ISSN: 2577 - 8005

Review Article

Medical & Clinical Research

Molecular Bases for Pharmacotherapy of COVID -19

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Submitted: 11 Apr 2021; **Accepted**: 19 Apr 2021; **Published**: 01 May 2021

Citation: *Anna Sh Archvadze, N. Gongadze, PhD, I Migriauli, Candidate K Chirakadze, T Mgeladze (2021) Molecular Bases for Pharmacotherapy of COVID -19. Medical & Clinical Research 6(5): 119-128.*

Annotation

The most large-scale challenge aroused at the beginning of Y2020 was the global spread of the coronavirus disease 2019 (COVID-19), caused by a zoonotic beta-coronavirus. One year after we have nearly 270 thousand confirmed cases with mortality rate 1.3% in Georgia, and almost 120 billion confirmed cases with mortality rate 2.2% worldwide.

As it is known, COVID-19 is triggered by coronavirus species 2 or SARS-CoV-2, which inters in the human body by binding to the angiotensin-converting enzyme 2 (ACE2) molecule on the host cell membrane via the viral spike protein and expresses complex pathological changes in many organs linked with vascular injuries. The most severe expression of this disease exposed by microscopic examination is bilateral diffuse alveolar damage with fibroblasts exudates, indicating Acute Respiratory Distress Syndrome (ARDS). Immune system plays crucial role in tissue damage. As clinical researches showed, the number of peripheral CD4+ and CD8 + T cells were significantly reduced, while their activity was hyper-expressed as evidenced by the high proportions of HLADR (CD4 3•47%) and CD38 (CD8 39•4%) double-positive fractions. Moreover, there was identified an amplified concentration of highly pro inflammatory CCR6+ Th17 in CD4 T cells. This date explains that severe tissue injury in later stages of COVID-19 is depend on the immune system abnormalities, but not on SARS-CoV-2 direct cell destruction.

In the same time the scientists and doctors found out abnormalities in coagulation function in most of the severe COVID-19 patients, which were expressed in elevation of D-Dimer level and prolongation of prothrombin time, some of whom terminated in disseminated intravascular coagulation (DIC), deep venous thrombosis (DVT) or fatal pulmonary thromboembolism (PTE). At the later stage in some severe patients it was identified thrombocytopenia as a result of excessive platelets consuming, which significantly affected on treatment and prognosis.

More than 300 drugs are used for the treatment of COVID-19 worldwide. Now, the most popular treatments include Remdesivir, Hydroxychloroquine, Betamethasone, Tocilizumab, anti HIV drugs, and convalescent plasma. In the same time, WHO supports vaccines distribution for immunization. Currently, almost 8 vaccines are approved by different countries and more than 180 vaccines are under the clinical trails.

Conclusion & Significance: *Up till now it is challenging problem to combat SARS-CoV-2 with not well-defined origin and inexplicable biological characteristics as well as to control a pandemic of COVID-19 with such a high R0, a long incubation period and different disease outcomes. Unfortunately, we have limited understandings of particular mechanisms running to abnormal expression of immune system and coagulation processes. In the same time, we don't have complete picture of vasculopathy leading to the tissue injury and patient death. Therefore, it is problematic to manage SARS-CoV-2 induced processes successfully using available drugs with no significant restoring effect on the organ damages in severe COVID-19 patients. So, we need new targets and new drugs for the prophylaxes and treatment of COVID-19 even we have vaccines available.*

Keywords: SARS-CoV-2, Cytokine Storm, Lymphopenia, Thrombosis, Thrombocytopenia, Vasculitis, ACE/ACE2, Vaccines.

Introduction

Coronavirus disease 2019 (COVID-19) is triggered by a zoonotic beta-coronavirus seventh encountered strain of the family Coronaviridae, and named as the newly emerging severe acute respiratory syndrome related coronavirus species 2 (SARS-CoV-2).

COVID-19 was suddenly recognized as a major health problem prompting the World Health Organization in January 2020 to declare an international public health emergency [1, 2]. One year after we have nearly 270 thousand confirmed cases with mortality rate 1.3% in Georgia, and almost 120 billion disease cases with mortality rate 2.2%. [3]. The existing public health strategies to diminish transmission are rapid identification of cases, isolation, contact discovering, and self-quarantine of those exposed. Once a person is exposed, observation and quarantine during 14-day incubation period is the standard of care. Till now, no medication has been specified to prevent SARS-CoV-2 transmission among population [4].

In general, COVID-19 is an acute curable disease but it can also be fatal. SARS-CoV-2 forms new type of respiratory infectious with complex pathological changes in many organs linked mostly with vascular damage. Basic reproductive number (Ro) has been identified to range from 1.4 to 4.0 in current studies, and similarly, case fatality rates for the disease varies substantially between countries ranging from 0.04% to 16.33% [3, 5-7]. Couse of death reported is massive alveolar damage and progressive respiratory failure [8, 9]. To check all of the death cases an estimated 84.1% of patients had presence of one or more comorbidity [10]. Early reports from China suggested that the COVID-19 mortality rate was highest (13.2%) among patients with cardiovascular disease (CVD) compared with other comorbidities, such as diabetes (9.2%) and hypertension (8.4) paralleled with around 1% for patients without such comorbidities [11, 12]. But, latest date obtained from different countries indicates slightly different rates. Namely, mortality rate is higher in patients with comorbidities of Hypertension (HTN) (27.4%), Diabetes (17.4%), compared patients with CVD (8.9%), COPD (7.5%). Major comorbidity specific to countries included in the study were China (HTN 39.5%), South Korea (CVD 25.6%), Italy (HTN 35.9%), USA (HTN 38.9%), Mexico, (Other 42.3%), UK (HTN 27.8%), Iran (Diabetes 35.0%) [10].

SARS-CoV-2 is enveloped, positive-sense, single-stranded RNA virus from Coronaviridae family, which typically causes mild or severe respiratory disease in human [13, 14]. Natural reservoir of Coronaviridae are certain bat species, but genetic adaptation of the zoonotic viruses in intermediate hosts seems to play a key role for crossing species genetic barriers and the subsequent transmission to humans. But up till now, we have not
exact information about intermediate hosts for SARS. There is some probability that civet cats and raccoon dogs are intermediate hosts for SARS but for SARS-CoV-2 pangolins might have served as such vectors, whereas camels play this role in MERS [15]. Genetically, SARS-CoV-2 is a bat origin and partially looked like MERS-CoV and SARSCoV. Particularly, clinical presentation and pathology of COVID-19 significantly resembled SARS and MERS, with less upper respiratory and gastrointestinal symptoms and more exudative lesions in post- mortems. But to differ from other similar viral infections, COVID-19 generally had a high reproductive number, a long incubation period, a short serial interval and low case mortality rate [16].

For the body penetration SARS-CoV-2 needs special molecule for the attachment on the host cell surface. Angiotensin-converting enzyme type 2 (ACE2) has been identified as a functional receptor allowing entry of the virus into host cell. ACE2 is normally highly expressed in the lung, heart, ileum, kidney, and bladder. In the lungs, ACE2 is greatly expressed on ciliated airway epithelial cells and alveolar type 2 pneumocytes as well as in the endothelial cells which comprise about a third of resident pulmonary cells [17].

Body response to the SARS-CoV-2 infection is highly complex. Generally, at the beginning the host immune system mediates inflammation and cellular antiviral response to inhibit viral replication and dissemination. Finally, the special antibodies and complement system eliminate viruses from the body. However, excessive immune response can be harmful leading sever organ damage. As the clinical data indicate, patients with SARS-CoV-2, and especially those requiring special care, have elevated plasma level of pro-inflammatory cytokines [17].

Endothelial injury is the common key lesion leading to organ failure. Some authors suggested that SARS-CoV-2 infection may facilitate direct endothelial destruction, but other researchers postulated that endothelities is a result of body inflammatory response to the viral infection [18]. In addition, the liver biopsy specimens of COVID-19 patients showed micro vascular steatosis leading to liver injury caused by either SARS-CoV-2 infection or drug toxicity [8].

Finally, Immune system responses to the virus depend on the antigen presenting cell function. Therefore, genetic polymorphism linked to the major histocompatibility complex (MHC) class I is crucial in antiviral response. The researchers suggested that genetic variability across the three MHC class I genes such are HLA-A, -B, and -C genes, may explain diversity and severity of the disease caused by SARS-CoV-2 [19].

Pathogenesis

Molecular mechanisms involved COVID-19 pathogeneses haven't been recognized completely yet. One-year careful observation and detailed analyses could not clarify completely diversity of disease manifestations. As the clinical researches identified, the pathological characters of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection [20]. Pathological analyses of lung tissues samples, generally obtained from autopsy material, indicated diffuse alveolar damage (DAD) with cellular fibromyxoid exudates, desquamation of pneumocytes and hyaline membranes, and all of the pathological findings of early stage of acute respiratory distress syndrome (ARDS). Moreover, edema, interstitial mononuclear inflammatory infiltrates and multinucleated syncytial cell with viral cellinjury like changes were also presented in the lung tissues [1, 21]. In Italy, the main pathological findings from 38 autopsies done were DAD, organizing pneumonia, reactive type II pneumocytes, ARDS and chromic interstitial pneumonia [1, 16, 22]. In more complex scenario was found in another autopsy

studies reporting complex immune and coagulation abnormalities expressed in systemic vascular damage and coagulopathies [1, 23, 24].

Immune System, Cytokine Storm vs Lymphopenia

In any infection disease for fighting with infection agent body activates immune system to provide cell meditated and antibody dependent immune response with involving a complementary system. As the SARS-CoV-2 viral pandemic is announced around the world by WHO, much research has focused on the immune system's role in patients who become seriously ill. A popular theory has it that the immune system gets so expressed up fighting the virus that, after several days, it produces a so called cytokine storm that results in potentially lethal organ damage, particularly to the lungs [25]. Therefore, in such condition, immunosuppression will be good solution for patients surviving in COVID-19 disease. But new findings from a team of researcher's point to another theory and suggest that patients become ill because their immune systems can't do enough to protect them from the virus, landing them in intensive care units. They suggested that boosting immunity could be a potential treatment strategy for COVID-19 [25]. So, treatment protocols for COVID-19 patients should consider patient's particular condition and cause of tissues damage.

For more clear understanding of diseases pathogenesis, researches analyses symptoms and injures in COVID-19 and SARS patients. General observation showed less fibrosis and consolidation, and instead more exudative lesions in COVID-19 than SARS. Microscopically it was seen bilateral diffuse alveolar damage with cellular fibromyxoid exudates, indicating ARDS [8]. In addition, it was identified lymphocytes induced interstitial mononuclear inflammatory infiltrates and multinucleated syncytial cells with atypical enlarged pneumocytes, without obvious intra-nuclear or intra-cytoplasmic viral inclusions. Results from different detailed analysis demonstrated that the counts of peripheral CD4+ and CD8 + T cells were substantially reduced, while their status was hyper-activated as evidenced by the high proportions of HLA-DR (CD4 3•47%) and CD38 (CD8 39•4%) double-positive fractions [26]. Moreover, there was an increased concentration of highly pro-inflammatory CCR6+ Th17 in CD4 T cells [8]. This finding indicated severe immune injury in later stages of COVID-19, but not viral direct destruction of cells [26]. In the same time other researchers detected some capillary injury accompanied by extensive complement deposition of C4d and C5b-9. But other authors described thrombogenic vasculopathy linked with COVID-19 spike glycoproteins related complement fractions, accordingly postulating virus-related complement pathway activation [27].

It is also fact described by some researchers that lymphopenia as a common feature of the COVID-19 patients, which might be a critical factor associated with severity and mortality of disease [20]. In infected children, where the mortality rate is close to zero, lymphopenia is rarely observed. However, in the elderly, where there is a higher mortality rate, lymphopenia occurs more frequently, especially in severe cases. There are not clear understanding of the underlying mechanisms leading to increase neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, and increase levels of cytokines, such as IL-2R and its ratio to lymphocyte count [28]. These results suggested that an inhibition of the immune system and usage of corticosteroids in COVID-19 should not be routinely recommended for the treatment of ARDS induced by SARS-CoV-2 [8].

Moreover, recent reports revealed, that RNA viruses could affect to the cell metabolism by different ways. It is now evident that immune cell effector function strongly depends on the metabolic pathway in which cells are involved in at a particular point in time, the activation conditions, and the cell microenvironment. Six main and interconnected metabolic pathways have a role in the immune response. Namely: glycolysis, the pentose phosphate pathway (PPP), the tricarboxylic acid cycle (TCA), also known as Krebs cycle, the fatty acid oxidation (FAO), also known as β-oxidation, as well as the fatty acid and amino acid synthesis pathways [29]. Thus, envelope viruses alter lipid metabolism, drugs, such as statins can be considered for the treatment of COVID-19.

Furthermore, viruses may affect to mitochondrial proteins and regulate the production of ATP by interfering with mitochondrial calcium mobilization and mitochondrial enzymatic activities, which may be the cause of cytotoxic T lymphocyte exhaustion [29]. So, any defects affecting to any of metabolic pathway can leads to expression of altered immune response.

Finally, as a conclusion, COVID-19 linked limphopenia can be result of exhaustion of T cell or impairment of T cell proliferation process by the SARS-CoV-2 virus. In addition of that, it is also important to consider a gene polymorphism linked with the MHC I HLA and T-cell Receptor (TCR), which are necessary for normal immune response to the viral infection by Antigen Presenting Cell (APC) and T lymphocyte effective interaction.

Coagulation Abnormalities Thrombosis vs Thrombocytopenia

Coagulopathy in COVID-19 patients is one of the severe problems that jeopardizes the clinical course and is associated with poorer outcomes [30, 31]. As the clinical data show, coagulation function abnormalities were reported in most of the severe COVID-19 patients worldwide, by elevated levels of D-Dimer and prolonged prothrombin time, some of whom ended in disseminated intravascular coagulation [26]. Starting from the beginning of SARS-CoV-2 pandemic, in the practice of front-line clinicians in Wuhan, they found that abnormal coagulation function happened in more than 20% of COVID-19 patients expressed in deep vein thrombosis or fatal pulmonary thromboembolism, which significantly affected in the treatment and prognosis [5]. Almost in the same period, other investigators reported deep venous thrombosis in a high percentage of patients (58%) [32]. The authors suggested that a combination of both lesions (DAD and thrombosis) could explain the rapid clinical deterioration in severe COVID-19, and that more proactive expansion of current anticoagulant strategies is desirable [33].

Moreover, in some clinical studies, the partial thromboplastin time (PTT) has been found to be prolonged in many patients with COVID-19 and may indicate the presence of Lupus Anticoagulants (LA). Most patients with COVID-19 have elevated levels of

C-reactive protein (CRP). This may explain some sudden deaths of clinical recovery patients and serve as an indication for diseases verity [34-36].

To find the reasons of coagulation abnormalities, it is important to discuss some related issues linked with SARS-CoV-2. Namely, as the study results indicated, many viruses interact with platelets and their precursor cells, megakaryocytes, leading to the enhanced expression of type I interferon genes, activation of platelet-mediated transport, and stimulation of protease synthesis. SARS-CoV-2 is known to enter endothelial cells, and
resulting endothelial damage may cause platelet recruitment to the infection sites. The subsequent activation and degranulation of platelets may worsen the progression of the disease [37].

In the same time scientists emphasized that the prevalence and intensity of endothelial necrosis, increased megakaryocytes in alveolar capillaries, which leaded to widespread arteriolar fibrin platelet thrombi formation. Some histopathological findings explained that very high serum D-dimer levels suggest ante mortem disseminated intravascular coagulation [1, 38, 39]. So, SARS-CoV-2 induced endothelial damage leads to activation of the coagulation cascade expressed at early stage in subsequent microvascular high permeability, micro thrombi formation and at late stage of disease in fatal thrombocytopenia.

Finally, thrombocytopenia detected in COVID-19 patients is associated with high mortality rate. Some scientists feel that COVID-19 may reduce the platelet count by several mechanisms. For instance, platelet production may be reduced, while more platelets are destroyed or consumed in intravascular clots [40].

SARS-CoV-2 and ACE/ACE-2 ratio

Renin angiotensin aldosterone system (RAAS) is one of the key pathways involved in normal body function especially in the hemodynamic stability of cardiovascular system. In response to RAAS activation two genes are expressed leading to synthesis of angiotensin converting enzymes (ACE) to produce Angiotensin II (AngII) from Ang-(1- 9) and angiotensin converting enzymes 2 (ACE2), which hydrolyses Ang II into Ang-(1-7). So, substrate for ACE2 is AngII but not Ang I. There are many peptidases, which can hydrolyze Ang II to Ang-(1-7), but ACE2 appears to be the prior for this conversion. It is significant to mentioned that Ang I (1-7), produced by ACE2 stimulates nitric oxide synthase (NOS) and antagonize the effects of AngII. The findings suggest that ACE2 gene expression is activated by compensatory mechanisms in acute inflammation and chronic tissues remodeling process. The balance between the ACE2/Ang-(1-7) and ACE/Ang II is crucial to prevent organ damage [41-49].

The investigations results identified that SARS-CoV-2 binds to ACE-2 molecule on the host cell membrane via the viral spike (S) protein cleaved by host cell proteases. Particular amino acids (319-510) on S protein have been recognized as the receptor-binding domain (RBD), which mediates binding of the SARS-CoV to ACE2 on susceptible cells [1, 42, 43]. SARS-CoV can use the endosomal cysteine proteases cathepsin B and L (CatB/L) and the serine protease TMPRSS2 for S protein priming in cell lines. However, only TMPRSS2 activity is essential for viral spread and pathogenesis in the infected host whereas CatB/L activity is dispensable. Therefore, protease inhibitors, which block TMPRSS2, might help to establish new options for prevention and treatment of COVID-19 [44].

The effects of a circulating ACE2 are also very debatable in COVID-19 patients. High level of ACE2 enhances proportionally an entrance capacity of SARS-CoV-2 into the cells. But in the same time, the limited number of ACE2 expressed on the particular cells correspondingly increases risk of organ damage. As the clinical reports suggested that the men have higher expressed ACE genes than women, which might account for the differences in severity and mortality between sexes because other targets for SARS-CoV- 2 binding is not identified [16, 17]. Moreover, the only Asian male specimen has five more times as much ACE2 expressing as the white and African American donors. This might explain why SARS-CoV pandemic were concentrated in the Asian population and the intensified susceptibility of male patients. However, only 5.9% of pediatric cases are severe or critical, possibly due to lower binding ability of the ACE2 receptor in children or generally higher levels of antiviral antibodies [26, 45].

So, because the effects ACE2 oppose the harmful consequences of Ang II on the lung tissues by hydrolyzing of Ang II into Ang (1-7), suppression of ACE2 by SARS-CoV-2 via S protein binding may lead to severe lung injury. Accordingly, enhancement of ACE2 level is strongly suggested as a new therapeutic target to treat COVID-19 [46]. In addition, due to the zero effect of ACE inhibitors on the ACE2, there were additional speculations that ACE inhibitors and Angiotensin II receptors blockers may also increase risk of COVID-19 infection by up regulation of ACE2 gene expression and synthesizing more receptors for SARS-CoV-2 [47-49].

Recently, it was emphasized that Rho/ROCK signaling pathway through endothelial damages triggers acute lung injury and is indicated that by using specific Rho-kinase inhibitors the lung damage could be avoided. Interestingly, as the researchers found out, Rho-Kinase inhibitor Fasudil increased level of ACE2 as well as provided anti-inflammatory and immunomodulation effects in some patients [46, 48].

Diversity of Symptoms, Patient Death

Up till now we don't have any clear criterion of what is counted as a death from COVID-19 in respect of cross-country comparisons. Researchers from different countries tray to justify the country differences in the confirmed cases and the case fatality rate, explain common mistakes in interpreting mortality statistics. In a pandemic, deaths rise sharply, but causes are often inaccurately recorded, particularly when reliable tests are not widely available [50]. Therefore, we have definition so called "excess mortality" which include 'collateral damage' from other health conditions, left untreated if the health system is over occupied by COVID-19 cases, or by measured actions that prioritize patients with COVID-19 over those with other symptoms. Percentage of excess death in UK is 80%, in Italy, 67% and in Belgium 110% [50]. Generally, approximately 80% of infected
individuals have mild symptoms [19].

According to the clinical investigations the main cause of death in COVID-19 is severe endothelial injury, widespread thrombosis with micro angiopathy, and neo-angiogenesis. Generally, SARS-CoV-2 binds with ACE2 expressed on the epithelium of the nasopharyngeal airway, the type II pneumocytes of the alveoli, vascular endothelial cells, pericytes and the macrophages of the lung tissue to form focal and diffuse bronchopneumonia [51-53]. As researchers suggested, in some cases formation of tracheitis may be explained as an iatrogenic lesion in some patients particularly in those who received invasive ventilation, but the finding of these lesions may also frequently occur in patients without invasive ventilation, which suggests that the trachea is an important target of SARS-CoV-2 [54].

We see large differences between countries, as every day global COVID-19 statistics indicated. Among the countries we see the highest mortality rate in US, Brasil and Mexico while some countries shows us successful responses to the pandemic. Vietnam, South Korea and Germany were example of emerging success story. To explain such success, it is important to mention that Vietnam and South Korea have had experience of other zoonotic SARS-CoV-1, MERS and the both countries rapidly scaled up capacity for testing whereas other countries, such are Georgia and New Zealand, they quickly put in place widespread restrictions during the first wave on SARS-CoV-2 pandemic [55, 56].

One year after, worldwide, the mortality rate is reduced from 3.7% (February 2020) till 2.2% (February 2021), but in European Union from 4.2% till 2.4% and is still different by countries [57-79]. To understand differences in diseases outcomes there should be discussed not only medical services provided also virulence severity of different viral generation as well as genetical polymorphism of country populations.

At the beginning of pandemic, among the most frequently observed symptoms identified in COVID-19 patients predominate fever, cough and shortness of breath. In Georgia there were revealed mild cases mostly to compare with figures from Wuhan [56, 57].

Table 1

#	Countries	HLA-A*02:02
1	USA African Americans	3.7
2	Asians	2.3
3	India, North Dehli	1.7
4	China, Qinghi Hul	1.4
5	Tbilisi, Georgia	1.0

Because of viruses are replicated in host cells using host genetic materials, individual genetic variation may help us to explain different immune responses to a virus across populations. Particularly, scientists identified that six HLA-A, -B, and -C alleles indicate correlation between allele frequency and disease forms. Particularly, low frequency of HLA-A*02:02, HLA-B*15:03, and HLA-C*12:03 as well as HLA-A*25:01, HLAB*46:01, and HLA-C*01:02 are linked with low prevalence of mild form of COVID-19 [19, 58]. As the table 1 indicates high prevalence of SARS-CoV-2 among USA African Americans and Asians may be is linked with high frequency of HLA-A*02:02 [56].

Wildtype vs Mutations (B.1.1.7; B.1.351; B.1.526; B.1.427/B.1.429; P.1)

It is fact that any mutation in SARS-CoV-2 genome will be the one of the main reasons of different responses to the disease in different population at different time. Mutation is usually a random process often due to mistakes made when DNA is copied. But scientists investigating the evolution of the virus that causes Covid19 say that its mutation is not random and it seems to be directed by human proteins that degrade it [59]. The team looked at over 15,000 virus genomes from all of the sequencing efforts around the world and identified over 6000 mutations linked with U residues in RNA. The viruses that have too much U in them simply doesn't survive well enough to reproduce [59-84].

Several new variants of SARS-CoV-2 attracted our attention because of their different features in the regard of the transmission and immune responses. Unfortunately, we have limited information regarding the differences in virulence and transmitting capacity in different variations. The most knowns SARS-CoV-2 mutated viruses are differed to each other by a) high transmission capacity such as new variant detected in UK (B.1.1.7); or b) high demand to oxygen in variation identified in California B.1.427/B.1.429; and c) persistence to antibody production after vaccination such as variation found in New York (B1.526), in South Africa (B.1.351), and in Brazil (P.1) [83, 84].

Finally, if we will look at gene mutations form treatment perspective using the research results, it can be found that even we are facing the global shift of the SARS-CoV-2 variant — from D614 (January 11-february 22) to G614 (From February 22-till now in Europe) both the D614 and G614 variants should react similarly to vaccines, studies suggest, as the mutation does not change RBD on the S protein [60].

Prevention and Treatment

Management of Viral infection is the biggest challenge for the modern medicine. Till now we have limited capacity to manage viral infection because of high speed of replication and of course high frequency of possible mutation. Even after diagnosis of viral infection, the targets for the drugs are the organic molecules of host cells, which limits our intervention to kill or to suppress intracellular viral replication process. Furthermore, extreme number of viral generations needs high doses of antiviral drugs, toxic for the host cells especially for the immune cells necessary for final eradication of infection.

Nowadays, COVID-19 patients are treated by special treatment protocols approved by different countries; even we have vaccines available a specific effective antiviral therapy is still critical for management COVID-19 in general. The search for effective drugs is progressively underway. During las year, scientists were examined nearly 300 potential treatments including studies of antiviral monoclonal antibodies, drugs that minimize out of control immune systems, blood thinners to prevent problems caused by blood clots and etc [61]. Because SARS-CoV-2 activates complex pathological processes in many organs by

expression of immunodeficiency with cytokine storm and coagulation abnormalities with thrombocytopenia leading to the organ failure to find clear therapeutic target for management of COVID-19 patient is extremely complicated. Now, Treatment strategy depend on a stage of disease development and severity of disease expression. To achieve successful treatment results, it is favorable to fight with SARS-CoV-2 at the penetration stage to target S-protein-ACE2 interaction.

Recently, medical interventions can be divided into four major categories: general treatment for enhancement of body responses, immunosuppression to reduce cytokine storm, antiviral treatments and others. General treatments included nutritional interventions, immune enhancers and special medicines to improve body health indicators. Now, we have ongoing and completed COVID-19 studies listed on the WHO international clinical trials registry platform (WHO ICTRP) [62]. One of the largest trials is "Solidarity", which was updated on 4 June 2020, by Trial's international Steering Committee and accepted by WHO to discontinue the hydroxychloquine and lopinavir/ritonavir administration to hospitalized patient because of little or no results on reduction in the mortality rate to compare with standard care [63].

Antivirals

Remdesivir: Remdesivir (also GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase with inhibitory activity against SARS-CoV (in Vero E6 cells) and MERSCoV, was identified early as a promising therapeutic candidate for COVID-19 [64-67]. Remdesivir is an adenosine analogue, which is incorporated into novel viral RNA chains and leads to premature termination. It has a broad antiviral spectrum including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses [68-69]. Remdesivir reduced the recovery time for infected patients and dexamethasone reduced mortality for the sickest patients. Therefore, this drug is used under emergency FDA approval. Survival rates in hospitals have improved [61].

Two studies evaluated effectiveness of remdesivir in COVID-19 patients. The Chinese study published in "The Lancet" explained that there was not difference between placebo and drugs effects. But in preliminary report published in "The New England Journal of Medicine" [66] informed that recovery period of disease was shortened from an average of 15 days to about 11 days. Expectation and attention were shifted to Ramdesivir that may be the wide-spectrum drug for antiviral treatment of COVID-19.

Lopinavir/ritonavir and abidol: The combination of lopinavir and ritonavir is used with other medications to treat human immunodeficiency virus (HIV) infection. Lopinavir and ritonavir are in a class of medications called protease inhibitors. When lopinavir and ritonavir are taken together, ritonavir also helps to increase the amount of lopinavir in the body so that the medication will have a greater effect. Arbidol, namely umifenovir, inhibit viral replication for SARS coronaviruses. The latest study results show that lopinavir/ritonavir and abidol exhibited no remarkable effect on clinical improvement or virus clearance [68, 70, 71]. Single arbidol was significantly associated with reduced SARS-CoV-2 infection and might play a preventative role among health professionals [70]. But to compare with Favipiravir results from study conducted on enrolling patients within 12 days of symptom onset found that favipiravir was superior to arbidol in terms of the clinical recovery rate at day 7 in patients with mild illness but not in those with critical illness [68].

Chloroquine/Hydroxychoroquin: Chloroquine and hydroxychloroquine, old Chinese medicines for treatment of malaria and autoimmune disease, had demonstrated notable inhibition in the spread of SARS-CoV by affecting with ACE2 in Vero E6 cell lines. Some resercehrs from china demonstrated that chloroquine functioned at both entry and post entry stages of the SARS-CoV-2 infection, as well as provided an immune-modulating activity that probably enhanced the antiviral effect in vivo [26, 72, 73]. Scientists thought that Hydroxychloroquine impair the terminal glycosylation of the ACE2 receptor, which is the binding site for the envelope spike glycoprotein and has been shown to inhibit endolysosome function. In addition, hydroxychloroquine may have greater in vitro activity against SARS-CoV-2 than chloroquine [73].

The majority of clinical studies of chloroquine or hydroxychloroquine for COVID-19 have focused on hospitalized patients [73-76]. Small, nonrandomized, noncontrolled cohort studies have suggested that the use of hydroxychloroquine might reduce or even eliminate the risk of infection. Whether short-term high dose hydroxychloroquine can prevent disease soon after a high-risk exposure remains unknown [4].

Molnupiravir EIDD-2801 Molnupiravir was developed at Emory University together with Drug Innovation Venture at Emory (DRIVE) and is currently being evaluated in Phase 2/3 clinical trials for treatment of outpatient and hospital patient with confirmed cases of COVID-19. This drug is experimental and originally is developed against Influenza. As many other synthetic nucleoside analogs Molnupiravir is orally active prodrug N4-hydroxycytidine analog and has been evaluated against coronavirus including SARS-CoV-2. The primary hypothesis is that molnupiravir is superior to placebo. The primary completion date for the phase 2/3 studies is May 2021 [82]. Drug Manufacturer is Ridgeback Biotherapeutics.

The serine protease inhibitors: Additionally, potential therapies targeting RAAS may be developed to treat COVID-19 in the future. Now, it is already seen in some studies, that the serine protease inhibitor camostat mesylate against TMPRSS2 can efficiently block SARS-CoV-2-S-protein driven cell entry, which could be a promising treatment for COVID-19 [44]. The relevance of Camostat mesylate for treatment of COVID-19 is currently being evaluated in a clinical trial together with Gabexate mesylate and Nafamostat mesylate. The results reached indicated that Nafamostat mesylate blocked SARS-CoV-2 infection of human lung cells with markedly higher efficiency than Camostat mesylate [44, 77].

Immunosuppressants

Tocilizumab: The COVID-19 is associated with a cytokine storm triggered by overactivated immune system similar to SARS and MERS. Ongoing trials of the IL-6 antagonist tocilizumab, is one of the investigations to get restored T cell population for treatment

of severe SARS-CoV-2 [26].

Glucocorticoids: Because of formed lymphopenia corticosteroids should not be routinely used in ARDS induced by SARS-CoV-2 [8].

Supplements

Vitamins D, Vitamin C, Vitamin E, omega-3 fatty acids, metals Zn, Se

As the clinical researches show Vitamin D is involved in the regulation of immune response against foreign agents. Especially, it suppresses anti-inflammatory cytokines, such as IL-2 and INF-s. There are research works done to compare disease outcomes in patients with dietary supplements and without but till now we don't have clear result indicating the benefits of Vitamin D supplements in the management of COVID-19 [80]. As the Lancet "Diabetes & Endocrinology" (February 2021) shows, the result of D-Health randomized clinical trials conducted in 20 000 Australian adults indicated that monthly doses of Vitamin D did not reduce the risk of severity of acute respiratory tract infection. Clinical studies have demonstrated that Vitamin C plays significant role in regulation of immune system by suppressing of IL-6 production trough increasing IL-10 production in peripheral mononuclear cells [80].

In proteins, Zinc is associated with amino acids to regulate DNA/RNA metabolism, signal transduction, gene expression and cell apoptosis. Therefore, Zinc supplements may have the potential to be a supportive treatment in COVID-19 patients. Australian refreshers tray to determine the benefits of Zinc supplements in SARS-CoV-2 positive patients [81].

Epidemiological studies show that deficiency of antioxidants such as Vitamin E and trace metal Selenium alters to the immune response against respiratory tract infection. The effect of Vitamin E and selenium is linked with cell mediate immune response especially T lymphocytes and NK cell activity. But still now we have limited information regarding the benefits of such antioxidants in the management of COVID-19 patients [80].

The usage of omega-3 supplements in COVID-19 is still controversial. From one side, omega-3 fatty acids may increase oxygenation capacity in impaired lung tissues, but from another side there is big risk of acceleration of inflammation and oxidative stress in high susceptible to damage alveolar cells [80].

Conclusively, because the maintaining of homeostasis is the key component to keep the normal body functioning administration of vitamins and trace metals will restore the processes in case of its deficiency.

Vaccines

mRNA and DNA Vaccines: The most rapid and safe technology for antiviral vaccines are mRNA and DNA vaccines. Pfizer and BioNTech developed lipid-soluble nanoparticle preparation of mRNA vaccines called BNT162b1 and BNT162b2 containing mRNA for S-protein domain. The difference between BNT162b1 and BNT162b2 is that antigen of BNT162b1 is a mRNA for RBD sequence of s-protein, while BNT162b2 contains full length of s-protein and produces strong cell mediated responses by Th1, CD4+ and CD8+ T cells. In the same time S protein full mRNA containing vaccine mRNA-1273 was developed by the US-based biotechnology company Moderna and S protein RBD sequence containing mRNA vaccine called ARCoV was innovated by Chinese PLA Academy of Military Medical Sciences. In parallel with mRNA containing vaccines Inovio Pharmaceuticals published the results of animal studies of DNA vaccines known as INO-4800. A sequence encoded S protein was inserted into the pGX9501 vector. The results in animals shows that after vaccination the T and B cell immune responses are activated [85].

Viral vector vaccines: AstraZeneca-University of Oxford Company developed vaccine using replication-deficient chimpanzee viral vector linked with genetic materials of the spike protein from SARS-CoV-2. Vaccine has 70% efficacy against UK, South African but little effect against Latin American Variants. In the same time Jonson & Jonson used inactivated common cold virus to develop similar to AstraZeneca-University of Oxford company vaccine with high effectiveness against UK, but less so against South African and Latin American Variants. The same Adenovirus vector was used by Russia's to introduce Sputnik V Vaccine with known effectiveness 91.6% against the original strain of the SARS-CoV-2 [85].

Inactivated viruses containing vaccines: China-based Sonovac Biotech vaccine is composed by inactivated SARS-CoV-2 virus with 50.38% efficiency. The sensitivity against the new variants is not known.

Antigen Containing vaccines: Novavax contains a full-length, prefusion spike protein with efficacy 89.3% and is affective against UK and South African variants [82, 84, 85]. According to the existed data, a vaccine is not a silver bullet. People will continue to contact the virus because some won't get vaccinated and because the vaccine may not be effective for everyone [61]. On the other hand, the success of anti-viral antibody responses depends on plasma cell functioning and lifespans [78]. As we discussed above, viruses specifically target plasma cell metabolism. Therefore, long lasting antiviral immune responses may be contingent on SARS-CoV-2 effects on the plasma cell metabolism [29]. Conclusion & Significance: Up till now it is challenging problem to combat SARS-CoV- 2 with not well-defined origin and inexplicable biological characteristics as well as to control a pandemic of COVID-19 with such a high R0, a long incubation period and different disease outcomes. Unfortunately, we have limited understandings of particular mechanisms running to abnormal expression of immune system and coagulation processes. In the same time, we don't have complete picture of vasculopathy leading to the tissue injury and patient death. Therefore, it is problematic to manage SARS-CoV-2 induced processes successfully using available drugs with no significant restoring effect on the organ damages in severe COVID-19 patients. So, we need new targets and new drugs for the prophylaxes and treatment of COVID-19 even we have vaccines available.

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