Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.54.008559

COVID-19: Molecular Aspects of the Disease, Diagnosis and Treatment. What do we Know so Far?

Rodolfo Matías Ortiz Flores[1]* and Corina Verónica Sasso[2]

[1]*Department of Human Physiology, School of Medicine, CAMPUS TEATINOS C/Boulevar Luis Pasteur, University of Malaga 29010, Spain*

[2]*Department of Medicine and Dermatology, School of Medicine, CAMPUS TEATINOS C/Boulevar Luis Pasteur, University of Malaga 29010, Spain*

***Corresponding author:** Rodolfo Matías Ortiz Flores, Department. Human Physiology, School of Medicine, Campus Teatinos C/Boulevar Luis Pasteur, University of Malaga 29010, Malaga, España, Spain

ARTICLE INFO

Received: November 15, 2023

Published: January 10, 2024

Citation: Rodolfo Matías Ortiz Flores and Corina Verónica Sasso. COVID-19: Molecular Aspects of the Disease, Diagnosis and Treatment. What do we Know so Far?. Biomed J Sci & Tech Res 54(3)-2024. BJSTR. MS.ID.008559.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by a virus called SARS-CoV-2. It first emerged in December 2019 in Wuhan, China, and has since spread to every country in the world. As of October 4, 2023, the World Health Organization (WHO) has reported over 628 million confirmed cases of COVID-19 and over 6.5 million deaths. SARS-CoV-2 is a respiratory virus that can spread through respiratory droplets produced when an infected person coughs, sneezes, or talks. It can also spread through contact with contaminated surfaces or objects. The most common symptoms of COVID-19 are fever, cough, fatigue, shortness of breath, and muscle aches. In some cases, COVID-19 can lead to more serious complications, such as pneumonia, acute respiratory distress syndrome (ARDS), and death. There is no specific cure for COVID-19, but there are treatments that can help relieve symptoms and prevent complications. The most effective way to prevent COVID-19 is to get vaccinated. COVID-19 vaccines have been shown to be highly effective in preventing infection, hospitalization, and death. Other ways to help prevent the spread of COVID-19 include wearing a mask, social distancing, washing your hands frequently, and practicing respiratory etiquette. The COVID-19 pandemic has had a devastating impact on the world. It has caused millions of deaths, disrupted economies, and changed the way we live our lives. The pandemic is not over, and it is important to continue to take steps to protect yourself and others from COVID-19. In this review we will address the molecular characteristics of the virus, the pathogenesis, and we will discuss the types of diagnosis and treatment according to the scientific reports available to date.

Keywords: COVID-19; SARS-CoV-2; Protein S; ACE-2; RT-PCR

Abbreviations: SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; ACE-2: Angiotensin-Converting Enzyme Type 2; AT2: Alveolar Type II; ER: Endoplasmic Reticulum; PCR: Polymerase Chain Reaction; ELISA: Enzyme-Linked Immunosorbent Assay; ARDS: Acute Respiratory Distress Syndrome; WHO: World Health Organization

Introduction

The pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has represented a great threat to global health, being more severe than that caused by other coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). During the epidemic in 2002, SARS- CoV infected more than 8000 people worldwide, causing 800 deaths, representing a mortality rate of 10%. While MERS- CoV in 2012 infected 857 people and caused 334 deaths, causing a mortality rate of 35% [1]. As of October 4, 2023, the COVID-19 pandemic has continued to spread around the world, with the World Health Organization (WHO) reporting over 628 million confirmed cases and over 6.5 million deaths. In Argentina, the number of confirmed cases has reached 4,296,000, with 102,000 deaths. In Mendoza, the number of confirmed cases has reached 12,000, with 300 deaths. In Spain, the number of confirmed cases has reached 16,200,000, with 108,000 deaths. In Málaga, the number of confirmed cases has reached 220,000, with 4,000 deaths. The pandemic has had a devastating impact on the world, causing millions of deaths, disrupting economies, and changing the way we live our lives. The pandemic is not over, and it is important to continue to take steps to protect yourself and others from COVID-19:

- The number of cases and deaths continues to increase. As of October 4, 2023, the WHO has reported over 628 million confirmed cases and over 6.5 million deaths. This represents an increase of over 200 million cases and 2 million deaths since July 21, 2020.

- Vaccination rates continue to increase. As of October 4, 2023, over 70% of the world's population has received at least one dose of a COVID-19 vaccine. This represents an increase of over 50% since July 21, 2020.

- New variants continue to emerge. The Omicron variant, which was first identified in November 2022, is now the dominant variant in most countries. Omicron is more transmissible than previous variants, but it is generally less severe.

SARS-CoV-2 was first isolated and identified in December 2019, in patients who had been exposed at a seafood market in Wuhan City, Hubei Province, China [2]. The COVID-19 epidemic was declared by the World Health Organization (WHO) as a public health emergency of international concern on January 30, 2020. SARS-CoV-2 quickly began to spread globally, and the On March 11, 2020, the WHO officially declared the disease a pandemic.In this review we will address the molecular characteristics of the virus, pathogenesis, diagnosis and treatment according to the scientific reports available to date.

Molecular Characteristics of SARS-COV-2

SARS-CoV-2 belongs to the group of coronaviruses, which are a highly diverse group of enveloped single-stranded RNA viruses [3]. These viruses belong to the Coronaviridae family, the virions are pleomorphic and have a size of 118-136 nm, which is why they are considered "large and heavy" viruses. The structure of the viral particle consists of a nucleocapsid formed by the viral genome to which multiple copies of the N protein or nucleocapsid protein are attached. The nucleocapsid adopts a helical structure and is shaped like a ball. As can be seen in Figure 1, surrounding this structure is the envelope composed of a lipid bilayer in which the viral proteins are inserted: S (spike), E (envelope) and M (membrane), which makes it treat of an enveloped virus. The virus has a single-stranded RNA genome of positive polarity, 26-32 kb in length. From this molecule, the total number of proteins necessary to complete the complete replication cycle are synthesized. The viral genome encodes at least 27 proteins, including 16 non-structural proteins and 4 structural proteins: S, E, M and N (nucleoprotein) [4]. These viruses cause various diseases that affect the respiratory, digestive and neurological systems, with varying severity in humans and animals. Coronavirus infections have traditionally caused a low percentage of annual respiratory infections. In the last two decades, two novel coronaviruses have emerged that have caused severe disease in humans: severe acute respiratory syndrome coronavirus (SARS- CoV) and Middle East respiratory syndrome coronavirus (MERS- CoV) [5,6].

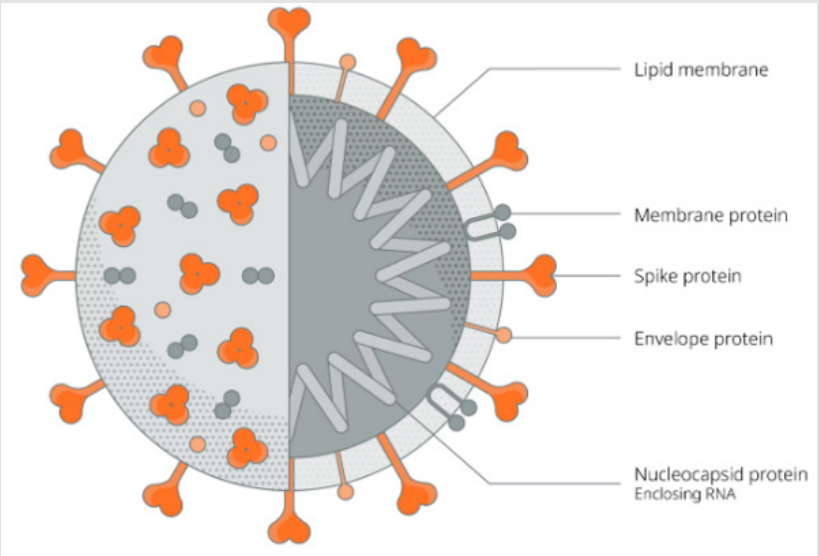

Figure 1: Structure of SARS-CoV-2. The main Structure of SARS-CoV-2 are highlighted, simplified [61].

The genetic sequence of SARS-CoV-2 shows 80% similarity with SARS- CoV and 50% with MERS- CoV [7,8], the origin of the latter two viruses being in bats [9]. Therefore, it is likely that SARS-CoV-2 originated in bats, although the intermediate host animal that caused infection in humans is still unknown. Therefore, evidence from phylogenetic analysis indicates that SARS-CoV-2 belongs to the betacoronavirus genus, which includes SARS- CoV, and that it can infect humans, bats, and wild animals [2]. Spike envelope protein (S) is a glycoprotein present in the virus membrane, and is responsible for entry into cells. The binding of this protein to a receptor present on host cells is the first step for a viral infection, followed by fusion with the cell membrane. Protein S projects in the form of spicules and is responsible for the crown-shaped appearance. In the case of SARS CoV-2 it is longer, since it is between 16 to 21 nm. It has been described that in the case of SARS- CoV, MERS- CoV and SARS-CoV-2 the protein has between 1104 to 1273 amino acids and comprises an (N)-terminal subunit called S1 and a C-terminal subunit called S2. The S1 domain is responsible for receptor binding; and the S2 domain, causes fusion with the cell membrane [10]. It has been reported that transmission of SARS-CoV-2 in humans occurs through the union between the S protein and the receptor called angiotensin-converting enzyme type 2 (ACE-2). This enzyme is an aminopeptidase that can be bound to the cell membrane or in soluble form that represents ACE-2 circulating in the blood and has a vital role in the cardiovascular and immune systems [11].

ACE-2 is particularly involved in cardiac function and the development of hypertension and diabetes mellitus. This receptor is highly expressed in the respiratory tract, especially in Alveolar Type II (AT2) cells of the lung, esophageal cells and stratified epithelial cells, in addition to other cells, such as enterocytes, myocardial cells, proximal tubule cells of kidney and bladder urothelial cells [12]. Therefore, patients infected with this virus not only experience respiratory tract problems, but also present disorders in the heart, kidneys, and digestive tract.

As shown in Figure 2, once fusion with the cell membrane occurs, activation of the S protein and consequent conformational changes occur, allowing the virus to enter the cells. The genetic material released by this virus is messenger RNA (mRNA), which is ready to be translated into a variety of proteins, both structural and non-structural, that play an important role in its survival, as well as in its virulence power [13]. Finally, the proteins are assembled together with the replicated genome in the endoplasmic reticulum (ER) and in the Golgi complex, forming small vesicles that will be exported out of the cell by exocytosis. Structural and biophysical analyzes have shown that SARS-CoV-2 binds to ACE-2 with approximately 10 to 20 times greater affinity than the S protein of SARS- CoV . The high affinity of the S protein to the human ACE-2 receptor could facilitate the spread of the virus in the human population [14]. Understanding the genetic and phenotypic structure of COVID-19 in pathogenesis is important for the production of drugs and vaccines.

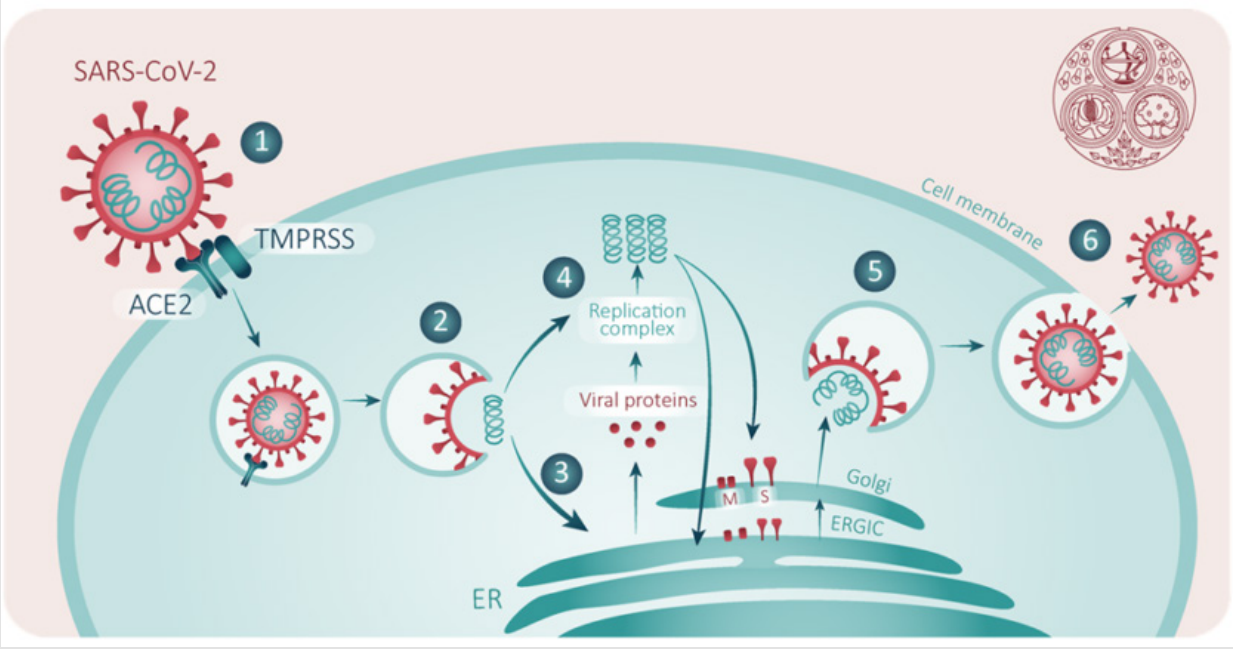

Figure 2: Schematic model of the SARS-CoV-2 virus life cycle. The spike protein binds to the ACE-2 receptor on the host cell to facilitate virus entry. After fusion of the viral and plasma membranes, the virus RNA is replicated and transcribed to produce its proteins. Finally, the viral proteins and new RNA are assembled in the endoplasmic reticulum (ER) and Golgi complex, giving rise to the new virus [1].

And many studies focus on those structural proteins that interact (as already mentioned) with the cell that SARS-CoV-2 infects. Even so, little information is found on those proteins that also favor the infectivity and pathogenesis of the virus but that are classified as non-structural proteins of the virus. Angeletti et al. (2020) propose a segment within non-structural regions of the SARS-CoV-2 genome, which has no homology with other coronaviruses and suggest that this mutation could explain the contagiousness of SARS-CoV-2 [15,16].

Pathogeny

The incubation period (initial infection until symptoms appear) of COVID-19 can be between 0 and 24 days, with an average of 5-7 days [17,18]. 95% of patients experience symptoms within 12.5 days of contact. This information suggests 14 days of medical observation or quarantine for those who have been exposed to the virus or who have had close contact with a positive patient. The main symptoms include fever, dry cough and fatigue. Other uncommon symptoms may include loss of taste and smell, sputum production, headache, diarrhea, dyspnea, and lymphopenia [14]. There are also some reports of patients presenting with gastrointestinal symptoms, including abdominal pain and diarrhea [19]. People of all ages are susceptible to the disease, including newborns and pregnant women. Most patients have mild to moderate symptoms. However, there is growing evidence that many people develop the disease asymptomatically. These patients present positive detection of the virus by qPCR, but do not present clinical signs or symptoms [20]. This represents a high risk, as they can still transmit the virus to other people and can contribute to the rapid spread of COVID-19. Therefore, it is a great challenge to prevent and control these types of patients globally. Approximately 20% of COVID-19 patients develop severe respiratory disease. Patients with severe disease typically present with fever, dry cough, dyspnea, and bilateral pulmonary infiltrate on chest images.

Complications include respiratory failure, liver injury, acute myocardial injury, acute kidney injury, septic shock, and even multiple organ failure. Risk factors for disease progression are older patient age, male sex, and those with underlying comorbidities.

Diagnosis

During an infection, the virus actively multiplies. When it begins, the virus can be detected in biological samples (throat or nasopharyngeal swab, tracheal aspirate, or bronchoalveolar lavage). In a latency period, it is not possible to detect the immune system response, but after a few days, antibody production begins. Antibodies of the IgM type are first produced until reaching a maximum after 7-10 days and later almost disappear [21]. This primary response is indicative of an acute infection. Subsequently, the secondary immune response will occur, which is faster, more intense and prolonged. IgG type antibodies will be produced and will last longer in the blood. Latest studies show that these antibodies decrease in quantity after 90 days [22]. Furthermore, at the level of mucosal secretions, such as respiratory secretions, IgA plays a predominant role [23]. To detect the presence of the virus (direct detection), two types of tests are used: the Polymerase Chain Reaction (PCR) that detects the genome of the virus or immunological tests that detect the proteins (antigens) of the virus. The third type of test is the one that detects the antibodies that you produce in response to the infection; they are serological tests for indirect detection of the virus. The general process of each test is explained here (Figure 3).

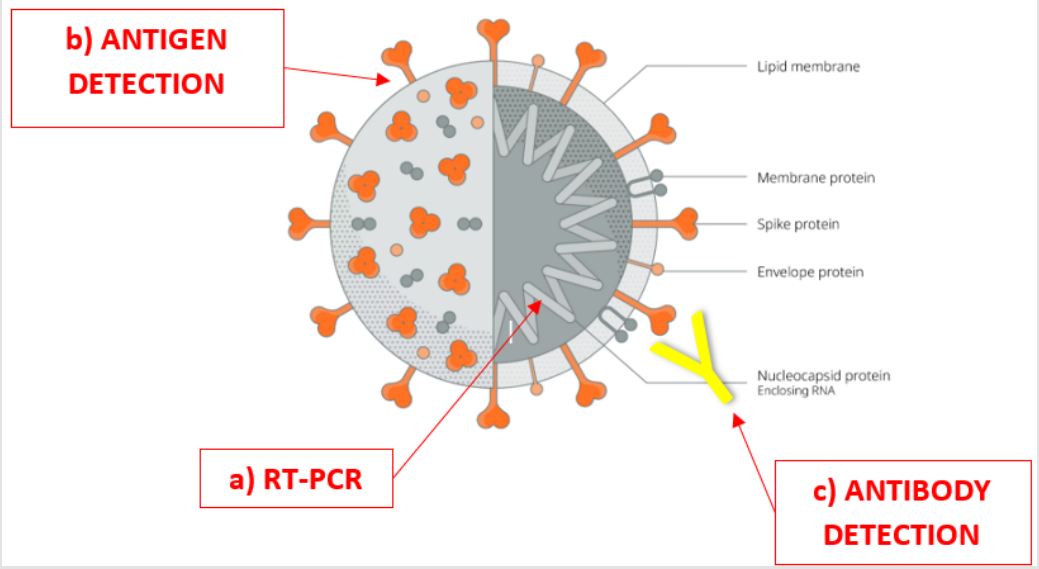

Figure 3: Molecular targets for COVID-19 Diagnosis. To detect the presence of the virus, reverse transcription polymerase chain reaction (RT-PCR) (a) is used to detect the virus genome, or immunological tests (b) are used to detect the virus proteins (antigens). Tests are also used to detect the antibodies (c) that the body produces in response to infection.

Retro-Transcription-PCR (RT-PCR): Single-stranded RNA molecule of about 30 kb. Once the sample is taken using a nucleic acid extraction kit, viral RNA is obtained. Next, retro-transcription is carried out from the RNA to DNA, using a kit that uses an enzyme called reverse transcriptase or Retro Transcriptase (hence the "RT", from the name RT-PCR). The virus genome in the form of DNA is then amplified by PCR. This amplification consists of making millions of copies of a DNA fragment, so that we can "visualize" it or detect it using a specific system. The real-time PCR system even allows us to quantify the sample, that is, to know how many copies of the virus we have by quantity. If the reaction is positive, it shows that there was RNA from the virus, meaning that the person was infected. Since the first thing we obtained about the virus was its genome, these types of tests are the first to be developed. In fact, since January 13, the WHO has already published the first protocol [24]. Normally, two tests are carried out: one for screening and a second confirmatory. You can even do an additional third-party confirmation. These three RT-PCR assays are designed to detect three different genes of the virus. These PCR tests are very specific and sensitive. They usually take a few hours to complete. They require specialized equipment and technical personnel. They can test positive in people before they show symptoms, but who already have the virus. Throughout the illness they can allow us to monitor how the infection is going, because when the person has already been cured and does not have the active virus, in principle they should test negative. It is important to highlight that it cannot be ruled out that convalescent patients "without symptoms" may test positive in the RT-PCR and continue to be carriers of the virus.

Antigenic Test: Another way to confirm the presence of the virus is to detect its proteins or antigens. The most common technique here is called enzyme-linked immunosorbent assay (ELISA) based on the nucleocapsid protein (N) and spike protein (S) of SARS-CoV-2. Specific antibodies are fixed on a support that will react against some protein of the virus [25]. If there are viral particles in the sample (the same as for RT-PCR), they will be fixed to the antibody. It is as if the virus has been captured by the antibody [26]. Next, a second antibody against the virus is added so that a sandwich or "sandwich" is formed: antibody- virus-antibody. This second antibody will be labeled or labeled in some way to reveal the reaction. If the reaction is positive, it shows that there were virus proteins, meaning that the person was infected. This type of test based on the detection of molecules is very common in clinical diagnosis. Its basis is the same as traditional drug testing or pregnancy tests. The advantage is that they are much faster, they do not require specific equipment or highly qualified technical personnel. The disadvantage is that they are less specific and less sensitive than RT-PCR, so a specific ELISA method for COVID-19 can be used as a complementary method for RT-PCR to detect SARS-CoV-2 [27]. An additional comment is that although the reaction is positive, it does not imply that the virus is active and infectious. That is, we can detect its genome or its proteins but the virus is not complete, that is, we may be detecting "remnants" of the virus.

Serological Tests: The third approach consists of detecting the immune response to the virus, the antibodies. It is an indirect detection, that is, the virus is not detected, but rather we reveal the immune response to it [28]. In this case, the sample we are going to use is a drop of blood, because we are going to detect the antibodies that you have generated against the virus. In this case, virus proteins are fixed to the support, normally the proteins most exposed to the outside, such as the envelope protein S. If there are antibodies against the virus in the sample, they will stick and become fixed to the proteins of the virus. Next, a second antibody against the human antibody is added. This second antibody will be labeled or labeled in some way to reveal the reaction. If the reaction is positive, it shows that there were antibodies against the virus, that is, that the person has at some point been in contact with the virus and their immune system has reacted by producing antibodies. This does not necessarily mean that you are infected, perhaps you have been cured, or you have simply been in contact with the virus and have not had symptoms [29,30]. The advantage is that they are much faster than PCR, and depending on the type of support, they can be performed in less than a few minutes, and do not require specific equipment or highly qualified technical personnel. The disadvantage is that they are much less specific than RT-PCR, and this type of test requires our body to produce antibodies in detectable quantities. That is, a person can be infected, but during the first days do not test positive in this type of test. Some antibody tests can distinguish the type of immunoglobulin: whether it is IgM, indicative of a recent infection, or IgG, indicative of a secondary response, and therefore more prolonged. However, recent studies have shown that after 90 days, the antibodies generated against SARS-CoV-2 decrease in quantity, returning to the initial levels of the infection [22].

In Argentina: In Argentina, two relevant tests have been produced to help diagnose COVID-19, detecting either parts of SARS-CoV-2 or its genome. The "COVIDAR IgG" test detects anti-SARS-CoV-2 antibodies in blood and serum using the ELISA technique, the same one used, for example, for the detection of HIV and hepatitis B infection. The "NEOKIT- COVID-19" allows testing RNA samples and obtaining results in less than two hours (with similar sensitivity as current RT-PCR techniques) and does not require complete equipment (real-time thermocyclers). Qualitatively determines a positive or negative test for SARS-CoV-2. Its variant is the ELA-CHEMSTRIP which accompanies the kit, a device for incubating at 60°.

In Spain: Two main types of diagnostic tests are available for COVID-19 in Spain: molecular tests and serological tests. Molecular tests detect the genetic material of SARS-CoV-2, the virus that causes COVID-19. The most common molecular test is RT-PCR. RT-PCR tests are highly sensitive but can be time-consuming and require specialized equipment. Serological tests detect antibodies against SARS-CoV-2. Antibodies are proteins produced by the immune system in response to infection. Serological tests can be used to identify individuals who have been infected with SARS-CoV-2 in the past, even if they are no longer contagious. Antigen tests are also available for

COVID-19 diagnosis. Antigen tests detect the presence of SARS-CoV-2 proteins in respiratory samples. Antigen tests are less sensitive than molecular tests, but they are faster and easier to perform.

Treatment

There are no specific treatments for COVID-19 at this time. However, therapies being investigated include drugs that have been used to treat malaria and autoimmune diseases; antiviral medications that were developed for other viruses and antibodies from people who have recovered from COVID-19.

Convalescent Plasma: When people recover from COVID-19, their blood contains antibodies that their bodies produced to fight the coronavirus and help them recover. Antibodies are found in plasma, which is the acellular fraction of blood. Convalescent plasma, literally plasma from recovered patients, has been used for more than 100 years to treat a variety of diseases, from bacterial diseases, cancer, and measles to polio, chickenpox, and SARS [31,32]. In the current situation, plasma containing antibodies from a recovered patient is administered by transfusion to a patient suffering from COVID-19. The donor's antibodies would appear to help the patient fight the disease, possibly shortening the duration or reducing the severity of the disease, as well as providing other blood components that the patient himself cannot produce in his convalescent state. Although convalescent plasma has been used for many years, and with varying success, not much is known about how effective it is in treating COVID- 19, since, for example, experts also do not know the best time during the course of the disease. disease to administer plasma, or if hyper immunity does not affect other processes in the body [33].

Immunomodulators: According to data collected by hospitals, around 20% of their coronavirus patients develop this cytokine storm (immunomodulators), especially Interleukin-1 (IL-1) and IL-6, among others, which consists of an excessive and uncontrolled response of the immune system with hyperinflammation, confined, in the case of COVID-19, especially in the lung. This causes severe pneumonia that can cause acute respiratory failure, described as the main cause of mortality from this disease [34,35]. Anakinra is an antagonist of the recombinant human IL-1 receptor, that is, it competes with greater affinity on the specific IL-1 receptors of cells that will participate in said inflammation. Anakinra is approved to treat rheumatoid arthritis and cryopyrin- associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease [36], however there are very few clinical trial data on the use of IL-1 inhibitors in patients with COVID-19. On the other hand, the selective blockade of IL-6 has been explored with antibodies directed at the IL-6 receptor, such as T ocilizumab and Sarilumab, or directed towards IL-6 itself, such as Siltuximab, and thus achieve inhibit the inflammatory signaling cascade triggered by this interleukin [37]. Again, there is very little clinical trial data on the use of IL-6 inhibitors in patients with COVID-19. Finally, there are insufficient data to recommend for or against the use of interleukin inhibitors [38].

Antiretroviral Drugs: Antiretroviral drugs are specific antiviral medications for the treatment of retrovirus infections. There is currently no specific antiretroviral treatment for COVID-19. However, medications previously developed to treat other viral infections are in the testing phase and could be effective against SARS-CoV-2. Remdesivir It is a prodrug that belongs to the group of nucleotide analogues, specifically adenosine. It has demonstrated in vitro activity against SARS-CoV-2 [39], and in vitro and in vivo activity (based on animal studies) against SARS and MERS [40-42]. Remdesivir binds to viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. An interesting study that emerged specifically for SARS-CoV-2 was that, in a rhesus macaque model infected with SARS-CoV-2, treatment with Remdesivir It started shortly after virus inoculation. Animals treated with Remdesivir had lower levels of lung virus and less lung damage than control animals [43]. Remdesivir _ It is one of the few antiretroviral drugs I recommend for the treatment of COVID-19 in hospitalized patients who require supplemental oxygen, that is, of a serious nature, but there is insufficient data on the optimal duration of therapy, nor that I recommend for or against of Remdesivir for the treatment of patients with mild or moderate COVID-19 [44]. Chloroquine /Hydroxychloroquine has been one of the most studied medications against SARS, but it has been concluded not to be recommended for treatment against SARS-CoV-2 [45,46].

Even the combination of hydroxychloroquine plus azithromycin is not recommended due to the potential for toxicity [47]. Thus, the molecular action of both chloroquine and hydroxychloroquine has been demonstrated in several trials, demonstrating that both compounds increase the endosomal pH , inhibiting the fusion of SARS-CoV-2 and the host cell membranes [48]; that chloroquine inhibits the glycosylation of the cellular receptor of angiotensin-converting enzyme 2, which may interfere with the binding of SARS-CoV-2 to the cellular receptor [49]; and finally, that in vitro , both chloroquine and hydroxychloroquine can block the transport of SARS-CoV-2 from early endosomes to endolysosomes , which may be necessary for the release of the viral genome [50]. However, the available clinical data on the use of chloroquine and hydroxychloroquine to treat COVID-19 come primarily from patients with mild disease. Clinical data on the use of these medications in patients with severe and critical COVID-19 are very limited and the doses used appear to be toxic. Replication of SARS-CoV-2 depends on the cleavage of polyproteins in an RNA-dependent RNA polymerase and a helicase.1 The enzymes responsible for this cleavage are two proteases, 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro) Antiviral medications such as Lopinavir / Ritonavir They are inhibitors of 3CLpro of coronaviruses, in vitro, and this protease seems highly conserved in SARS-CoV-2 [51,52]. Even so, Lopinavir / Ritonavir has in vitro activity against coronaviruses, and is believed to have a poor selectivity index, indicating that higher than tolerable levels of the drug may be required to achieve significant inhibition [53].

Apparently, Lopinavir / Ritonavir or other HIV protease inhibitors have not proven to be favorable, due to their unfavorable pharmacodynamics. Lopinavir is excreted in the gastrointestinal tract and therefore coronavirus-infected enterocytes may be exposed to higher concentrations of the drug [54]. These antiviral medications have simply not demonstrated clinical benefit in COVID-19 patients.

Interferons: Interferons, a family of cytokines with antiviral properties, have been suggested as a potential treatment for COVID-19 due to their antiviral properties in vitro and in vivo. However, studies so far have shown that there was no benefit when interferons were used in patients with other coronavirus infections, and the significant toxicities of interferons outweigh the possibility of benefit. Additionally, clinical trial results for COVID-19 patients are lacking. Interferon beta used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes [55-57]. During SARS-CoV-2 infection, patients with severe clinical presentation have greatly decreased type I and III IFN activity [58]. On the other hand, the administration of IFN-λ (type III) to infected monkeys confers partial protection against SARS-CoV-1 [59]. But a latest study on ACE2, which is the receptor that SARS-CoV-2 uses as a route of entry into the cell, has shown that the ACE2 gene is modulated by IFN, that is, the levels of ACE2 receptors that " "open the doors to the virus" could increase in the presence of interferons, and that would facilitate its entry [60].

In Argentina: The Ministry of Health of the Nation clarifies, in its latest modification, that there is not sufficient clinical data to recommend for or against the use of immunomodulatory therapies, chloroquine or hydroxychloroquine, Remdesivir , Lopinavir / Ritonavir , nor immunomodulators or interferon for the treatment of COVID-19, and these recommendations are under permanent review and are subject to updating according to the evolution of the pandemic at a local and international level and the available scientific evidence [61].

In Spain: The Spanish Ministry of Health does not recommend the use of immunomodulatory therapies, chloroquine or hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir, or immunomodulators or interferon for the treatment of COVID-19. The available evidence does not support the effectiveness of these treatments, and some of them can have serious side effects. The Ministry of Health emphasizes the importance of continuing research into potential treatments for COVID-19.

Final Considerations

There are several clinical trials underway worldwide (some of them with active participation of hospitals in our country), but at the moment the results are not conclusive, and the success stories refer to small-scale trials, without statistical validity. More than one hundred vaccines are also in process, in different phases of development and clinical stages. We must be optimistic, but patient. In these circumstances, research is carried out under great pressure and based almost exclusively on the concept of trial and error that has sometimes been used previously against other viruses. This pandemic must help us to definitively make world governments realize the urgent need to invest in the generation of knowledge, and that investment in Science, Education and Health must be the basis on which a fair, egalitarian and society is built. prosperous We cannot forget that, according to a study by researchers at the Boston School of Public Health recently published in the journal Science, even in the case of the apparent elimination of the pandemic in the coming months, estimates for the post-pandemic periods foresee occasional resurgences until 2024 and we have no choice but to be prepared.

References

1. He F, Deng Y, Li W (2020) Coronavirus disease 2019: What we know? J Med Virol John Wiley and Sons Inc 92(7): 719-725.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, et al. (2019) A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382(8): 727-733.
3. Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen KY (2016) Coronaviruses-drug discovery and therapeutic options. Nature Reviews Drug Discovery 15(5): 327-347.
4. Kandeel M, Ibrahim A, Fayez M, Al-Nazawi M (2020) From SARS and MERS CoVs to SARS-CoV-2: Moving toward more biased codon usage in viral structural and nonstructural genes. J Med Virol 92(6): 660-666.
5. Chan JFW, Lau SKP, To KKW, Cheng VCC, Woo PCY, et al. (2015) Middle East Respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev 28(2): 465-522.
6. Cheng VCC, Lau SKP, Woo PCY, Kwok YY (2007) severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clinical Microbiology Reviews 20(4): 660-694.
7. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, et al. (2020) Identification of a novel coronavirus causing severe pneumonia in humans: a descriptive study. Chin Med J (Engl) 133(9): 1015-1024.
8. Lu R, Zhao X, Li J, Niu P, Yang B, et al. (2020) Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395(10224): 565-574.
9. Cui J, Li F, Shi ZL (2019) Origin and evolution of pathogenic coronaviruses. Nature Reviews Microbiology 17(3): 181-192.
10. He Y, Zhou Y, Liu S, Kou Z, Li W, et al. (2004) Receptor-binding domain of SARS-CoV spike protein induces highly potent neutralizing antibodies: Implication for developing subunit vaccine. Biochem Biophys Res Commun 324(2): 773-781.
11. Turner AJ, Hiscox JA, Hooper NM (2004) ACE2: From vasopeptidase to SARS virus receptor. Trends in Pharmacological Sciences 25(6): 291-294.
12. Xu H, Zhong L, Deng J, Peng J, Dan H, et al. (2020) High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci.
13. Astuti I, Ysrafil (2020) Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr Clin Res Rev Elsevier Ltd 14(4): 407-412.
14. Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity.
15. Benvenuto D, Angeletti S, Giovanetti M, Bianchi M, Pascarella S, et al. (2020) Evolutionary analysis of SARS-CoV-2: how mutation of Non-Structural Protein 6 (NSP6) could affect viral autophagy. J Infect WB Saunders Ltd 81(1): e24-e27.

16. Angeletti S, Benvenuto D, Bianchi M, Giovanetti M, Pascarella S, et al. (2020) COVID-2019: The role of the nsp2 and nsp3 in its pathogenesis. J Med Virol. John Wiley and Sons Inc 92: 584-588.

17. Shi Y, Wang G, Cai X peng, Deng J wen, Zheng L, et al. (2020) An overview of COVID-19. Journal of Zhejiang University: Science B.

18. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. (2020) Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. New England Journal of Medicine.

19. Xu Z, Shi L, Wang Y, Zhang J, Huang L, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8(4): 420-422.

20. Gao Z, Xu Y, Sun C, Wang X, Guo Y, et al. (2020) A systematic review of asymptomatic infections with COVID-19. Journal of Microbiology, Immunology and Infection 54(1): 12-16.

21. Van der Heide V (2020) Neutralizing antibody response in mild COVID-19. Nat Rev Immunol. Nature Research 20(6): 352.

22. Seow J, Graham C, Merrick B, Acors S, Steel KJ, et al. (2020) Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. medRxiv, p. 1-24.

23. Padoan A, Sciacovelli L, Basso D, Negrini D, Zuin S, et al. (2020) IgA-Ab response to spike glycoprotein of SARS-CoV-2 in patients with COVID-19: A longitudinal study. Clin Chim Acta. Elsevier BV 507: 164-166.

24. Corman V, Bleicker T, Brünink S, Drosten C, Landt O, et al. (2020) Diagnostic detection of 2019-nCoV by real-time RT-PCR. Who 1-13.

25. Chen S, Lu D, Zhang M, Che J, Yin Z, et al. (2005) Double-antigen sandwich ELISA for detection of antibodies to SARS-associated coronavirus in human serum. Eur J Clin Microbiol Infect Dis 24(8): 549-553.

26. Woo PCY, Lau SKP, Wong BHL, Tsoi HW, Fung AMY, et al. (2005) Differential sensitivities of severe acute respiratory syndrome (SARS) coronavirus spike polypeptide enzyme-linked immunosorbent assay (ELISA) and SARS coronavirus nucleocapsid protein ELISA for serodiagnosis of SARS coronavirus pneumonia. J Clin Microbiol 43(7): 3054-3058.

27. Liu W, Liu L, Kou G, Zheng Y, Ding Y, et al. (2020) Evaluation of nucleocapsid and spike protein-based enzyme-linked immunosorbent assays for detecting antibodies against SARS-CoV-2. J Clin Microbiol. American Society for Microbiology 58(6): e00461-20.

28. Wu F, Wang A, Liu M, Wang Q, Chen J, et al. (2020) Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv.

29. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, et al. (2020) Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med Nature Research 26: 1200-1204.

30. Cao WC, Liu W, Zhang PH, Zhang F, Richardus JH (2007) Disappearance of antibodies to SARS-associated coronavirus after recovery. New England Journal of Medicine. Massachusetts Medical Society 357(11): 1162-1163.

31. Rajam G, Sampson J, M Carlone G, W Ades E (2010) An Augmented Passive Immune Therapy to Treat Fulminant Bacterial Infections. Recent Pat Antiinfect Drug Discov. Bentham Science Publishers Ltd 5: 157-167.

32. Virdi V, Depicker A (2013) Role of plant expression systems in antibody production for passive immunization. Int J Dev Biol Int J Dev Biol 57: 587-593.

33. Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, et al. (2020) Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev John Wiley & Sons Ltd 7(7): CD013600.

34. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng C-TK (2009) severe acute respiratory syndrome (SARS) Coronavirus-Induced Lung Epithelial Cytokines Exacerbate SARS Pathogenesis by Modulating Intrinsic Functions of Monocyte-Derived Macrophages and Dendritic Cells J Virol 83(7): 3039-3048.

35. Ong EZ, Chan YFZ, Leong WY, Lee NMY, Kalimuddin S, et al. (2020) A Dynamic Immune Response Shapes COVID-19 Progression. Cell Host Microbe 27(6): 879-882.

36. Waugh J, Perry CM (2005) Anakinra: A review of its use in the management of rheumatoid arthritis. BioDrugs 19(3): 189-202.

37. Atal S, Fatima Z (2020) IL-6 Inhibitors in the Treatment of Serious COVID-19: A Promising Therapy? Pharmaceut Med Adis 34(4):223-231.

38. Khan F, Fabbri L, Stewart I, Robinson K, Smyth AR, et al. (2020) A systematic review of Anakinra, Tocilizumab, Sarilumab and Siltuximab for coronavirus-related infections. medRxiv.

39. Wang M, Cao R, Zhang L, Yang X, Liu J, et al. (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Research 30: 269-271.

40. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, et al. (2017) Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 9(396): 3653.

41. De Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, et al. (2020) Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci US A 117(12): 6771-6776.

42. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, et al. (2020) Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 11(1): 222.

43. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, et al. (2020) Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature 585(7824): 273-276.

44. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, et al. (2020) Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med Massachusetts Medical Society 382: 2327-2336.

45. MH, TT, PP, ML, RM, et al. (2020) Treating COVID-19 with Chloroquine. J Mol Cell Biol J Mol Cell Biol 12(4): 322-325.

46. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. (2020) Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw open. NLM (Medline) 3: e208857.

47. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents Elsevier BV 56(1): 105949.

48. Wang M, Cao R, Zhang L, Yang X, Liu J, et al. (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Research Springer Nature 30(3): 269-271.

49. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, et al. (2005) Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J Virol J 2: 69.

50. Liu J, Cao R, Xu M, Wang X, Zhang H, et al. (2020) Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection *in vitro*. Cell Discovery Springer Nature, p. 1-4.

51. Liu X, Wang XJ (2020) Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. Journal of Genetics and Genomics 47(2): 119-121.

52. Tahir ul Qamar M, Alqahtani SM, Alamri MA, Chen LL (2020) Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. J Pharm Anal 10(4): 313-319.

53. Chen F, Chan KH, Jiang Y, Kao RYT, Lu HT, et al. (2004) *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 31(1): 69-75.

54. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, et al. (2004) Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. Thorax. Thorax 59: 252-256.

55. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA (2014) Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: An observational study. Int J Infect Dis 20: 42-46.

56. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, et al. (2014) Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: A retrospective cohort study. Lancet Infect Dis 14(11): 1090-1095.

57. Shalhoub S, Farahat F, Al-Jiffri A, Simhairi R, Shamma O, et al. (2015) IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: A retrospective study. J Antimicrob Chemother 70(7): 2129-2132.

58. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, et al. (2020) Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients. medRxiv 369(6504): 718-724.

59. Prokunina-Olsson L, Alphonse N, Dickenson RE, Durbin JE, Glenn JS, et al. (2020) COVID-19 and emerging viral infections: The case for interferon lambda. Journal of Experimental Medicine 217(5): e20200653.

60. Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, et al. (2020) SARS-CoV-2 ACE2 Receptor Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. Cell 181(5): 1016-1035.

61. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R (2020) Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.54.008559

Rodolfo Matías Ortiz Flores. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php