Literature Review
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"SARS COV-2/COVID-19 Pandemic". First is do no harm (Primum non nocere), the evolution of therapy and treatment COVID-19, a literature review

Abstract

The presence of COVID-19 was first reported in late 2019 in Wuhan, China, and since then the infection has spread widely in China and around the world. The first cases of COVID-19 were linked to a live animal market in Wuhan, China, suggesting that the virus was initially transmitted from animals to humans. The absence of an effective treatment against severe respiratory syndrome secondary to coronavirus infection has led clinicians to utilized drugs, that are to be effective for the other medical conditions, and that are produced side effects or adverse events.

We review the literature on SARS-CoV-2, of the diverse treatment of COVID-19 and describe, the side effects of the drugs, might to be inefficient , and the risk-benefit. How Critical Care Point view.

Keywords: SARS COV-2, Covid-19

Volume 17 Issue 2 - 2025

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Received: March 18, 2025 | **Published:** March 25, 2025

Introduction

From the End of 2019 December, Several cases of an epidemic pneumonia presented in patients at Wuhan (Hubei Province), China including several patients with exposure to a large seafood market selling live animals was announced by Chinese authorities, the pneumonia caused by a new coronavirus , evolving into a global pandemic.[1-3] Originally called new coronavirus 2019 (2019-nCoV), this virus was then Officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by WHO (World Health Organization). Coronaviruses are a large family viruses that some of them are more known such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). SARS-CoV-2 viruses are positive single-stranded RNA viruses, whose infection can be asymptomatic or lead to the coronavirus disease 2019 (Covid-19), has different pattern of respiratory manifestations but also another non-specific clinical manifestations, that including Fever, headache, hemoptysis, nausea, vomiting, diarrhea,[4,5] can complicate the course of COVID-19 Infection is the Neurological manifestations: seizures, ischemic and hemorrhagic stroke, Guillain-Barre syndrome, smell and taste disorders (anosmia, ageusia);[6-9] Myocardial injury is common in COVID-19 and portends a worse prognosis. The clinical cardiovascular manifestations include elevations of cardiac biomarkers, cardiac arrhythmia, arterial and venous thromboembolism (VTE), and cardiogenic Shock and arrest,[10] other clinical presentations is the myocarditis.[11] To level Pulmonary, the features were vascular angiogenesis, Endothelialitis, and thrombosis ("Endotheliopathy").[12] Another parts of the body affect for the COVID-19, is the ophthalmological changes such as conjunctivitis, and the ocular lesions could include retinitis and optic neuritis.[13,14] Dermatological lesions: Five patterns of the cutaneous manifestations can be stablished: chilblain-like rashes in acral areas, appear as areas of erythema or violaceous, vesicles and pustules, are frequently asymptomatic , vesicular eruptions , urticarial lesions , maculopapular lesions and livedo-reticularis or necrosis.[15]

Is important remember, the principal reasons for Critical Care Unit admission for patients with severe coronavirus disease 2019 (COVID-19) is hypoxemic respiratory failure leading to mechanical ventilation or hypotension requiring vasopressor or vasoactive amines support, but the human Kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[16,17] The importance of the disseminated intravascular coagulation, with affection in others organ system, for example splenic infarction or renal infarction.[18,19] The absence of an effective treatment against severe respiratory syndrome secondary to coronavirus infection has led clinicians to utilized drugs, that are to be effective for the other medical conditions, and that are produced side effects. Due to the

affection of various organs, it is the origin of the various therapeutic schemes, which we analyze. There is an urgent need to better understand the host-pathogen biology of COVID-19 as this will offer important insights into treatment and management of the disease, including identification of new therapies. We review the literature on SARS-CoV-2, of the diverse treatment of COVID-19 and describe, the side effects of the drugs, might to be inefficient, and the risk-benefit. How Critical Care Point view.

Pharmacology therapy

Hydroxychloroquine/Chloroquine/ Azithromycin

The reposition drugs has been initiated in recent years.[20] It is important to use drugs that have been proven to be harmless and whose pharmacokinetics and optimal dosage are well known.[21] The interest increased in the use of hydroxychloroquine and chloroquine with the possible addition of azithromycin for the treatment of COVID-19. However, research has been limited outcomes assessed, short follow-up, exclusion of patients still admitted, small sample size, and types of patients studied. Few studies have evaluated adverse events potentially linked to the use of hydroxychloroquine or chloroquine and azithromycin in patients with COVID-19.[22-25]

Based on available evidence, the US Food and Drug Administration authorized the emergency use of strategic national stockpile and chloroquine in hospitalized patients when clinical trials were unavailable or not possible.[26] The hydroxychloroquine is known to block human - ether- a- go-go- related gene (HERG) and can cause drug-induced long-QT syndrome.[26] The clinical arrhythmic toxicity (syncope and torsade de pointes) is largely limited to chronic use (due to the agent's long half-life of 40 days), use of multiple concomitant QT-prolonging medications (e.g. azithromycin), metabolic derangements, renal failure, or in the setting of an acute overdose. To date, HCQ has been, widely tolerated in most populations as an antimalarial medication and is safely used in rheumatoid arthritis and systemic lupus erythematosus population without electrocardiogram (ECG) monitoring.[27] Mandeep Mehra and colleagues report the largest retrospective, observational study to date on the effects de chloroquine or Hydroxychloroquine, with or without a macrolide, in 96032 hospitalized patients from six continents. Their results indicate an absence of benefit of 4-aminoquinoline-based treatments in this population and suggest that they could even be harmful. This study and their results have had a considerable impact on the clinicians and research.[28]

The WHO has paused recruitment to the Hydroxychloroquine arm in their SOLIDARITY trial. The UK regulatory body, MHRA, request the temporary pausing of recruitment into all Hydroxychloroquine trials in the UK (treatment and prevention), and France has changed its national recommendation for the use of Hydroxychloroquine in COVID-19 treatment and also halted trials.[29] The principal problem, in the countries is the use overutilization by health professionals who are depleting supply by prescribing antimalarials for preexposure prophylaxis, and the patients with systemic lupus erythematosus and rheumatoid arthritis, who are having difficulty for obtaining their medication [30].

Considering that in many countries the compassionate use the Chloroquine or hydroxychloroquine to treat COVID-19 has already been indicated with severe disease, it would be unethical to test efficacy owing to the lack of a placebo group as comparator. This study suggest that the higher Chloroquine dosage not be recommended for critically ill patients with COVID-19, because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir, and these findings cannot be extrapolated to patients with nonsevere COVID-19.[31]

ACE (angiotensin-converting enzyme) inhibitors and ARBS (angiotensin-receptor blockers)

A critical host susceptibility factor, known as angiotensin-converting enzyme II (ACE II), has been identified for both SARS (SARS-CoV) y SARS-CoV-2, in humans and animals. It is fundamental for entry into target cells with the help of the cellular protease TMPRSS2.[4,5] ACE 2, which is highly expressed in the heart, lung, Kidneys, brain, testes, liver, and small intestine.[32,33]

Thus, the SARS-CoV-2 spike protein was predicted to also a strong binding affinity to human ACE2. The SARS-CoV-2 spike protein directly binds with the host cell surface ACE-2 receptor facilitating virus entry and replication.[34] The ACE2- expressing cells were alveolar epithelial type II cells, suggesting that these cells can serve as a reservoir for viral invasion.[35] The interaction between the SARS viruses and ACE 2 has been proposed as a potential factor in their infectivity,[36,37] and there are concerns about the use of the renin-angiotensin-aldosterone system (RAAS) inhibitors that may alter ACE2 and whether variation in ACE2 expression may be in part responsible for disease virulence in the ongoing Covid-19 pandemic.[38,39] In patients Asian (eastern) with hypertension urinary ACE2 levels were higher among patients who received long-term treatments with the ARB (angiotensin-receptor blocker) Olmesartan than among untreated control patients, but that association was not observed with ACE inhibitor enalapril or with other ARBs (losartan, candesartan, valsartan, and telmisartan).[40-42] Because ACE (Angiotensin-converting Enzyme) inhibitors and ARBs (angiotensin-receptor blockers) have different effects on angiotensin II, the primary substrate of ACE 2, the effects of these is agents on ACE2 (Angiotensin-converting Enzyme) levels and activity may be anticipated to differ. Despite substantial structural homology between ACE and ACE2, their enzyme active sites are distinct. ACE inhibitors in clinical use do not directly affect ACE2 activity.[41,42]

Antiviral therapy for COVID-19

There is no specific antiviral treatment that has been proven effective for COVID-19. Current treatment options are mainly based on previous experiences that showed clinical benefits in Influenza, Ebola, MERS, SAR, among other viral infections. In this review, we will update and summarize the most common and plausible drugs used to treat COVID-19. These drug therapies include antiviral agents such as remdesivir, lopinavir, favipiravir, oseltamivir, baloxavir, darunavir y rivabirin.[45]

Remdesivir

Among the drugs that have been used as part of the treatment is remdesivir, a pro-drug derived from a nucleotide analog, monofosforamidato,[1,4] which goes through an intracellular metabolism to become an adenosine triphosphate analog, capable of inhibiting viral RNA polymerase.[44] It has broad spectrum activity against members of several viral families including filovirus, paramyxovirus, pneumovirus,[45] coronavirus, and has shown prophylactic and therapeutic efficacy in clinical models of coronavirus infected patients.[45,46] Among the adverse effects that can condition the use of remdesivir are hypotension during loading dose, transaminase elevation, phlebitis, and gastrointestinal symptoms.[47]

We searched (remdesivir; covid) in medical portals such as Pubmed and Ovid, and found 182 related articles in Pubmed, one of which was a clinical trial, zero metanalysis, one randomized trial, 56 reviews and one systematic review up to June 09, 2020. We found in-vitro studies where they observed that remdesivir inhibits all human and animal coronavirus, including SARS-CoV-2, SARS-CoV-1, and MERS, by being a potent replication inhibitor in respiratory epithelial cells, reducing the viral load and consequently, the pulmonary infiltrates.[45] A study by Giled Sciences, The most relevant results are that 13% of patients died after completing treatment, 15% of patients worsened, and 68% presented clinical improvement with progressively lower supplemental oxygen requirements.[44] Adverse effects were reported in 60% of patients and included hepatic enzyme elevation, diarrhea, and rash. These adverse effects were observed more frequently in patients requiring invasive mechanical ventilation. Twelve patients (23%) presented severe adverse effects such as: multiple organ failure, septic shock, and acute kidney injury.[44] Another study that included 10 hospitals in Wuhan, Hubei China with patients aged 18 or older who were admitted to hospitalization ward and had diagnosis of severe COVID-19.[45] The clinical trial concluded that IV remdesivir did not significantly improve mortality or viral clearance time compared to COVID-19 patients receiving placebo. No significant difference was found in lowering viral load either.[45]

Lopinavir / Ritonavir

Lopinavir is a protease inhibitor antirretroviral agent. Most in-vitro studies have demonstrated that SARS-CoV may be inhibited by lopinavir.[48,49] The therapeutic relationship of lopinavir-ritonavir was first found in in-vitro studies that showed inhibition of type 3- chymotrypsin protease which is found in new coronavirus and is structurally different since it lacks a catalytic C2 site.[48] Among its known adverse effects are gastrointestinal intolerance, diarrhea that generally improves within the first two weeks, hepatitis, liver failure, pancreatitis, and prolongation of the PR interval.[48] A search in PubMed found a total of 4 clinical trials, 0 metanalysis, 3 randomized clinical trials, 38 reviews and 6 systematic reviews.[49,50] Cao, Wong and collaborators designed a randomized clinical trial called LOTUS, where they evaluated the efficacy and safety of oral administration of Lopinavir-Ritonavir in patients with active SARS-CoV-2 infection.[49] No significant differences were observed as far as clinical improvement, however, mortality at 28 days was lower in the lopinavir-ritonavir patient group compared to the standard care group.[49] Adverse effects were present in 46% of patients that received lopinavir-ritonavir (nausea, vomiting, diarrhea).[49] For patients with a history of long QTc syndrome, fist degree AV block, bundle branch block, bradycardia, and those with AST or ALT elevation three times the upper limit, dosing was limited to once a day.[51] The randomized trials did not find a clinical benefit. Observational studies were non-conclusive and the certainty of tests was low or very low.

Favipiravir (generic Avifavir in Russia)

Favipiravir (Avigan MR) was developed by Fujifil Toyama Chemical in Japan, in 2014, with intended use against aviar influenza or strains resistant to neuraminidase inhibitors, even though its activity is reduced in presence of nucleosides due to competition mechanisms. Favipiravir is a pro-drug that intracellularly transforms into bofuranosil phosphate favipiravir; which induces a destructive mutagenesis in RNA virus. It is not, however, effective against DNA virus.[52,53] For the moment, there is no published clinical trial available in medical literature. Avigan was not as useful in severely ill patients and did not show promising results. It must be administered before viral load reaches its maximum point. Up until mid-April, 2020, there are 8 clinical trials in China and 2 in Japan that study favipiravir's anti-SARS-CoV-2 potential. These tests include non-randomized and randomized controlled trials that evaluate the efficacy and safety of favipiravir alone or in combination with α interferon, baloxavir, tocilizumab or chloroquine phosphate.[52,53] Favipiravir is contraindicated in pregnant women due to teratogenicity and embryotoxicity observed in animals (Delang, Abdelnabi y Neyts, 2018; Shiraki y Daikoku, 2020).[54,55] Reported adverse events associated to favipiravir include altered hepatic function tests with abnormal transaminase levels, psychiatric symptoms, gastrointestinal discomfort, and hyperuricemia.[56,57] Favipiravir has not been approved by the FDA and is usually not available in the United States.

Darunavir

Darunavir (Prezista), another antiviral agent that acts as a HIV-1 protease inhibitor and is used in combination with other inhibitors of cytochrome P450 such as ritonavir or cobicistat, has proved inhibitory effects against SARS-CoV-2 in preclinical trial results. Regardless, Johnson and Johnson announced on March 18, 2020, that there was no evidence to back up the activity of darunavir against SARS-CoV-2. The Shanghai Public Health Clinical Center (SPHCC) designed a randomized, controlled, open, single-center phase 3 trial to evaluate the efficacy of the combination of darunavir/ cobicistat in 30 patients with COVID-19 and the results found that the combination was not effective in reducing symptoms of duration of treatment.[58]

Ribavirin

Ribavirin's antiviral activity is through intracellular depletion of guanosine, and has an indirect effect in viral replication by increasing expression of the IFN gene and modulating immune response. Ribavirin (RBV) inhibits RNA synthesis by viral RdRp, and also acts as an inhibitor of limitation of mRNA. As monotherapy, RBV has shown resistance with SARS and MERS so it is given in combination with other antiviral drugs like lopinavir, chloroquine analogues and with αinterferon (IFN). The main adverse effects of RBV are hypoglycemia, hemolytic anemia, and hypomagnesemia. RBV must be avoided in patients with pre-existing cardiac disease and in patient with impaired kidney function. It is known that RBV has teratogenic effects and must therefore be avoided in pregnant women.

Oseltamivir

Oseltamivir is a neuraminidase inhibitor (NAI) that is used to treat influenza A and B, and reduces mortality in patients, especially in those admitted to the ICU. Oseltamivir and sanamivir are first line drugs in the treatment and prophylaxis of the flu. According to the latest investigations, neuraminidase inhibitors such as oseltamivir, peramivir, ganciclovir, aciclovir, ribavirin, and zanamivir are not valid therapies for COVID-19, and are not recommended for patient treatment.

Baloxavir

Baloxavir marboxil, founding member of the AP class of endonuclease inhibitors is licensed in Japan and the United States since 2018. Baloxavir marboxil is the first of a new class of drugs against influenza approved in 2 decades for the treatment of non-complicated influenza infection in patients older than 12 years. In clinical trials, participants showed a significant reduction of viral load on day 1 after beginning treatment, compared to placebo group. The time for improvement of clinical signs of disease reduced in an average of 26 hours, similar to those that can be achieved with

neuroaminidase inhibitors (NAI). As monotherapy, there is no use in the treatment of COVID-19, however there are several clinical trials that report favorable results when combined with favipiravir.59-61

Antiparasitic therapy in SARS CoV2 – COVID 19

Ivermectin

Ivermectin has proved a remarkable experimental efficacy that could be potentially used to treat COVID-19. Ivermectin is a macrolide produced by streptomyces avermitilis and is widely used in treatment of pediculosis, scabies, onchocerciasis, and lymphatic filariasis. It has also proven antiviral activity in-vitro against Influenza A, dengue, and Venezuelan equine encephalitis. A recent in-vitro experiment found that ivermectin reduced approximately 5000 SARS-CoV-2 RNA copies, only 48 hours after the dose was applied. The first study published on the use of ivermectin in patients with COVID-19 was multicentric, international, observational, and included patients that were hospitalized from January 1 to March 3 2020, with a total of 704 patients who received treatment with ivermectin 150 mcg/kg. This study's analysis found that ivermectin was associated with a higher probability of survival.[62,63] Among patients that required mechanical ventilation, mortality was significantly lower in those that received ivermectin (7.3%) versus those who did not (21.3%). Mortality rate was lower in patients treated with ivermectin (1.4%) versus those without ivermectin (8.5%).[62-66]

Even though severe adverse events have been reported during pregnancy (frequency of 1.36% in observational studies, and 0.6% in a RCT (Randomized and controlled trials), a causal relation between ivermectin and an unfavorable clinical outcome is difficult to evaluate; the number of registered exposures is too low to reach a statistical value, and it is not possible to rule out selection bias due to the lack of blinding and randomization in the trials.[67] Even though clinical trials have not reported its efficacy and safety in context of COVID-19, we expect to see new information on its potential therapeutic action in a clinical context.

Niclosamide

Niclosamide has a great potential and is being reused to treat a variety of viral infections such as SARS-CoV, MERS-CoV, Zika Virus, Japanese Viral Encephalitis, Hepatitis C Virus, Ébola virus, Human Rinovirus, Chikungunya Virus, Human Adenovirus, and Epstein Barr virus. These signaling pathways were briefly reviewed by Chen, Wu et al. and discovered that Niclosamide was able to inhibit SARS-CoV replication and suppress synthesis of viral. Possible mechanisms against SARS-CoV-2 is preventing viral entry by altering the endosomal pH and inhibiting viral replication by inhibition of autophagy. Clinical efficacy is yet to be evaluated.[68-70]

Nitazoxanide

Nitazoxanide is a broad spectrum antiparasitic pro-drug that is rapidly converted into active metabolites tizoxanide and tizoxanide conjugates. These metabolites seem to be safe and free of mutagenic effects. Similarly, nitazoxanide is also known to boost production of beta and alfa interferon, and to have in-vitro activity against MERS-CoV and other coronavirus .A review on clinical investigation on nitazoxanide using EMBASE and MEDLINE databases, complemented by ClinicalTrials.gov, searched for phase 2 or 3 RCT (Randomized-controlled trials) that compared nitazoxanide with placebo or active control during 5-14 days in participants with acute infections of any kind. No significant differences were found in any of the criteria evaluated in the RCTs (Randomized-controlled trials), trials or subgroup analysis. Mild gastrointestinal adverse effects increased with higher doses. No hepatic, cardiovascular problems were identified, but little information was registered. There were no teratogenic references, but the base of evidence was very limited. Currently we are waiting on evidence that nitazoxanide can guarantee antiviral activity, immunomodulating effects, and safety profile in additional studies in order to consider it a formal treatment option for SARS-CoV-2 infection.[71-73]

Steroids

In coronavirus disease, pulmonary inflammation and diffuse alveolar damage have been demonstrated, therefore, the use of systemic steroids has been proposed. Due to their immunosuppressive effect, glucocorticoids have been used in hyperinflammatory syndromes, such as ARDS. Unfortunately, its effects on mortality are not consistent in clinical trials.[74] The use of steroids in inadequate time and doses could aggravate the lung condition. An early start can suppress the body's immune response. Likewise, high doses can delay viral clearance.[75] Bacterial or fungal superinfection is also a cause for dismay. A meta-analysis published by Shuya Lu, et al.[76] collected 23 studies, including one randomized-controlled study and 22 cohort studies, for a total of 13,815 patients. The results concluded that in patients with COVID-19, the use of systemic steroids did not reduce mortality (RR = 2.00, 95% CI: 0.69 to 5.75, I^2 = 90.9%), nor the duration of the pulmonary inflammatory process (WMD = - 1 days, 95% CI: -2.91 to 0.91). In SARS patients of any etiology, steroids also failed to reduce mortality (RR = 1.52, 95% CI: 0.89 to 2.60, I^2 = 84.6%) or the duration of lung inflammation (WMD = 0.95 days, 95% CI: -7.57 to 9.48, I^2 = 94.6). Patients who used systemic steroids had a longer hospital stay.

Zhikang Ye, et al.[77] published a meta-analysis in May evaluating steroid use in COVID-19 and other severe respiratory diseases. They concluded according to a cohort study conducted in patients with COVID, and seven randomized-controlled studies in non-COVID patients, that in the presence of ARDS, steroids can reduce mortality (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.55 to 0.93, mean difference 17.3% fewer; low-quality evidence). In the absence of ARDS, according to two observational studies conducted in COVID patients, it was observed that steroids can even increase mortality (hazard ratio [HR] 2.30, 95% CI 1.00 to 5.29, mean difference 11.9% more; low-quality evidence).

The dose, the type of steroid to be administered, the time to start the therapy and the time that it must be maintained are also controversial.

1. **Methylprednisolone**

A retrospective study of 201 COVID-19 patients who developed ARDS showed that treatment with methylprednisolone (1-2 mg / kg / day IV for 5-7 days) can reduce the risk of death.[78] Likewise, a small retrospective study conducted in 46 patients showed encouraging results with the use of methylprednisolone in severe pneumonia due to COVID-19. Patients who received the drug showed a shorter course of the disease.[79]

2. **Dexamethasone**

The RECOVERY study has revealed that this steroid, at doses of 6 mg daily for 10 days, is the first drug that reduces mortality in patients with COVID-19.[80] The study aims to end controversies such as heterogeneity in the type of steroid to be administered, the dose, the clinical characteristics of the patients and the time of treatment. The results show the prevention of one death for every 8 patients in

invasive mechanical ventilation, one of every 25 patients with oxygen requirement, and lack of benefit in patients without supplemental oxygen requirement.

Recommendations in clinical guidelines regarding the use of systemic steroids

The American Society for Infectious Diseases recommends the use of systemic steroids in COVID-19 only in patients who have developed ARDS, ruling out their routine use.[81] Similarly, the campaign surviving sepsis recommends against the use of systemic steroids in patients with COVID-19 and mechanical ventilation if they have not developed ARDS.[82]

Immune therapies

Other immunomodulating therapies are being repurposed and developed according to the pathophysiology observed in severe COVID-19. Each day, researchers share their findings of clinical, cellular, and molecular aspects of infection by SARS-CoV-2.[4] A universally accepted concept that is closely related to the pathogenesis, disease progression and death, is the cytokine storm phenomenon (defined as the overproduction of cytokines caused by an aberrant immune activation). Patients admitted to an ICU had significantly higher levels of IL-2, IL-7, IL-10, granulocyte colony stimulating factor, IFγ-induced protein-10 (IP-10), macrophage chemoattractant protein-1, macrophage inflammatory protein 1α, and TNF compared to those not admitted to ICU.[83] To this moment, management of COVID-19 has been attempted by repurposing immune modulating therapies such as disease modifying anti-rheumatic drugs (DMARDs) (e.g. conventional synthetic DMARDs, biologic DMARDs, targeted synthetic DMARDs). Other immune-modulating therapies under clinical investigation include the use of convalescent plasma. This is not a new concept; this therapy has previously been used in severe infections such as MERS, SARS and Ebola, where there was an absence of vaccines. Its use in COVID-19 is currently being evaluated.[4]

An important point to consider is the general acceptance of a vaccination campaign against COVID-19. In the long term, vaccines against SARS-CoV-2 are necessary to end the pandemic but require cooperation of the general population. This becomes a public health issue that is not unfamiliar to us. We have seen new cases of previously eradicated diseases (e.g. measles) that are clearly linked to the anti-vaccine "trend" that is quickly spreading worldwide. An online survey done in a sample of the adult French population after de nationwide confinement revealed discouraging results. It found that 26% of participants would not use a vaccine if it became available. What is even more discouraging and even worrisome is the fact that the reluctant responders were mainly: low-income people who are more exposed to infectious diseases, women (aged 18-35 years), and people older than 75 years old.[84]

1. Tocilizumab

Tocilizumab is a monoclonal antibody that selectively binds to IL-6 receptors (interleukin 6). It is capable of inhibiting the signal transduction dependent on this interleukin, reducing inflammation. The main concerns in the use of this drug are bacterial superinfection, reactivation of latent tuberculosis, or elevation of liver enzymes. No evidence has been established regarding the precise dose and timing for use in SARS-CoV-2.[85] A small randomized study in China included a sample of 21 patients who met criteria for severe or critical COVID-19. After starting treatment, the patients stopped presenting fever, reduced their supplemental oxygen needs, and their lung tomography study showed a reduction in the infiltrates. Peripheral blood lymphocytes and C-reactive protein returned to normal levels. Only IL-6 levels were measured before the test.[86] Despite the encouragement generated by the use of tocilizumab in COVID-19, the results of the COVACTA study have not been very encouraging. The clinical study randomized 450 patients with severe COVID-19 pneumonia. Differences in the primary endpoint of the study (improvement in clinical status according to a seven-category ordinal scale) were not statistically significant between tocilizumab and the placebo group (odds ratio [OR], 1.19; 95% confidence interval [CI], 0.81 to 1.76; P = 0.36). At the fourth week the mortality rate was not different between the group treated with the drug compared to the placebo group (19.7% vs. 19.4%; difference, 0.3%; 95% CI, -7.6% to 8.2%; P = 0.9410). The difference between days without mechanical ventilation between the group treated with tocilizumab versus the placebo did not reach a statistically significant difference either (22 days vs 16.5 days; difference, 5.5 days; 95% CI, -2.8 to 13.0 days; P = 0.3202). The infection rate at four weeks was 38.3% in the tocilizumab group and 40.6% in the placebo group, and the rates of severe infection were 21.0 % and 25.9%, respectively.[87] The results of at least 20 clinical studies regarding the use of tocilizumab in COVID-19 are currently pending, which could offer a clear perspective regarding its use, as well as its adverse effect profile.

2. Ruxolitinib

Ruxolitinib is a JAK-1 and JAK-2 inhibitor drug, approved for the treatment of myelofibrosis, polycythemia vera, and steroid-resistant graft-versus-host disease.[88] Inhibition of the IL6 / JAK / STAT3 signaling pathway results in potent inhibition of interleukin 6.[89] There are concerns that their use may lead to the emergence of opportunistic infections. Patients who have used ruxolitinib have had reactivation of hepatitis B, Herpesvirus and Varicella Zoster, reason why it is feared that ruxolitinib could favor the replication of some viruses.[89] A clinical trial carried out in China with 43 patients with severe acute respiratory failure due to COVID-19 showed that patients who received ruxolitinib adequately tolerated the administration of the drug without presenting adverse effects, and also experienced decreased serum levels of 6 interleukins. However, it had no statistically significant effects on mortality or on clinical recovery time.[90] A controlled intention-to-treat clinical trial studied the combination of ruxolitinib and eculizumab in 17 patients with confirmed COVID-19 and ARDS. Patients treated with this combination showed significant improvement in respiratory symptoms, decreased lung injury, and decreased serum D-dimer levels.[91] The results of this study should be extrapolated to a much larger population in order to be taken into account.

3. Anakinra

Anakinra is an interleukin 1 receptor (IL-1) antagonist approved for the treatment of patients with rheumatoid arthritis. A retrospective cohort study in Milan Italy observed the clinical outcome in 29 patients with confirmed COVID-19 who were found to have moderate-severe acute respiratory failure and under non-invasive mechanical ventilation, who received two doses of 5 mg / kg every 12 hours. Anakinra for an average of 9 days, compared to a control group of 16 patients who were under non-invasive mechanical ventilation and standard treatment. At 21 days survival was 90% in patients receiving Anakinra and 56% in the standard treatment group. Bacterial superinfection was documented in 14% of the patients who received Anakinra and in 13% of the patients under standard treatment.[92] We still have to collect more important clinical evidence to offer this therapy safely.

Recommendations on biological therapy in clinical guidelines.

The guide on surviving sepsis in critically ill patients with COVID-19 mentions that there is insufficient evidence to make a recommendation regarding the use of tocilizumab in critically ill patients with this pathology.[81] The position of the American society for infectious diseases is the same as that found in the vast majority of guidelines for the management of this disease, recommending the use of these drugs only in the context of a clinical trial.[80]

4. Neutralizing monoclonal antibodies

The search for neutralizing monoclonal antibodies (mAb) for SARS-CoV-2 is being pursued in parallel to vaccine development. The concept of neutralizing mAb is not new. These antibodies have been observed and isolated in SARS-CoV, but despite sharing common epitopes with SARS-CoV-2, they have not proved a neutralizing capacity for the latter. Studying the SARS-CoV-2 S glycoprotein structure, an ideal target epitope could be the B domain of subunit 1 (S^B). This is the domain of the S glycoprotein that binds to its receptor, angiotensin converting enzyme 2 (ACE2) with high affinity. Could mAb isolated from individuals infected with SARS-CoV-2 confer a neutralizing capacity by binding to S^B? This scenario sounds promising, but meanwhile, previously isolated neutralizing mAb against SARS-CoV are being studied in hope of finding cross reactivity with SARS-CoV-2.[93]

A recent study[93] approached this precise task by obtaining diverse human mAb from B-cells found in stored blood samples that were drawn from a SARS-CoV infected individual. 25 mAb were included in this study that analyzed the binding and neutralizing capacity by cross reactivity. mAb S309, by forming a complex with S glycoprotein, effectively neutralized SARS-CoV-2. This mAb recognizes an epitope within S^B that is distinct to the receptor site. This means that S309 does not compete with ACE2 and can neutralize SARS-CoV-2 in its free form, as well as bound to ACE2.

While an adequate neutralization was observed with mAb S309 Fab unit (80%), a "cocktail" of IgG (S309 + S304 or S315) found 100% neutralization. The authors of the study explain this enhanced neutralization by Fc dependent mechanisms such as the activation of Natural Killer (NK), cross-linking, and antibody dependent phagocytosis. This finding is extraordinary and is taking a step towards future development of Fc variants with longer half-life and more effector functions. The medical and scientific community will be waiting anxiously for clinical trials. The passive administration of these neutralizing mAb confers immediate protection against SARS-CoV-2 and could complement prophylactic vaccination and help control the current pandemic. These human mAb could be indicated in cases such as exposed and high-risk individuals.[94-96] All tasks in search of immunity against SARS-CoV-2 are running at an accelerated pace; our only hope is that these projects are developed in time to mitigate the second wave of the pandemic.[97] Thus, AGD-2(engineered human monoclonal antibody) represents a promising candidate for the prevention and treatment of not only COVID-19, but also future respiratory diseases caused by pre-emergent SARS-related CoVs (Coronaviruses).[98]

Antifibrotic medications. Pirfenidone and Nintedanib

The development of pulmonary fibrosis seems an inevitable complication in the patient with SARS-CoV-2 pneumonia, especially in those with severe disease, or with a longer evolution time.[99] Antifibrotic treatment can have beneficial effects through different mechanisms, such as the prevention of viral replication, inhibition of viral signaling, anti-inflammatory effects and on the renin-angiotensin-aldosterone system.[99] Pirfenidone and nintedanib are two antifibrotic drugs that have been effective in attenuating the deterioration of lung function in the patient with idiopathic pulmonary fibrosis, or of other etiologies. An important future slope of the SARS-COV-2 virus-associated lung disease will be to determine if these drugs have any utility in the treatment, and if they should be used at the acute moment of the disease, when they could have a higher utility profile clinical, although on the other hand, they could also enhance their toxicity, especially liver and kidney.[99]

Although the results in the treatment of pulmonary fibrosis were evaluated after one year of treatment, both in idiopathic pulmonary fibrosis (through the INPULSIS study),[100] and in pulmonary fibrosis of other etiologies (INBULID study),[101] the positive results began to be observed after 4 to 6 weeks of treatment. A clinical study studying the early effect of antifibrotic drugs in the patient with SARS-COV-2 virus pneumonia seems essential.

Extracorporeal clearance therapies in cytokine release syndrome (CytoSorb)

In April 2020. The FDA temporarily authorized the emerging use of CytoSorb for the management of cytokine release syndrome in COVID-19. Although experience with the use of these types of cytokine remover devices is still limited, the FDA (Food and Drugs Administration) concluded that the CytoSOrb device may be effective in treating some patients with confirmed COVID-19. It should not be forgotten that these types of treatments are still under scientific investigation, are considered salvation or compassionate therapy, and may represent an option in refractory patients.[102]

Plasma transfusion of convalescent patients

Plasma treatment of convalescent patients is a passive immunization strategy that has already been used for the management of infectious diseases. It is obtained by apheresis of survivors of infections caused by pathogens that are capable of producing an antibody-generating immune response. There is already clinical experience in the use of this therapy in pandemics. It was used in the epidemic of influenza A (H1N1), SARS-CoV, and MERS-CoV, where no adverse effects associated with its administration were found, but neither were strong benefits.[103] A systematic review conducted by Rajendran et al, included the results of five clinical studies, four of them conducted in China, with 27 patients in total. The results of this review mention that plasma therapy from convalescent patients can reduce mortality in critically ill patients, in addition to increasing the neutralizing antibody titers favoring the disappearance of the RNA of the SARS-CoV-2 virus in most patients, and favor the clinical improvement of patients, reducing symptoms. The therapy appears safe, clinically effective, and could reduce mortality. Unfortunately, there are still not enough clinical trials to support its use.[104]

Anticoagulation in patients with COVID-19

Infection by SARS-CoV-2 not only produces a severe acute respiratory distress syndrome in affected patients, it is also associated with a high prevalence of coagulopathy. Drug interaction of antiplatelet and anticoagulation agents with specific therapies under investigation for treatment of COVID-19 have increased the risk of thrombotic events and in some cases even condition thrombocytopenia. Bevacizumab, a monoclonal antibody, is associated to an increased risk of cardiovascular events including myocardial infarction, cerebrovascular events, and venous thromboembolism. Finfolimod, another immunomodulator can reduce reperfusion injury and

improve the evolution of patients with an ischemic cerebrovascular event. Hydroxychloroquine may induce its antithrombotic properties especially against anti-phospholipid antibodies. Lopinavir/Ritonavir inhibits CYP3A4 metabolism, conditioning a reduction in the effective dose of clopidogrel, and increasing effects of ticagrelor, leaving prasugrel as an antiplatelet alternative. It also affects Vitamin K antagonists like apixaban and betrixaban, that will require dose adjustment. Adoxaban and rivaroxaban should not be administered with Hydroxychloroquine. In another scenario, adjusting oral antiplatelet agents while receiving treatment with tocilizumab is not recommended.[105]

In patients infected by SARS-CoV2, systemic inflammation, severe disease, immobility and multiorgan failure are documented risk factors for prothrombosis and hypercoagulable state.[106] In case of sudden deterioration, hypoxemia disproportionate to the respiratory pathology, right heart failure, and/or shock, with typical symptoms of Disease venous thromboembolism (DVT), Pulmonary embolism (PE) must be suspected.[105,107]

Unfractioned Heparin

With a shorter half-life, this anticoagulant allows for a better monitoring, has protamine as an antidote, is administered intravenously, and is considered the first option in prophylactic treatment in severe COVID-19. Besides, it's preferable in patients that require invasive procedures (e.g. central venous catheter colocation, pleural catheter placement, surgery), and those with altered renal function.[105,108]

The only contraindications for the use of heparin are active bleeding and platelet count less than 25 $x10^9$/L.[107,109]

Low Molecular Weight Heparins (LMWH)

These are the first line therapy in patients with mild or moderate COVID-19 and in those who do not need invasive procedures. Anticoagulation is monitored according to anti Xa activity with a desired range of 0.6 to 1 UI/ml.[105,108]

The Chinese Hemostasis and Thrombosis Society suggest the following drugs as other treatment possibilities:

a) Argatroban: direct thrombin inhibitor, metabolized in the liver, causes a significant increase in thrombin time.[108]

b) Bivalirudin: specific thrombin activity inhibitor, has a half life of 25 to 30 minutes, has a reversible action, also adjusted according to activation partial thromboplastin time and viscoelastic tests.[108]

Antiplatelet therapy

Adding an antiplatelet agent to heparin administration can increase the risk of bleeding and adverse effects with little availability of agents capable of reverting its action;[107] however, if the patient previously used antiplatelet agents, suspending the drug is not indicated. In patients with high risk of bleeding, antiaggregating therapy with less potent antiplatelet agents such as Clopidogrel should be considered. Drug interactions between antiplatelet agents and COVID-19 therapy must be evaluated.[105] The main complication encountered with heparin, more frequently with unfractioned heparin, use is induced thrombocytopenia, with an incidence of 0.1 to 5% of all cases.[105] The excessive depletion of coagulation substrates causes dysfunction in the coagulation system, and a high risk of disseminated intravascular coagulation (DIC) that can evolve to a hemorrhagic state, multiple organ failure, and death.

The search for immunity in the pandemic (Vaccine)

In the specific case of the SARS-CoV-2 virus, vaccines will help reduce morbidity and mortality if the virus becomes established in the population. Most vaccine production platforms (i.e. RNA vaccines, DNA vaccines, recombinant protein vaccines, and viral vector-based vaccines) target the S protein, while other platforms (i.e. live attenuated vaccines and inactivated vaccines) target the whole virion.[109] Feng-Cai Zhu et al.[110] recently published the results of a phase 1 trial that evaluated the safety, tolerability and immunogenicity of a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing the spike glycoprotein of a SARS-CoV-2 strain. This open-label, non-randomized dose-escalation clinical trial was done in a rehabilitation center in Wuhan, China and included 108 healthy adults aged between 18-60 years. Prior to their enrollment in the trial, the participants went through a series of tests that confirmed they had no current or past SARS-CoV-2 infection. The participants, with similar baseline characteristics, were assigned to one of three groups: low, middle, and high dose. The "low dose" group (n=36) received a single intramuscular shot of $5x10^{10}$ viral particles. The "middle dose" group (n=36) received a shot of $1x10^{11}$ viral particles and the "high dose" group (n=36) received $1.5x10^{11}$ viral particles.

At least one adverse event presented in each group: 83%, 83% and 75% in the low, middle and high dose group, respectively. The most common local adverse event (at site of application) was pain (54% of all participants); while the most common systemic adverse events reported were fever (46%), fatigue (44%), headache (39%) and muscle pain (17%). As for the vaccine's immunogenicity, both a humoral and a T-cell mediated response was elicited. Humoral response peaked at day 28 and cellular response peaked at day 14. The trial reports no serious adverse events at day 28, interpreting an adequate safety. The preliminary report[93] of another phase 1, dose-escalation trial included 45 healthy individuals who received two vaccinations with mRNA-1273 at different doses. Groups of 15 participants were formed to receive either 25 mcg, 100 mcg or 250 mcg of mRNA-1273. This mRNA vaccine encodes the S-2P antigen, i.e. the SARS-CoV-2 glycoprotein with transmembrane anchor and intact S1-S2 cleavage site. Participants were not screened for SARS-CoV-2 infection, and vaccines were administered on day 1 and 29, with follow-up visits scheduled at 7 and 14 days post-vaccination.

Antibody responses against S-2P were assessed by ELISA; and vaccine-induced neutralizing activity was assessed by a pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA) and by live wild-type SARS-CoV-2 plaque-reduction neutralization testing (PRINT). T-cell responses were assessed by intracellular cytokine-staining assay. No serious local or systemic adverse events were noted, and mild systemic adverse events (i.e. headache, fatigue) were more frequent after the second vaccination (7 participants in the 25 mcg group, 15 in the 100 mcg group, and 14 in the 250 mcg group). Binding antibody IgG geometric mean titers (GMTs) measured found seroconversion in all participants by day 15 with a dose-dependent response. Neutralization responses were measured before vaccination (0 participants), after the first vaccination (less than half of participants), and after second vaccination (all participants). Responses were also dose dependent, with the lowest PsVNA in the 25 mcg dose group, and similar responses for the 100 mcg and 250 mcg groups. There is an ongoing phase 2 trial with this mRNA vaccine, evaluating 50 mcg and 100 mcg doses. Researchers expect to begin a phase 3 efficacy trial later this year.

Numerous vaccine are currently being applied, AstraZeneca/Oxford, Pfizer/BioNTec, Moderna/NIH, Jansen/J&J, Gamaleya Russian (Spútnik V), CanSino Biologicals (adenovirus) China, Pakistan, Sinovac Biotech (inactive virus) Brazil, indonesian, Sinopharm-Wuhan (inactive virus) Arabian countries. The safety and efficacy of a heterologous prime-boost heterologous COVID-19 vaccine based on rAd26 and rAd5 vectors: an interim analysis of a phase 3 randomized controlled trial in Russia" showed an efficacy of 91.65%.[111] The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified.[112] On Monday, March 15,2021, vaccinations with the COVID-19 from Astra Zeneca (AZD 1222) were temporarily halted by German Ministry of Health and other European countries due to safety concerns regarding an elevated risk of thrombosis in vaccinated individuals. The vaccination is likely to induce the formation of antibodies against platelet antigens as part of the inflammatory reactions and immune stimulation. These antibodies subsequently cause massive platelet activation via the Fc receptor in analogy to heparin-induced thrombocytopenia. These antibodies appear 4 to 16 days after vaccination.[113]

Others Drugs used in COVID-19

Vitamin C

The reduction of the cytokines storm in the late stages of the Covid 19 infection is the most significant application of (IV) Vitamin C (Vit C). The antiviral properties of Vit C help to reduce symptoms and mortality in children and adults.[114] A large dose of IV ascorbic acid can be one treatment of choices for Covid 19 pneumonia.[115] The ARDS is the main mechanism for Covid 19´s action. This is followed by increased oxidative stress because of the release of free radicals and cytokines. Considering this mechanism of the process, a large dose of Vit-C should play a key role in the management of Covid 19.[116,117] This treatment is controversial; There cases where high dose Vit-C has shown benefits, in another cases there have been no benefits

Vitamin D

That Vitamin D3 is produced in the skin through the action of UVB radiation reaching 7-dehydrocholesterol in the skin, followed by a thermal reaction.[118] Vitamin D enhances cellular innate immunity partly through the induction of antimicrobial peptides, including human cathelicidin, LL-37, by 1,25-dihidroyvitamin D,[119,120] and defensins.[121]

Cathelicidins exhibit direct antimicrobial activities against a spectrum of microbes, including Gram-positive and Gram-negative bacteria, enveloped and nonenveloped viruses, and fungi.[122] Those host-derived peptides kill the invading pathogens by perturbing their cell membranes and can neutralize the biological activities of endotoxins.[123]Vitamin D also enhances cellular immunity, in part by reducing the cytokine storm induced by the innate immune system. The innate immune system generates both pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infections, as observed in COVID-19 patients.[124] Vitamin D can reduce the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor alpha and interferon gamma.[125] Also enhances the expression of genes related to antioxidation (glutathione reductase and glutamate-cysteine ligase modifier subunit).[125] The increased glutathione production spares the use of ascorbic acid (Vitamin C), which has antimicrobial activities[126,127] and has been proposed to prevent and treat COVID-19.[128]

Melatonin

The effect of SARS-CoV-2 on humans is clearly age related. The multiple function of melatonin in the studies including: can reduce immuno-suppression induced by chronic stress and sleep deprivation, and should be utilized in combination with drugs and treatments used to treat coronavirus infection, and reducing the inflammation caused when the coronavirus activates inflammasome, to as a vaccine adjuvant and antiviral immune stimulant, can prevent the main danger, post-COVID-19 lung fibrosis? And critical care can reduce the risk of mechanical ventilation?.[129,130] The melatonin modulates cellular function via a number of processes, including the activation pathways and transcription factors, which act to dampen inflammatory activity. Melatonin is also a powerful antioxidant and anti-inflammatory that mediates many of its effects via the optimization of mitochondrial function. The melatonergic pathways is evident in all cells, not only those of the pineal gland, and that it may be predominantly present within mitochondria. Melatonin can harm if used inappropriately, and/or if the population is large enough there will always be people oversensitive to any factor. However, the acute toxicity of melatonin was reported to be very low. The utility of melatonin is under-appreciated, by its availability, low cost, and very high safety profile.[130]

Pentoxifylline

Is a methyl-xanthine that inhibits phosphodiesterase IV (PDE IV), presenting interesting immunomodulatory and antiviral properties. The anti-inflammatory effects of pentoxifylline are additionally due to the reduction of proinflammatory cytokines as TNF-alpha or INF-gamma, also down-regulates the activation of NF-kappa B and NFAT transcription factors (involved in the replication of several viruses). cAMP elevation mediated by phosphodiesterase IV inhibition leads to a bronchodilatory effect.[131] Ardizzoia et al., studying acute respiratory distress syndrome in patients with advanced cancer treated with pentoxifylline. The anti-inflammatory, antiviral, immunomodulatory and bronchodilatory effects of pentoxifylline, along with its low cost and toxicity, make it a promising drug to be considered for SARS treatment, alone or as an adjuvant therapy in combination with other drugs.[132]

Streptokinase

This nebulized drug improves oxygenation and lung compliance, it may be promising for patients with ARDS-SARS CoV-2.[133]

Thalidomide

Anti-inflammatory drugs, an immunomodulatory drug, inhibits IL-6 has been shown to lead beneficial effects in the bacterial and viral Induced ARDS.[134,135]

Simvastatin

The reanalysis of a large negative RCT (Randomized-controlled trials) of simvastatin in ARDS using this approach suggested benefit in the hyperinflammatory group.[136]

Plitidepsin

Inhibits the activity of the host factor eEF1A and is predicted to interact with the same binding site as didemnin B, which is structurally related to Plitidepsin, and the structurally unrelated ternatin-4. Exogenous overexpression of a A399V mutant of eEF1A confers resistance in cancer cells to both didemnin B and ternatin-4 inhibition and we predicted that it may similarly impact Plitidepsin. This study establishes Plitidepsin as a host-targeted anti-SARS-CoV2 agent with in vivo efficacy.[137]

Nirmatrelvir–Ritonavir (Paxlovid)

Nirmatrelvir in combination with ritonavir is an antiviral treatment for mild-to-moderate coronavirus disease 2019 (Covid-19). The efficacy of this treatment in patients who are at standard risk for severe Covid-19 or who are fully vaccinated and have at least one risk factor for severe Covid-19 has not been established. Clinical trials of treatments for coronavirus disease 2019 (Covid-19) have not shown a significant benefit of postexposure prophylaxis.[138,139]

Conclusion

Viruses, including SARS, and influenza, can change quickly, thereby negating the efficacy of developed vaccines and targeted antiviral drugs. The efficacy of this medications in treatment of patients with COVID-19 deserves further exploration. SARS CoV-2, the transmissibility of the virus depends on human behavior, and the administration of the previously described medications delays medical care with increased morbidity and mortality, as well as the availability of ventilators in complicated patients, in hospital areas other than those Critical areas and their management by qualified medical personnel who are not specialists in Critical Care, increases the morbidity and mortality of patients with SARS CoV-2, as well as the health personnel involved. The bad administration and vision of public resources for the priority attention of this emergent case, the mainly part of those is focus in developing and maintain of public politics with infrastructure and social activities not relationated with public health.

Declarations

There are no conflicts of interest or sources of support.

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Citation: Manzo PE, García MGM, Fernández GJA, et al. "SARS COV-2/COVID-19 Pandemic". First is do no harm (Primum non nocere), the evolution of therapy and treatment COVID-19, a literature review. *J Anesth Crit Care Open Acces.* 2025;17(2):49–60. DOI: 10.15406/jaccoa.2025.17.00620