favipiravir is very effective against infections with influenza A, B and C viruses that resistant to oseltamivir [35]. Novel studies reported its efficacy in treatment of SARS Cov-2 infection [36]. In addition, in vitro studies suggested its efficacy against SARS Cov-2 [22,37]. In a study from China, authors reported that duration of viral clearance of SARS Cov-2 was reduced in patients received favipiravir

compared to those subjects received lopinavir/ritonavir [38]. Moreover, in the same study, radiological improvement rate on day 14 was higher and side effect rate was lower in favipiravir group compared to the patients received lopinavir/ritonavir treatment [38]. Therefore, it has been recommended in the management of this infection in China [39] and in Turkey [40]. Despite there are currently no randomized controlled clinical trial with large cohort about the efficacy of favipiravir in the treatment of SARS Cov-2, studies are on the way about this topic [39].

Starting dose of favipiravir is 1600 mg two times on day 1, 600 mg two times a day on 2nd to 5th days and 600 mg once a day on 6th day of the treatment [39]. Adverse effects of favipiravir include increase in serum uric acid levels, elevation in hepatic enzymes and gastrointestinal discomfort [38,41,42].

Remdesivir
Remdesivir is a nucleotide analogue that promote early termination of the viral RNA transcription by incorporation into genetic material of the virus [10]. Apart from other antiviral agents classified as nucleotide analogues, it has broad antiviral spectrum including Pneumoviridae Filoviridae, Paramyxoviridae, and Orthocoronavirinae (i.e. coronaviruses that cause SARS and MERS) families [43,44]. In an animal study, Remdesivir improved organ functions and decreased viral load in mice with MERS infection [45]. Moreover, it has evident antiviral effects against SARS and MERS infections [46]. Good responses achieved with Remdesivir in the treatment of some patients with SARS Cov-2 in China, where the outbreak of Covid-19 first started [47]. In a case report from United States, it was reported that Remdesivir was effective in treatment of a

patients with SARS Cov-2 pneumonia [48]. In a recent study, Remdesivir was suggested to be superior to placebo in achieving shorter recovery duration [49]. Furthermore, clinical improvement was noted in 65% of the subjects with severe SARS Cov-2 infection whom received remdesivir treatment [50]. However, a Chinese study reported that Remdesivir was not superior to placebo in terms of duration between drug initiation and clinical improvement [51].

Serious adverse reactions, including rectal hemorrhage, liver toxicity, and nausea and vomiting, have been reported relate to remdesivir [39]. Although these adverse events upraise questions about Remdesivir in treatment of SARS Cov-2, it has great in vitro efficacy against the virus [43,48]. An initial 200 mg/day of Remdesivir which followed 100 mg daily on 2nd day and after is advised in treatment of SARS Cov-2 infection [39].

Lopinavir/ritonavir
Protease inhibitors are drugs that developed for the treatment of human immunodeficiency virus (HIV) infection. New generation protease inhibitor, the combination of lopinavir and ritonavir, also shows its effect through inhibition of viral protease [10]. Papain-like protease and 3C-like protease in coronaviruses are target enzymes for protease inhibitors [52]. Lopinavir/ritonavir was suggested to be useful in SARS infection [53]. Several studies in literature suggested that this combination reduced the viral load in SARS Cov-2 infected subjects [54,55]. However, the effect of lopinavir/ritonavir treatment against SARS Cov-2 is controversial. In a novel study, remdesivir was suggested to be superior to lopinavir/ritonavir and interferon-beta combination in terms of reducing viral load and the improvement of pneumonia in subjects with

MERS [45]. On the other hand, there are studies in literature that reported no benefit of lopinavir/ritonavir combination greater than standard medical care in SARS Cov-2 infection [56].

Authors speculate that serum level of lopinavir/ritonavir could be much lower than the required serum concentration to inhibit SARS Cov-2 replication [57]. Advised dose of the combination is 400mg/100mg twice a day. Sleeping difficulty, nausea, vomiting and diarrhea are reported adverse effects of the lopinavir/ritonavir.

Umifenovir

Umifenovir is an antiviral agent that has broad antiviral spectrum. The drug prevents viral entry by blockage of the fusion between the virus and the cell membrane. It blocks viral fusion with the target membrane, thus providing viral entry into target cells. Umifenovir is an indole derivate and its antiviral spectrum covers influenza viruses [58]. Therefore, it is approved in both treatment of and prophylaxis for influenza infections [59]. Authors retrospectively analyzed subjects with SARS Cov-2 infection according to hypoxic (mean age 70 years) and non-hypoxic (mean age 37 years) patients and reported that 58.2% of the non-hypoxic and only 33% of hypoxic subjects were treated umifenovir [60]. Moreover, it was concluded in the same study that 33% of subjects received umifenovir were discharged while 19% of the subjects that not received umifenovir discharged from the hospital, in other way to say, despite the mortality rate of the study population was 7.5%, none of the subjects received umifenovir were deceased [60]. It shall be speculated that umifenovir could increase the discharge rate and decrease the mortality rate in SARS Cov-2 infection, nonetheless, age difference between

study groups may confound the results of that study.

Another study with small population compared umifenovir and lopinavir/ritonavir treatment to lopinavir/ritonavir treatment alone in patients with SARS Cov-2 and found that umifenovir and lopinavir/ritonavir combination was superior to lopinavir/ritonavir alone according to viral clearance on seventh day, improvement in thorax imaging, and viral clearance on 14th day [61].

Reported side effects of the umifenovir include nausea, diarrhea and elevation in serum bilirubin levels [59]. Larger prospective cohort studies are needed to suggest for or against the use of umifenovir in the treatment of SARS Cov-2 infection.

Steroids

Steroids (or namely corticosteroids) are immunosuppressive and anti-inflammatory agents with a broad clinical usage in many disorders. Methyl prednisolone and dexamethasone are two frequently prescribed steroids in daily practice. The use of steroids in patients with severe SARS, MERS and influenza infections reported either no improvement or an increase in mortality rates [62-64]. These nonsuggestive evidences did not discourage researchers to study the effects of steroids in the novel coronavirus pandemic. However, there are conflicting study results in literature about treatment of SARS Cov-2 with steroids. The role of steroids investigated in a small population with SARS Cov-2 whom were treated in intensive care unit because of moderate-severe ARDS, and the results of the study revealed that steroids did not decreased mortality despite hypoxia was improved in the subjects [65]. Similarly, addition of the steroids in treatment regimen reduced the fever but did not decreased the mortality, nor reduced the

resolution duration of pneumonia, nor decreased the length of hospitalization of SARS Cov-2 patients in a meta-analysis [66]. Moreover, low dose of steroids in short course to prevent cytokine storm in SARS Cov-2 patients with disease progression did not alter the clinical outcome of the cases [67]. In contrast, Lee et al proposed early use of steroids in treatment of SARS Cov-2, since it could be difficult to reverse advanced ARDS in these subjects [68]. Indeed, authors reported that short term dexamethasone improved the outcome of the patients whom infected with novel coronavirus [69].

These evidences bring a question in mind whether steroids should be given in an earlier phase of the SARS Cov-2 infection instead of delaying to the advanced stage. The results of prospective studies on the way might answer this question successfully.

Cepharanthine

Cepharanthine is an alkaloid agent that used for alopecia in Japan for nearly 70 years [70]. Indications of the drug also include exudative middle-ear catarrh [70], leukopenia due to radiation [71], viper and other venomous snake bites [70], alopecia areata [72] and immune thrombocytopenic purpura [73]. It has also been effective against other coronaviruses that cause mild infection in human [74].

It has also been suggested that cepharanthine reduces nitric oxide production in macrophages and prevent cell death in septic shock [75]. Besides nitric oxide production, it decrease lipid peroxidation, reduces nuclear factor-kappa B activity, and inhibit cyclooxygenase pathway, thus, provide anti-inflammatory effects and improvement in vascular endothelium [76]. Cepharanthine decreases the serum levels inflammatory cytokines which include interleukin-1 beta, tumor necrosis factor alpha and interleukin-6, the inflammatory predictor that to treat SARS Cov-2 related cytokine storm [77]. Replication of human immunodeficiency virus is shown to be inhibited by cepharanthine more than 2 decades ago [78]. Moreover, its use against SARS Cov-2 and other viral infections is suggested by anti-inflammatory, immuno-modulating and anti-oxidative features of that phytomedicine [70,72]. Indeed cepharanthine was suggested to be an effective treatment option in SARS in 2005 [79].

Cepharanthine has both effects in pre and post entry stages of the SARS Cov-2 infection. It reduces viral RNA in post entry phase [80]. In addition viral replication is also inhibited by cepharanthine [81].Moreover, authors showed that cepharanthine has inhibitor effect on S glycoprotein of SARS Cov-2 virus, which is essential for the virus entry to human cells [82]. Its utility in novel pandemic is also being investigated since SARSCov-2 has great homology with SARS in terms of genomic features. An animal study revealed that it was successful in treatment of SARS Cov-2 infection [80]. It has been reported in an unpublished cell culture model study that it has great efficacy against SARS Cov-2 [83]. Cepharanthine was proposed as a drug that has antiviral activity against SARSCov-2 [84], however, clinical human studies in randomized controlled trial form are required to demonstrate its efficacy in the treatment of SARS Cov-2 patients.

Convalescent plasma

Plasma of a patient who healed from an infection contains antibodies against a certain microorganism. Infusion of this plasma to another person suffering of the same infection is called as convalescent plasma therapy, which is a form of passive immunotherapy [59].

Convalescent plasma therapy was used in previous viral infections, such as, influenza, SARS and Ebola [85,86]. Authors speculate that this treatment option might reduce mortality in severe viral respiratory infections, however, the majority of the studies suggesting convalescent plasma treatment were low quality reports without a control group [87]. Plasma of the patients that recovered from SARS Cov-2 is being used in the treatment of the disease. The FDA was approved its emergency investigational use in subjects with severe SARS Cov-2 infection [88]. In a case series, convalescent plasma found to improve clinical symptoms and to promote resolution of ARDS in SARS Cov-2 patients [86]. A case report including two patients from Korea revealed that clinical improvement and radiological resolution were achieved with plasma therapy [89]. In a study with small cohort, it was suggested that convalescent plasma was improved outcome of the patients with SARS Cov-2 [90]. These data suggest that convalescent plasma treatment may be useful in SARS Cov-2 infection; however, studies with larger population are needed to confirm its effectiveness in the treatment of the disease. Adverse reactions related to plasma therapy include transmission of disease, circulatory overload, allergic reactions and transfusion associated lung injury [91].

Antibiotics
During SARS Cov-2 infection, the rate of co-infections with other microorganisms could be as high as 50% [39]. Influenza A virus is the most commonly reported virus that cause co-infection [92]. Other causes of co-infection include various bacteria (including M. pneumonia), fungi (Candida spp.), and viral pathogens (other coronaviruses, rhinovirus, human immunodeficiency virus) [39]. At the

early stages of the pandemic, antibacterial and antiviral agents against influenza were frequently added in the treatment regimens against SARS Cov-2. Moreover, patients that hospitalized for a week or longer may require effective antibacterial therapy against pneumococci, S. aureus, K. pneumonia, Pseudomonas spp. and Acinetobacter Baumanii [93,94].

Azithromycin is a macrolide antibacterial agent which prevents concomitant bacterial infections during viral respiratory infections [95]. Moreover, it has antiviral effects in vitro, suggested by Madrid et al, in 2015 [96]. During SARS Cov-2 pandemic, it was used along with hydroxychloroquine in treatment of patients in severe condition and triggered good clinical outcome [21]. Azithromycin may increase liver enzymes and combination with hydroxychloroquine warrant more attention on prolongation of QT interval in electrocardiogram.

Teicoplanin, a glycopeptide antibiotic, could be a promising antiviral agent as well. Cathepsins L and B in human cells are responsible of the release of viral genome into the cytoplasm by cleaving viral proteins [97]. Teicoplanin inhibits the activities of both cathepsins L and B, specifically [24]. Indeed, it prevents viral entry in Ebola, SARS and MERs infections [98]. These data suggest that viral infections that require cathepsin L to enter human cells may benefit from treatment with teicoplanin and its derivatives: dalbavancin, telavancin, and oritavancin [94]. Nevertheless, we think that randomized trials on teicoplanin treatment in patients with SARS Cov-2 infection are needed to confirm its effectiveness against the virus.

Monoclonal antibodies
Monoclonal antibodies are developed and used against viral infections such as influenza, SARS

and MERS infections [43,99,100]. Exacerbation of rheumatoid arthritis is being treated with tocilizumab, a monoclonal antibody that prevents binding of interleukin-6 to its receptors [94]. It can also be effective in alleviating cytokine storm in patients with severe SARS Cov-2 infection. Therefore, its effectiveness in the treatment of the infection is being studied. In a study from China, authors suggested that tocilizumab was effective in treatment of cytokine storm during severe SARS Cov-2 infection [101]. Since cytokine storm occur in a significant amount of subjects with severe infection, tocilizumab could prevent this cytokine related damage and death by inhibiting the effects of interleukin-6 [102]. Nevertheless, evidence will accumulate about the role of tocilizumab in the treatment of the infection by growing experience on its use against SARS Cov-2.

Anticoagulant treatment

Besides sepsis induced coagulopathy, disseminated intravascular coagulation and venous thromboembolism (driven by prolonged inactivity) could occur as complications in all critically ill subjects, thrombotic complications are especially predisposed by severe SARS Cov-2 infection [59]. Coagulation system is triggered by inflammation and infection during SARS Cov-2 infection. Over activation of the coagulant factors in blood may result in ischemic events, thrombi formation and disseminated intravascular coagulation [103]. Indeed, the rate of thrombotic complications (myocardial infarction, ischemic stroke and arterial embolism) was reported as high as 31% in SARS Cov-2 subjects whom treated in intensive care unit [104]. A similar study from China reported 25% of venous thrombosis in cases with severe SARS Cov-2 [105]. Anticoagulation therapy is advised in earlier

periods of the SARSCov-2 infection especially when the d-dimer levels are higher than the four times of upper limit of normal range [10]. Other markers of pro-coagulant state in SARS cov-2 infection are increased fibrin degradation product levels, inflammatory predictors, and prolonged prothrombin time and activated partial thromboplastin time levels, which all related with the increased risk of mortality [106]. On the other hand, it is useful in patients with severe condition, too. A study by Tang et al suggested that heparin (mostly low molecular weight heparin) treatment was related with better prognosis and reduced mortality in severe SARS Cov-2 cases [107]. In contrast, both the durations of hospitalization and viral clearance of severe SARS Cov-2 patients received low molecular weight heparin were not different from the subjects that not received anticoagulant therapy [108]. Nevertheless, World Health Organization recommends heparin or low molecular weight heparin as a prophylactic treatment against venous thromboembolism in severe SARS Cov-2 patients [109]. Furthermore, not only intensive care population but also all hospitalized SARS Cov-2 subjects are suggested to be prescribed low molecular weight heparin if it is not contra indicated (i.e. active bleeding, a platelet count lower than 25000 per microliter) [110].

Other possible treatment options

Hepatitis C virus, several hemorrhagic fever viruses and respiratory syncytial virus are being treated with ribavirin, a nucleotide analogue. It has previously been used against SARS infection [111]. It was also proposed as an effective treatment option against SARS Cov-2 in a study from Saudi Arabia [112]. Moreover, authors supposed that ribavirin, as a direct anti-viral agent, could be used against SARS Cov-2 infection [113]. Reduction in blood hemoglobin

is the most important side effect of ribavirin which may limit its use since that is harmful in subjects with respiratory distress [44].

Interferon 1 beta is used in the treatment of MERS infection [111]. However, its effect against SARS was uncertain [52]. In a multicenter, prospective, open-labeled, randomized, phase 2 trial, 81 subjects enrolled to the treatment group that received combination of lopinavir 400 mg and ritonavir 100 mg twice daily, ribavirin 400 mg twice daily, and three doses of 8 million IU of interferon 1 beta on alternate days for 14-days while 41 subjects received lopinavir 400 mg and ritonavir 100 mg twice daily for 14 days and authors concluded that combination of lopinavir /ritonavir plus ribavirin plus interferon 1 beta treatment was superior to lopinavir/ritonavir treatment alone in shortening viral shedding duration, in reducing hospitalization time and in alleviating of the symptoms in mild to moderate SARS Cov-2 cases [114].

Melatonin has anti-inflammatory, anti-cancer and anti-oxidative properties. Acute lung injury and ARDS is prevented by melatonin [115]. Since it has high safety profile [116] and it reduces the risk of cytokine storm [117], growing data suggest that melatonin could be beneficial in treating viral infections, as well as SARS Cov-2 [115]. Authors found that increased activity of ACE2 might decrease the severity of the infection with respiratory syncytial virus [118]. On the other hand, statins improve endothelial functions which was deteriorated by viral infection, therefore, a combination with angiotensin receptor blocker and statin may enhance recovery of endothelium and facilitate healing of the patients own [119,120].

Nitazoxanide is an antiparasitic and antiviral drug with broad spectrum which is converted to its active form; tizoxanide following oral intake [121]. Five day course of treatment of influenza with nitazoxanide 600 mg twice daily has been suggested to be effective in relieving symptoms with mild adverse events [122]. Interferons alpha and beta production are upregulated by nitazoxanide. Therefore, its activity against MERS and other coronaviruses were tested and found to be effective in vitro [123]. Promising results of the drug in other viral infections drive a proposal that nitazoxanide could be used in early SARSCov-2 infection in adjunctive to azithromycin [124]. Moreover, authors compare the efficacy of hydroxychloroquine and hydroxychloroquine plus nitazoxanide in patients with SARS Cov-2 and expect better outcome in subjects received combination therapy [125]. Although it is a promising treatment alternative in novel coronavirus infection, controlled trials that suggest its efficacy in management of the disease is still lacking. Studies in recent years revealed the antiviral effects of ivermectin. It is an anti-microbial agent against parasitic infections, however, it has also broad range of antiviral effects. Ivermectin has been shown to inhibit replication of human immunodeficiency virus [126]. Subsequently, it was reported that ivermectin ameliorate the infections with influenza, West Nile, pseudorabies and dengue viruses [126,127]. In contrast, it has shown to be ineffective against Zika virus [128]. Caly et al showed in an in vitro study that ivermectin was potently inhibit the replication of SARS Cov-2 [127]. These encouraging results enabled the authors propose ivermectin as a promising candidate of SARS Cov-2 treatment [129]. On the other hand, randomized controlled trials should suggest the efficacy of the drug in order to recommend ivermectin evidently in the treatment of novel coronavirus pandemic.

Futuristic perspective

It is speculated that inflammation and tissues damage driven by ARDS might be ameliorated with mesenchymal stromal cells [130]. The interaction between viral proteins and ACE2 might be targeted in following research to develop effective treatment options [131,132]. Isolation and amplification of cytotoxic T lymphocytes against SARS Cov-2 would be beneficial in the treatment of the disease [133]. T lymphocyte mediated inflammatory pathway would be stimulated by canakinumab or roflumilast [134,135]. This list may be prolonged as the knowledge about the SARS Cov-2 virus grows.

Vaccines against SARSCov-2: Will full eradication be possible?

Effective prophylactic strategy in disease control and prevention of new cases could be achieved with the development of a successful vaccine, therefore, nearly 100 vaccine research is ongoing worldwide [136].

There have been 115 vaccine candidates worldwide as of the first half of April, 2020 [137]. As of 25 August 2020, 31 vaccines are reached the level of clinical evaluation and phase 3 trials have been initiated for six of the vaccine candidates [138]. These 6 vaccine candidtes are being developed by University of Oxford/AstraZeneca, Sinovac, Wuhan Institute of Biological Products/Sinopharm, Beijing Institute of Biological Products/Sinopharm, Moderna/NIAID, and BioNTech/Fosun Pharma/Pfizer [138].

Technologies used in the development vaccine against SARS Cov-2 include DNA, RNA, inactivated, live attenuated, non-replicating vector, protein subunit and replicating viral vector [139]. The first vaccine candidates are expected to be in clinical use by the end of 2020 or in 2021. This accelerated vaccine development race has some risks. If a vaccine stimulate production of antibodies against virus that not neutralize its infectivity, additional consequences may occur via increased viral replication or immune complex formation which accumulate in the tissues and attract inflammatory mediators and trigger complement system [140].

The first and the only confirmed vaccine by state health authorities against SARS Cov-2 is the Sputnik V vaccine of Russian researchers. The vaccine registered in 11th of August in 2020 and developed by Gamaley Epidemiology and Microbiology National Research Center in Russian Federation. Despite public opinion is diverse and trust to the vaccine is distinct in the world, results of the vaccine on volunteers are eagerly and excitedly being awaited.

There are currently over 169 COVID-19 vaccine candidates under development, with 26 of these in the human trial phase [141]. Of those, the phase 3 trial of the vaccine developed by Oxford University has been interrupted due to transverse myelitis, which developed in two of the volunteers, then the trial resumed by the developers [142].

Sputnik V SARS Cov-2 vaccine from Russia, Sinovac's Covid-19 vaccine from China, BioNTech and Pfizer's Covid-19 vaccine from Germany are some of the other vaccine candidates with ongoing phase III trials.

Novel developments in the subject

The U.S. Food and Drug Administration (FDA) decided to broad the scope of emergency use authorization of remdesivir to include treatment of all adult and pediatric SARS Cov-2 patients in hospital era regardless of the severity of the disease and both in confirmed and suspected cases [143]. Moreover, the Solidarity trial which was established by WHO, discontinued

the hydroxychloroquine and lopinavir/ritonavir arms due to little or no reduction in the mortality of hospitalized COVID-19 patients [144]. In addition, as of 31 August 2020, the efficacy of the investigational Covid 19 vaccine; AZD1222 has been started in 80 sites in United States involving 30000 volunteers [145]. Unusual and admirable efforts of the researchers continue to end the pandemic in the world.

The novel study about the role of corticosteroids in treatment of SARS Cov-2, namely, RECOVERY trial showed that mortality rates of the hospitalized Covid-19 patients who require supplemental oxygen or mechanical ventilation were significantly decreased with early initiation of corticosteroid treatment [146].

Conclusion

Millennium pandemic SARS Cov-2 is globally changed our lives and daily habits of our life. General measures such as patient isolation and supportive care are the mainstay of the SARS Cov-2 treatment. Luckily, encouraging developments are being achieved in terms of discovery of an effective treatment and production of a potent vaccine. We believe it is only a matter of time before we overcome the epidemic in cooperation.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical statement: Since this study is a review paper, no ethics committee decision was required.

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