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CORONAVIRUS: Pathology, Immunology and Therapies

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1. Abstract

Coronavirus is a family of positive single-stranded RNA virus belonging to the family of *coronaviridae*. Coronavirus-19 infection (COVID-19) has appeared in 2019 and so there is no effective treatment that can eradicate it. The objective of this review is to present data on cellular and molecular characteristic of virus infection and also elucidate all molecular associated events with covid-19 infection in patients. The infection in humans can cause diseases ranging from a common cold to more serious diseases such as severe acute respiratory syndrome (SARS). The disease that it transmits (Covid-19) cannot be cured with conventional treatments.

However, a large number of protocols have been implemented based on the sequels that it produces. In this review we summarize 1) the role of immune system against this pathogen as well as the biochemical mechanism by which squealed is responsible for disease progression 2) the possibility or not that patients who have suffered the disease have antibodies against the virus and 3) the clinical protocols used in order to mitigate induced-damage by virus.

2. Keywords: Coronavirus; COVID-19; SARS-CoV-2; ECA2; S Protein; Cytokines storm

3. Introduction

The ancestor of the coronavirus dates from the 9th century BC where it was known that they came from bats and birds. The common human coronavirus was discovered in the 1960s and the Middle East respiratory syndrome (MERS) was associated with bats.

The virus was first isolated from a patient who died from a severe respiratory illness in June, 2012, in Jeddah, Saudi Arabia [1]. The (SARS-CoV) was associated with bats but this is not totally accepted [2-10].

The provenance of the current coronavirus-19 is unknown although it is speculated that this virus moves from bats or another animal.

Human's coronavirus is characterized symptomatology more or less severe.

In 2003, a virus called SARS-CoV was discovered and more coronavirus species were further discovered, mainly responsible for outbreaks of human respiratory illness such as the common cold. *Coronavirinae* form four subgenres called alpha-, beta-, gamma- and delta-. Alpha and beta CoVs infect mammals, gamma coronaviruses infect birds and delta coronaviruses infect both mammals and birds.

Four of them have been identified as common causes of human respiratory

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system illnesses: 229E and NL63 (alpha coronavirus) and OC43 and HKU1 (beta coronavirus). Three new human coronaviruses have been identified as cause of SARS syndromes: 1) MERS-CoV causing Middle East respiratory syndrome (MERS), 2) SARS-CoV responsible of severe acute respiratory syndrome (SARS) and 3) SARS-CoV-2 (a novel beta coronavirus) causing coronavirus disease (COVID-19). The last one was discovered in 2019 when an outbreak of pneumonia was demonstrated in Wuhan, (China), concluding that this outbreak was caused by a new coronavirus, listed as 2019-nCoV by the World Health Organization (WHO). In a few months, this coronavirus, known as coronavirus-19, gave rise to a pandemic that revolutionized the entire world since its infection was very fast in conjunction with a high mortality. This virus has been called SARS-CoV2 because its RNA has 82% similarities to SARS-CoV [11]. Like other virus that cause pneumonia, it is transmitted through the respiratory route in humans from coughs, sneezes, or when people who carry the virus speak. The nose, pharynx and lung are the first targets for this pathogen. SARS patients suffer a pathology characterized mainly by fever, dry cough, lymphopenia, various degrees of pancytopenia, hypoxia, rapid progression on chest radiography, loss of smell and taste and others less characterized symptoms [12]. It has been observed that some SARS patients have elevated levels of circulating inflammatory cytokines [13,14]. The entire world had to undergo confinement without being able to leave home in order to prevent the progression of pandemic and the economy suffered a great punishment. The health workers had to improvise different protocols to alleviate detrimental consequences of Covid-19 infection, such as inflammation and thrombosis, among the most common disease. Since it is a virus, it cannot be treated with antibiotics and there are no available vaccines against this virus. On the other hand, the virus is not very well known and protocols are being progressively developed in patients. It is known that this virus can live for several hours and even days, on surfaces such as metals or plastic; so, the WHO has suggested hygienic measures such as washing hands and disinfecting objects, as well as wearing masks in order to prevent viral transmission between subjects. It has also known that carriers of the virus, even without symptoms, are very contagious; their isolation substantially prevents the contagious between subjects. This review explains cellular and molecular mechanisms by which SARS-CoV-2 enters into the cell, how replication takes place and also analyzes the immune activation in infected patients. The possible involved mechanisms associated to inflammation and thrombosis, as well as the possible treatments are discussed in the present review.

4. Coronavirus Structure

All viruses of the Nidoviral order have an envelope in conjunction with unsegmented RNA. SARS-CoV2 is a virus of 120 nm diameter, 80 nm of envelope and 20 nm of length of spicules [15]. Its long genomic RNA contains 33,5 kilobases (Kb) and a high genomic conservation, with a gene for replicase preceding the rest of genes [16-17]. The coronaviral genome encodes four major structural proteins: the envelope (E) protein, the protein membranes (M), the spike protein (S) and the nucleocapsid (N) [18-21]. However, CoVs does not need some of these proteins to form the complete virus [18], maybe because they are capable of encoding other proteins with compensatory functions [21-23]. The viral envelope of all coronavirus is formed by a lipid bilayer**,** in which the proteins are anchored as spicules.

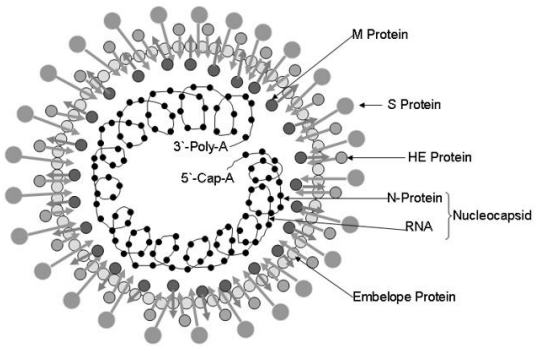

Figure 1: Coronavirus-19 structure.

These proteins include: The envelope 8 to 12 KDa

protein (E) is believed to be a protein found in small amounts. This protein facilitates the assembly and the exit of virus from the host cell, but also has other functions. In case of the SARS-CoV, this protein is not necessary for viral replication although it is necessary for pathogenic mechanisms [24].

The membrane protein (M) is the most abundant; it is a small protein of 25 to 30 KDa. It is thought to be the one that shapes the virus. This protein is also called 3CLpro and it controls the activity of the coronavirus replication complex due to its role in processing the polyproteins that must associated with the viral RNA after replication [25,26].

This would make this protein a good target for therapy. The nuclear protein (N) is the only protein of nucleocapsid. It is bound to virus RNA and to the membrane (M) and forms part of the replication complex [27]. It has two domains, one that interact with the viral RNA leading to its correct encapsulation in the virus and another multifunction domain that acts as an INF antagonist and as a repressor of interference RNAs, which is very important for avoid the antiviral immune action and it is beneficial for its replication. The protein (S) is a glycoprotein of the spicule whose main function is the viral anchorage on the host cell. It is a 150 KDa protein and is responsible for binding to the receptor through which the virus enters into the cell. This protein consists of two subunits, S1 and S2 [28-30], which are important for binding to the angiotensin-converting enzyme (ECA2); thus, ECA-2 is the cell's receptor for the virus entry. All of these proteins are encoded by the genome of virus.

The virus also codes for other proteins with protease activity as a replicase, which is a polymerase and also helicase, as well as hemagglutinin esterase [31,32].

5. Entry of the Virus into the Host Cell

The entry of the virus into the cell and its replication is the first step for viral infection. Even though there are several theories about the entry of the virus into the cell; the glycoprotein S seems to be a key player. Many coronavirus use peptidase as their receptor, but there are several investigations in which they propose that the entry of the SARS-CoV, SARS-CoV2 and HCoV-NL63 viruses is through the binding of the virus with the enzyme convertase 2 (ECA2) of the Renin-Angiotensin system [33-35].

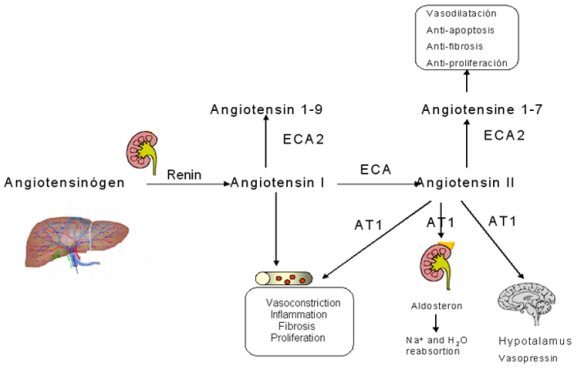

Figure 2: Renin-Angiotensin system. ECA = angiotensin converting enzyme, AT1 = angiotensin 1 receptor.

In most coronavirus, protein S is cleaved by a host cell protease into two separate polypeptides called S1 and S2 [36]. The S1 and S2 polypeptides establish the binding mechanism to the ECA2 receptor [37] located on the cell membrane [28,29]. ECA2 is located on the surface of the cell membrane, with its active centre located outside the cell [2,38]. It seems that the expression of ECA2 is the same at all ages, from children to the elderly [39], however, there are some conflicting opinions. Recent studies have observed that activation on the rennin-angiotensin system is related to lung damage [40]. The observed lower risk of severe SARS-CoV-2 respiratory illness among children may be due to differential expression of ACE2 in persons of younger age. However, rretrospective examination of biopsy samples previously taken during 2015 to 2018 from individuals aged 4 to 60 years found age-dependent expression of ACE2 in nasal epithelium, with lower expression in children relative to adults [41]. ECA2 mediates the entry into the cell of three coronaviruses SARS-CoV, NL63 and SARS-CoV2 [42]. As this receptor is an enzyme, the binding of the virus inactivates it, thus preventing the conversion of angiotensin II into angiotensin 1 to 7 (Figure 2) [43,44]. The virus hemagglutinin esterase protein appears to be responsible for this inactivation. ECA2 is expressed by

the vascular endothelium [45] and to a greater extension by lung, mainly epithelial cells from the pulmonary alveoli [35] but also it is expressed by liver, kidney as well as heart cells [45-47]. It has recently demonstrated in autopsies from infected individuals that not only lungs but also kidney, heart and brain are damaged organs by coronavirus-19.

A recent hypothesis launched by Belen-Apak and Sarialioglu [48] suggest that a furin inhibitor could prevent the entry of virus into the cell. The explanation of this hypothesis is based on the fact that for the virus S protein to bind to its ECA2 receptor, it needs to separate into two S1 and S2 polypeptides, as it was say before. At the site of protein S cleavage an amino acid sequence is recognized by furin, a protease that is highly expressed in the lung [49,50] and that could be responsible for cleavage of protein S. Thus, a furin inhibitor may be a good candidate for preventing the entry of virus in the cell. Another Japanese study used "Nafamostat" and Camostat" in order to prevent the entry of the SARS-CoV2 virus into cells since these drugs are protease inhibitors. These drugs were used to treat acute pancreatitis and cystic fibrosis in Japan. In search of effective furin inhibition, researchers from Murcia Institute for Biosanitary Research (IMIB) will evaluate the efficacy of low molecular weight heparin and other approved drug as possible inhibitors of this protein.

Inhibition of ECA2 would lead to Angiotensin II accumulation, which could bind to its AT1 receptor, leading to a series of alterations such as inflammation, vasoconstriction, fibrosis and proliferation. This would partially explain the inflammation and pulmonary thrombosis found in COVID-19 patients (Figure 2). If SARS-CoV2 enters the cell via ECA2, it is conceivable that ECA2 inhibitors and angiotensin AT1 receptor antagonist may have some therapeutic action. Taking into account this consideration, if ECA2 inhibitors are used, the entry of the virus into the cell could be avoided and therefore its destruction would be achieved. The combination of angiotensin AT1 receptor antagonist administered plus an ECA2 inhibitor could have additional synergic effects; under these conditions, the virus can be destroyed without induced-damage by binding of angiotensin II to its AT1 receptor. ECA2 inhibitors along with angiotensin II AT1 receptor antagonist have been therapeutically used for preventing cardiovascular disease [47]. However, several authors have demonstrated that this treatment in rats increased the expression of ECA2 receptors [51]. An increase in ECA2 receptors does not prevent the attack of the virus but everything contracted. Therefore, care should be taken with this treatment, especially in the case of hypertensive or cardiac patients infected with coronavirus-19 [42]**.** Other authors do not support this idea [52]. Another possibility, supported by some authors, is to administer medication that increases plasma soluble ECA2 levels using a recombinant ECA2 (rhECA2) treatment; this treatment could have great therapeutic relevance [53-55] since the virus could bind to soluble ECA2, which would neutralize the binding of the virus into the cell. However, this treatment has been suspended. All these reflections require a greater number of data for treatment of COVID-19 disease.

With regard to the involved mechanism of the rennin-angiotensin system, we must consider that an excess of angiotensin II, mediated by the inhibition of ECA2 by Covid-19, could provokes a thrombotic effect. Dipyridamole acts as anti-inflammatory agent, antiplatelet as well as antiviral agent in +RNA viruses [56,57]. Then, due to its antithrombotic action, dipyridamole could be considered useful for a hypercoagulability in some patients with COVID-19 [58].

6. Replication of Coronavirus within the Cell

As compared with other +RNA viruses coronaviruses have a polycistronic organization, with proteins involved in host cell interaction. This means, that within the cell, the virus creates an optimal environment for its replication and a hostile environment for the host cell, altering the expression of its genes and counteracting its antiviral defences [59].

The organization of SARS-CoV with +RNA genome is arranged in a certain order. The gene for replicase protein replication is the first, followed by the synthesis of protein S, protein E, Protein M as well as nucleocapsid protein together another set of accessory proteins [60].

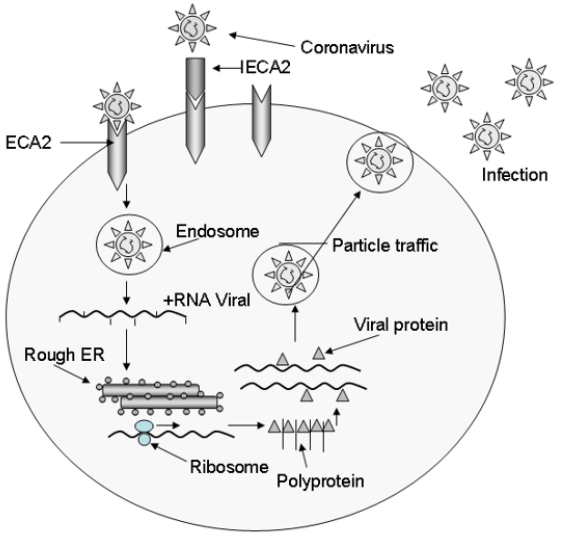

Figure 3: Virus entry, replication and infection.

Inside the cell, viral RNA forms a long and unique mRNA that encodes the synthesis of several proteins. This is like having a specific mRNA sub genome to synthesize each viral protein. When the virus genome migrates to the host cell endoplasmic reticulum (ER) and binds to ribosomes, the signal translation process begins to synthesize the different virus proteins. Since the RNA of the coronaviruses are polycistronic, this synthesis will be done as a single polypeptide chain that will be cut it protein by the viral protease called Mpro of 3CLpro [26].

The sites of cleavage recognition by proteases are between Leuc-Glu….. Ser, Ala, Gly. amino acids. The viral replication could be blocked by inhibiting the activity of this enzyme/s. Some attempts have been made in order to find inhibitors of this enzyme [55,61,62] but unsuccessfully. The first protein that will be free from this long chain of polyprotein will be the replicase because this will be the enzyme that gives rise to the replication of the RNA chain of the virus. These proteins alert the host cell to trigger its antiviral immune system. Many RNA viruses also modulate the synthesis of some of the host proteins [63] in order to alter the immune functions of the cell. Since ER is important for replication, viruses often induce alterations in the ER [64]. Knowledge of the interactions between virus and the cell during virus replication can be a starting point for antiviral drugs. Anti-malaria drugs such as chloroquine and hydroxychloroquine have been shown to block virus entry, including SARS-CoV and MERS-CoV [65]. Chloroquine could be more effective in the early stage of infection; however, its effectiveness is probably limited and its use is based on weak and conflicting evidence due to the poor results with its treatment. In addition, drugs that able to prevent viral fusion with the cell membrane have been also developed [66].

Remdesivir (C27H35N6O8P) an antiviral for Ebola treatment in Africa seems to give good results for Covid-19. These drugs inhibit the viral RNA polymerase enzyme that participates in viral RNA replication. In the case of SARS-CoV2, this drug has been tested in China, Italy and Japan with good results. Intravenous remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19 compared with placebo. However, among patients who were treated within 10 days of symptom onset, remdesivir was not a significant factor but was associated with a numerical reduction of 5 days in median time to clinical improvement [67]. Benefit was seen in the number of days to recovery (median, 11 days, as compared with 15); rate ratio for recovery. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. In conclusion: it reduces by 30% the stay in ICU of patients to be recovered, but it does not decrease mortality or viral load [68].

However, there is insufficient data and in our opinion, we believe that Remdesivir should be administered in treatments.

7. Function of the Immune System and

Consequences Produced by Coronavirus 19

The infected cells alert to the immune system and it is immediately activated. This system has two responses to the foreign element, an innate or non-specific immunity and another acquired or adaptative immunity that is highly specific. The innate immune system can be recognized two types of signals, a so-called danger signal, DAMP (damage-associated to molecular patterns) and another is the signal emitted by the pathogen. This signal may be a protein or DNA or RNA from pathogen and are called PAMP (molecular patterns associated with the pathogen). These signals are recognized by the patterns knowing receptors, the Toll-like Receptors (TLRs) [69]. The virus-specific protein that is recognized by the immune system is not yet known although, however, it has been seen that the SARA-CoV protein M can directly promote activation of both β-interferon (IFN-β) and NFκB through a TLR-related signal pathway independent of TRAF3 route, what suggest that SARS-CoV M protein may function as a cytosolic PAMP stimulating [70]. The activation of this receptor by this protein induces several signal between them, a transcriptional factor IFNγ and NFκB that encode the synthesis of proinflammatory cytokines that, in turn, activate a signal cascade mediated by JAK-STAT, which induce the expression of antiviral proteins able to prevent viral replication [71]. Chen et al. [44] examined whether patients recently recovered from COVID-19 had anti-SARS-CoV2 S1 protein IgG antibodies in sera and observed that the most part were able to produce SARRS-CoV2 S1-specific IgG antibodies in a great extent and only three patients had relatively lower anti-S1 IgG responses. However, when they examine the blocking function of these antibodies, they found that only three out 26 patients showed effective blockade of SARS-CoV2 RBD to hACE2.

Infections called acute respiratory Syndrome (SARS) begin by infecting the epithelial cells of the lungs. This infection, through intracellular signals, (cytokines, chemokines), alerts the innate immune system, which help to macrophages to reach the site of infection and also contribute to phagocyte viruses and dead cells.

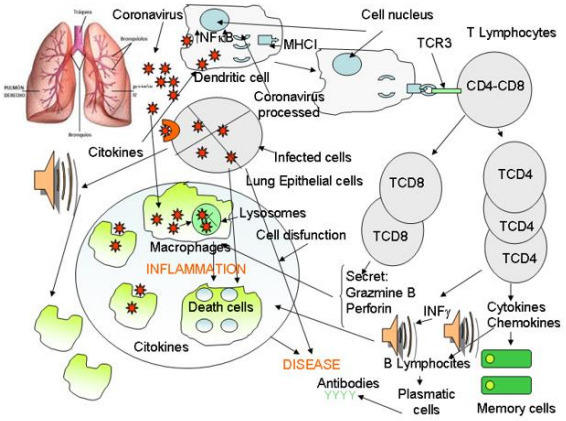

Figure 4: Mechanism of functioning of the immune system.

In addition, other types of cells that are part of the adaptative immune system are activated. They are the antigen presenting cells (dendritic cells) that recognize viral proteins (S, M and N) through their specific TRL3 receptor and migrate through the lymph to the area of the lymph nodes. These presenting cells fragment the viral proteins by the action of proteases and one fragment bind to a factor called histocompatibility (MHCI or MHCII) and present it to specific T lymphocytes. These, through their TCR receptor, recognize the antigen and activate, proliferate and migrate to the site of infection [29,30]. The activated T lymphocytes can be of the type CD8 (cytotoxic) or CD4 (collaborators) cells. CD8-type lymphocytes release cytotoxic molecules as granzyme A and B and perforin. These cells, along with macrophages, are responsible for destroying and eliminating the virus and also kill infected cells. Depending on the stimulus received, CD4 type cells release antiviral cytokines as INFγ, IL-2, proinflammatory interleukins etc and chemokines, (CXCL-9, CXCL-10 and CXCL-11) [35].

INFγ, inhibits viral replication and increases antigen presentation [34]. Cytokines and chemokines recruit: 1) more innate cells (macrophages) that engulf infected cells, 2) adaptive cells to control the pathogen load and 3) stimulate other antibody-synthesizing cells of the immune system. The toxic molecules granzyme A and B and perforin helping to eliminate the pathogen [33].

During this process, inflammation take place. Some cytokines and chemokines secreted by T lymphocytes activate type B lymphocyte, which will transform into plasma cells able to synthesize antibodies against the pathogen. In the acquired immune system, B lymphocytes can also act as antigen presenting cells by recognizing the antigen through their BCR receptor [72] or they can be transformed into antibody synthesizing plasma cells. These antibodies mark antigens which are recognized and destroyed by macrophages preventing that they infect new cells.

Cytokines and chemokines can also activate T lymphocytes CD4 and CD8, which may transform in memory cells capable of rapidly starting up against the new pathogen. All of these events will contribute to viral clearance but also could provoke inflammation; therefore, this process has to be highly regulated. Dysfunction of the cells invaded by the virus will lead to cell death and the development of the disease. The pathological consequences of coronavirus-19 or SARS-CoV are associated to dysfunctions or exacerbation of the innate immune response. e.g. in the case of SARS-CoV, SARS-CoV2 or MERS-CoV, the highest lethal response occurs in elderly patients or in people with compromised immunity [7,31]. The steps to establish the relationship between the pathological response and the functionality of the immune system is not known for Covid-19 (SARS-CoV2) because, the type of cytokines and other molecule that are activated against it are not known and there are only a few details for SARS-CoV. It would be interesting to know which of these molecules are activated against the coronavirus-19 because this would give an idea of the intracellular signals produced in the cells when they are attacked by this virus. The knowledge of specific signal induced by STAR-CoV2 would allow the use of specific drugs able to counteract the damage that they cause in these patients.

Wang et al. [14] studied the total lymphocytes of type CD4 T, CD8 T, B cells and nature killer in SARS-CoV2 infected individual observing that these cells decreased in the most seriously ill patients in relation to the milder patients. They found a significant relationship regarding the stage of inflammation in COVID-19, mainly in CD8 T cells and in the relationship between CD4 T/CD8 T cells. Several studies have investigated the potential response of the immune system in SARS-CoV2 infected patients and most of these have shown an uncontrolled immune responses characterized by hyper activation of macrophages and monocytes that had led to an increase in neutrophils, IL-6 and C-reactive protein levels together with a decrease in the number of lymphocytes [73]. Some studies have presented different cytokine profiles in patients with severe COVID-19 [14,62].

Several lung infiltrations are believed to be due to deregulation in the synthesis of cytokines as TNFα, IL-2, IL-7, IP10, CXCL10, MOC-1 but not IL-6 [74]. Such as exaggerated response to cytokine synthesis is attributed to macrophages and monocytes over activation [75]. Studies with various animals injected with SARS-CoV observed that old mice infected with this virus had a large number of proinflammatory cytokines as well as chemokines (CXCL-1, CXCL-2, CCL-2 and CCL-5 [76]. When the virus was injected into young mice, there was a lower content of specific viruses in CD8 T cells of the lung [77]. Stains of influenza virus and SARS-CoV have been used to study the innate and adaptative response of the immune system [78]. Patients with and acute phase of SARS have been shown to have decreased CD4 and CD8 T lymphocytes compared to healthy individuals [79,80]. High plasma levels of proinflammatory cytokines as IL-2, IL-7, P10, MCP1, MIP1A, TNFα, IL-7, have been detected in COVID-19 patients admitted in the ICU, suggesting that a cytokine storm process may be developed in patients with severe disease [62].

The questions that can be suggested about the cytokine storm is the following why is the production of cytokines so intense in the face of an attack, for example viral? The answer could be: 1) due to an excessive entrance of virus (viral change load) 2) due

to the malfunction of the immune system of the patient or 3) because the virus induces the cell to this behaviour. If the host immune system is normal, it would function properly and will not lead to signal overload. However, if the immune system of the patient is not working properly or the virus induces this behaviour in the host cell, then, the use of antagonist of these cytokines could prevent exacerbated inflammation. The virus implication in the regulation of this system is not strange because it seems that when the virus enters the cell it caused cell deregulation [64].

8. Antibodies and Coronavirus-19

Measurement of the IgM and IgG antibodies determination for SARS-CoV-2 improve disease management. In fact, the knowledgement of serum IgM and IgG indicates us of the infection is recent (IgM) or has occurred after 8 or more days (IgG). Antibody assessment tests are currently carried out on the population in order to determine the status of the pandemic. The first line of defence of the immune system against SARS-CloV, SARS-CoV2 and MERS-CoV is the IgM antibody production, which are detected in plasma 3 to 6 days after infection while IgG usually appear 8 days after infection. The behaviour of the immune system against SARS-CoV2 is not yet known, but it is suspected that a longer immunoglobulins production is not a good feature/evidence. A fact that must be taken into account is that the prevalence of IgM type antibodies is less durable, about 12 days, whereas IgG type has a longer life time. Generally, infection by a pathogen tends to induce immune responses in infected patients since they have produce antibodies. However, there are no evidences for coronavirus-19 about this possibility. It is not known if those who have passed the disease have plasma antibodies against the virus that can be used as treatment for affected individuals. A Spanish study has observed that only 5% of infected patients have generated antibodies. However, it should be taken into account that this study was carried out with few samples. In addition, these tests only have 80% specificity, so could detect false positives and negatives. The IgM and IgG tests allow to know: 1) population that has never been infected, which are IgM and IgG negatives, 2) individuals who have recently have an acute infection (IgM positive and IgG negative), 3) the population that has had contact with the virus with an acute infection but cured (IgM negative and IgG positive), 4) Individuals who had an infection a week or months ago (IgM and IgG positive) and 5) cured people who have developed IgG. Korth, et al. [81] have studied the average SARS-CoV-2 seroprevalence. They reported a prevalence of 1.6 % among positive SARS-CoV2-IgG workers in the period between March 2020 to April 2020. Determination in SARS-CoV2 of IgM and IgG antibodies demonstrated that the median seroconversion time was about 12 to 14 days and the generation of antibodies was below 40% in the first week but increased to 90% for IgM as well as for 80% IgG around 15 days [82]. Recently, Grifoni et al. [83], have been measured the ability of CD4 T and CD8 T cell from COVID-19 recuperated patients and from patients with common cool. They found that the response to Spiker, M and N SARS-CoV2 protein was 100% in CD4 T cells and 70 in CD8 T cells of SARS-CoV2 and 50% and 20% in common cool. From these results deduce that may be a cross reactive T cell recognition between circulating T cell in both diseases. In addition, these authors found that these epitopes were also present in non-exposed individuals. This meeting is encouraging since it indicates that some population, even without too many antibodies, could have defences against coronavirus 19 since the results of Grifoni et al. [83] could also indicate the presence of memory cells capable of attacking the virus quickly.

9. Therapeutic Options for COVID-19 Disease Treatment

The only remedy against the virus is pharmacological treatments that can attacks the virus and also alleviates the sequel of the disease. Although there are clinical trials in progress in the world, there is no evidence from

controlled clinical trials recommending specific treatments for COVID-19. The general available information is yet indicative. Generally, it is recommended to follow the clinical protocols of each hospital given the absence of standardized procedure for treatments in patients. Some available treatments are newly developed molecules and another are new authorized drugs for other indications. Here, one describes some used treatments and the clinical efficacy. Among these are antiviral medicaments, which promote the destruction of virus. The problem is that these antivirals have been designed for different viruses, so their efficacy may be limited for SARS-CoV2 eradication. In addition, anti-inflammatory and anti-coagulants drugs have also been used in these patients.

9.1. Antivirals

Favipiravir: It is recognized as a substrate by RdRp and inhibits the RNA polymerase activity. Preliminary results from clinical trials have suggested that favipiravid may be effective in the treatment of patients with COVID-19 [84].

Lopinavir/Ritonavir: Lopinavir is an inhibitor of the VIH-1 and VIH2 viral proteases, which prevent cut gag-pol viral polyprotein and abolish viral infection. It has inhibitory activity “in vitro” against SARS-CoV. Ritonavir is combined with lopinavir to increase its plasma half-life by inhibiting cytochrome P450. Clinical trials have not shown its effectiveness [85]. Recently, a complex lovinavir / ritonavir / ribavirin / interferon beta-1b treatment have been administered by six hospitals in Hong Kong. When they were given within 7 days of symptom onset, is effective in suppressing the shedding of SARS-CoV-2, compared with lopinavir-ritonavir alone and were associated with clinical improvement as shown by the significant reduction in NEWS2 and duration of hospital stay. Triple combination of interferon beta-1b, lopinavir-ritonavir and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomized, phase 2 trial [86].

9.2. Immunomodulation Therapy

Corticosteroids

Dexametasone: In the UK national RECOVERY trial, the low-dose dexamethasone treatment was reported to reduce deaths by one-third in ventilated patients and by one fifth in other patients receiving oxygen but not mechanically ventilated. There was no benefit among those patients who did not require respiratory support. Based on these results, death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone [19].

Methylprednisolone: Treatment with methylprednisolone did not decrease the elimination of SARS-Co-V-2 or IgG production however; it arrested the cytokine storm [87].

Interferon beta-1B/interferon a-2B: the interferons are immunomodulators and are used for preventing and abolish the exacerbated responses of the own immune system.

Budesonide/Formoterol: The combination of Budesonide/formoterol is a potent local immuno-suppressant that it is predicted to precisely counter the cytokine/inflammatory cell storm that underlines the first stages of SARS. It is recommended to begin treating the patients at risk early on in the disease, thus emphasizing the need to begin treatment much before the appearance of dyspnoea during the second week of the disease. A prospective randomized controlled clinical trial is now pending [88,89].

Tocilizumab: It is a monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor, preventing signal transduction pathways involved in inflammation in B and T cells. Although a recent cohort study from the University of Michigan shows survival benefit with Tocilizumab in intubated COVID-19 patients [90]. It is recommending that tocilizumab only be used for hospitalized patients with COVID-19 in the context of a clinical trial [91].

Sarilumab: It is a human monoclonal antibody that acts as antagonist of the IL-6 receptor. Phase 3 trial in COVID-19 patients requiring mechanical ventilation

did not achieve better outcome compared to best supportive care alone (placebo) so the US-based trial has been stopped. https://www.sanofigenzyme.com/ en/about-us/newsroom/2020/2020-07 -02-20- 30-00.

Ruxolitinib: It is an inhibitor of JAK /STAT signaling pathway, involved in the inflammatory response. Efficient in myeloproliferative malignancies that acts reducing the cytokine storm, which is the worse condition in patients with intensive care and mechanical ventilation then; this is a good alternative drug to palliate detrimental consequences of COVID-19 in patients [92].

Siltuximab: It is an antagonist of the IL-6 receptor and as consequence it inactivates IL-6–induced signals. The Spanish Agency of Medicine has admitted the use of Sarilumab and Ruxolitinib drugs for COVID-19 pathology [93].

Baricitinib (Olumiant)**:** It is an anti-inflammatory activity drug that acts as an inhibitor of JAK1/JAK2 pathway that is approved in more than 65 countries for the treatment of adult patients with moderate to severe active rheumatoid arthritis. It has a dual action on COVID-19 therapy including the inhibition of cytokine release and SARS-CoV-2 endocytosis. In a recent study it was indicated a lower fatality rate and ICU admission in the baricitinib group compared with controls.

Anakinra (Kineret)**:** It is an antagonist of IL-1 receptor. This drug is used against COVID-19 and it is tested by up to ten Spanish hospitals and it is considered as an effective drug to cure COVID-19.

9.3. Macrophage Signaling Regulation

Acalabrutinib: It is a selective BTK inhibitor, was associated with improved oxygenation, normalization of IL-6 and normalization of CRP when administered to 19 nonrandomized, hospitalized patients with severe COVID-19. A prospective randomized controlled clinical trial is now pending.

Mavrilimumab: It is an anti-GM-CSF receptor-α monoclonal antibody, was associated with improved clinical outcomes compared with standard care in 13 non-randomized, non-mechanically ventilated patients with severe COVID-19 pneumonia. A global placebo-controlled phase 2/3 randomized clinical trial is pending.

9.4. Others

The later complications associated to Covid-19 are pneumonia, coagulation sepsis-induced and if is not properly controlled may progress in disseminated intravascular coagulation and venous thromboembolism such as it has been demonstrated in COVID-19 patients through immunologic and toxic activation. Generally, when there is deep respiratory failure or very low levels of blood O_2, it is necessary to use aeration mechanism administered in the UCI. With regard to this feature, the must be revised in the patient. Thus, the assessment of PT, PTT, D-dimer and platelets should be measured in order to know if the lack of O_2 is due to malfunctioning of the pulmonary alveoli or is a consequence of alterations in coagulation process. In the first case, respirators could keep the patient under the best possible circumstances until his immune system may counteract the inflammatory responses. The use of a respirator when blood is unable to exchange O_2/CO_2 does not make sense. In this case it would be better the use of anticoagulant such as unfractionated heparin or low-molecular-weight heparin. However, there are controversies on its effectiveness [94,95].

The intravenous administration of IgG immunoglobulin in conjunction with low-molecular weight heparina are good candidate for treatment [96]. Administration of tissue plasminogen activator (tPA). It was administered to three patients with COVID-19 with a good result [97,98].

10. Conclusion

From everything known about the SARS-CoV2, the following features can be deduced:

1) The entry of the virus into the cell is through ECA2, the enzyme that catalyse the pass of angiotensin II to angiotensin 1-7.

2) Angiotensin II can binds to the AT1 receptor, which

may provoke vasoconstriction, fibrosis and inflammation among other dysfunctions.

3) Induction of vasoconstriction and fibrosis may provoke blood coagulation

4) SARS-CoV2 activates immune system and according to the experience, in some cases, exacerbates cytokines production in the cytokine storm and also contributes to inflammation.

Thus, since there is no known drug able to eliminate the virus, we believe that according to SARS-CoV2 symptomatology, the treatment of Covid-19 pathology must be personalized.

Patients without symptoms: This means that the immune system of these patients works correctly to eliminate the virus. They do not need any treatments. They only need to be isolated to avoid the propagation of infection.

Patients with mild symptoms: We should immediately do a blood test in which inflammation (cytokines) and coagulation parameters are measured. If the patient has coagulation problems, they will be treated with: a) angiotensin receptor antagonists and anticoagulants. Administration of AT1 receptor antagonist drugs could prevent vasoconstriction. This treatment would possibly prevent blood clots formation in SARS-CoV2 patients.

If patients present inflammation without analytical parameters of coagulation: It may be correct to also use no-steroidal in spite of steroidal corticoids or natural anti-inflammatory drugs. The steroidal, corticoids drug, are good anti-inflammatory but, due to their immunosuppressive action, they are not recommended during the first step of viral infection. However, it could be effective if the patients present inflammation as a consequence of cytokine storm.

In most severe cases: The administration of oxygen through respirators in conjunction with anti-inflammatories and AT1 antagonist would also be indicated, but always in the event that there was no coagulation because under these circumstances the exchange of O_2/CO_2 would not be effective. Under this last circumstance, the administration of anticoagulants, anti-inflammatories and anti AT1 drugs in conjunction with respiratory machine should be necessary.

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