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INDEXING/ABSTRACTING

The WJV is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Virology

ISSN

ISSN 2220-3249 (online)

LAUNCH DATE

February 12, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3249/editorialboard.htm>

PUBLICATION DATE

September 25, 2021

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INSTRUCTIONS TO AUTHORS

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<https://www.wjgnet.com/bpg/gerinfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Scientific evidence in the COVID-19 treatment: A comprehensive review

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Author contributions: All authors contributed to this paper with conception and design of the manuscript, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Authors declare no potential conflict of interests for this article.

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Manuscript source: Invited manuscript

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Abstract

In December 2019, cases of unknown origin pneumonia appeared in Wuhan, China; the causal agent of this pneumonia was a new virus of the coronaviridae family called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). According to the clinical severity, symptoms and response to the different treatments, the evolution of the disease is divided in three phases. We analysed the most used treatments for coronavirus disease 2019 and the phase in which they are supposed to be effective. In the viral phase, remdesivir has demonstrated reduction in recovery time but no mortality reduction. Other drugs proposed for viral phase such as convalescent plasma and lopinavir/ritonavir did not demonstrate to be effective. In the inflammatory phase, corticosteroids demonstrated reduction of 28-d mortality in patients who needed oxygen, establishing that a corticosteroid regimen should be part of the standard treatment of critically ill patients. There are other immunosuppressive and immunomodulatory treatments such as anakinra, sarilumab, tocilizumab, colchicine or baricitinib that are being studied. Other treatments that were proposed at the beginning, like hydroxychloroquine or azithromycin, demonstrated no efficacy and increased mortality when combined.

Specialty type: Respiratory system**Country/Territory of origin:** Spain**Peer-review report's scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: March 17, 2021**Peer-review started:** March 17, 2021**First decision:** May 5, 2021**Revised:** May 12, 2021**Accepted:** August 9, 2021**Article in press:** August 9, 2021**Published online:** September 25, 2021**P-Reviewer:** Patel L, Tavan H**S-Editor:** Wang JL**L-Editor:** A**P-Editor:** Xing YX**Key Words:** COVID-19; SARS-CoV-2; Treatment; Viral phase; Inflammatory phase

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Core Tip: Severe acute respiratory syndrome coronavirus-2 is responsible for the unknown pneumonia that appeared in Wuhan, China, in December 2019. Lots of known drugs have been proved for coronavirus disease 2019. Corticosteroids demonstrated reduction of 28-d mortality in patients who needed oxygen and remdesivir proved to be effective reducing recovery time. Other drugs need more evaluation before establishing their effectiveness.

Citation: Iturricastillo G, Ávalos Pérez-Urría E, Couñago F, Landete P. Scientific evidence in the COVID-19 treatment: A comprehensive review. *World J Virol* 2021; 10(5): 217-228

URL: <https://www.wjgnet.com/2220-3249/full/v10/i5/217.htm>

DOI: <https://dx.doi.org/10.5501/wjv.v10.i5.217>

INTRODUCTION

In December 2019, cases of unknown origin pneumonia appeared in Wuhan, a province of China. It was determined that the causal agent of pneumonia was a new virus of the coronaviridae family called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1,2]. The spread of this virus was so fast that resulted in a pandemic in a few months, causing more than 2.5 million deaths worldwide as of the writing of this paper.

It has become a priority to establish a treatment that reduces mortality, the time of illness and the severity of the virus. For that reason, a wide variety of trials and studies have been developed to evaluate the effectiveness of different already known drugs. Boregowda *et al*[3] published a review of experimental treatments in coronavirus disease 2019 (COVID-19) in October 2020 concluding that the best method of dealing with the pandemic is to reduce the community spread. A lot of investigation has occurred since then, so we have reviewed the updated literature with focus on articles published in high impact journals.

Pathogeny

Siddiqi *et al*[4] proposed a three-phase classification of the evolution of COVID-19, according to the clinical severity, symptoms and response to the different treatments (Figure 1): (1) Viral phase or early infection: onset of infection and viral replication. The virus enters host cells through the angiotensin-converting angina 2 receptor, which is highly present in lung cells[5-7]. This phase includes the first seven days of symptoms; symptoms such as fever, myalgias and digestive inconveniences predominate. The polymerase chain reaction (PCR) of the virus is positive and there may be lymphopenia on laboratory tests and pulmonary infiltrates visible by computerized tomography; (2) Pulmonary phase: the virus continues to replicate and the host's humoral response develops. It appears approximately 7-14 d after the initial symptoms. It is technically divided into two sub-phases depending on whether the patient has respiratory failure (IIB) or not (IIA). The cytokine cascade is activated causing a severe inflammatory reaction in the lung tissue that can lead to respiratory distress. The most common manifestations are viral pneumonia, hypoxemia, cough and fever; and (3) Hyperinflammatory phase: it is the most severe phase and it is characterized by systemic inflammation with elevated blood levels of acute phase reactants and inflammatory cytokines[8]. It usually occurs 10-14 d after the initial symptoms. It can cause myocardial damage, shock, respiratory failure, *etc.* Only a few patients have this severe form of the disease. In this phase, treatment with immunomodulatory drugs or intravenous immunoglobulins may be useful.

Objective

The objective of this article is to do a brief review of the drugs that have been used the most to treat the disease since the beginning of the pandemic until today[9].

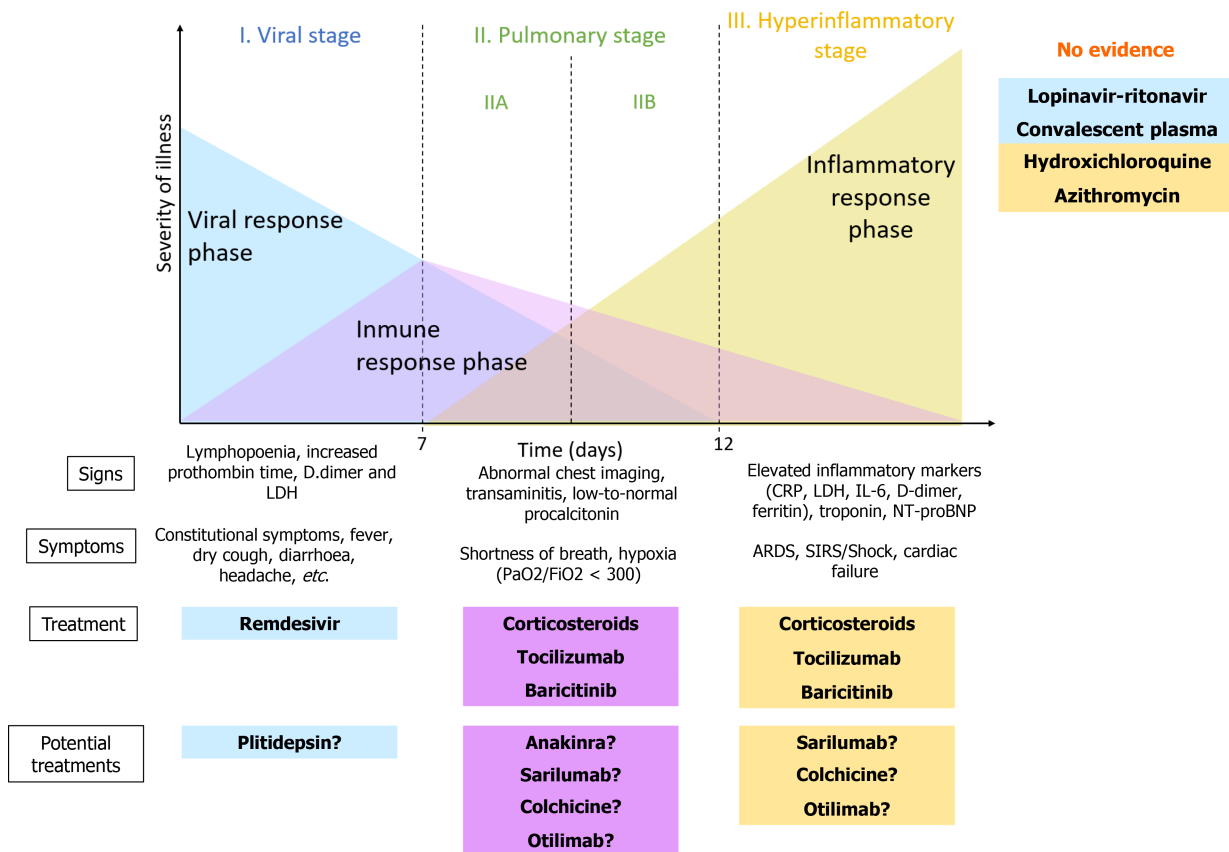


Figure 1 Classification of coronavirus disease 2019 states and potential therapeutic targets. Adaptation from Siddiqi *et al*[4]. LDH: Lactate dehydrogenase; CRP: C-reactive protein.

LITERATURE SEARCH

We performed a search in PubMed with the keywords “COVID-19” and the most frequent drugs (Corticosteroid, Hydroxychloroquine, Remdesivir, etc.) as well as “COVID-19 + TREATMENT”. The most relevant articles have been selected in order of mention and by scientific relevance, prioritizing those published in journals with the highest impact factor.

VIRAL PHASE TREATMENTS

Remdesivir

This RNA inhibitor drug has been studied since an early stage of the pandemic for its inhibitory effect on the viral replication of SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), demonstrating *in vitro* activity against SARS-CoV-2[10].

Since then, multiple studies and clinical trials have been conducted in order to prove its efficacy against COVID-19 infection. We highlight two of the largest: the Solidarity study and the Adaptive COVID-19 Treatment Trial (ACTT-1).

In November 2020, the final report of the clinical trial conducted by ACTT-1 group about the use of remdesivir for COVID-19 was published. In this clinical trial, 1062 patients with SARS-CoV-2 lower respiratory tract infection were enrolled. These patients were randomized to receive 10 d of treatment with remdesivir (200 mg as a loading dose, followed by 100 mg daily) *vs* placebo. The data obtained showed a significant reduction in recovery time compared to placebo (10 d *vs* 15 d). According to the results of this analysis, this effect was greater with the initiation of treatment in the early phase (first 10 d), and in patients in the 5th stage of severity. No clear results were obtained on its effect on mortality[11].

The Solidarity study carried out by the World Health Organization (WHO) confirmed the absence of effect of remdesivir on mortality in comparison with placebo

and in comparison with hydroxychloroquine, lopinavir/ritonavir and interferon[11].

Review articles on this drug have also been published, including information from the current literature and from smaller studies. A systematic review carried out by the American College of Physicians suggested that, according to the reviewed bibliography, there are studies that would demonstrate a similar benefit between the 5-d *vs* the established 10-d treatment regimen, with a consequent reduction in the reported adverse effects in patients with respiratory infection caused by SARS-CoV-2 who do not require mechanical ventilation or extracorporeal oxygenation[12].

Lopinavir/ritonavir

Lopinavir is a protease inhibitor antiviral drug used against human immunodeficiency virus; its combination with ritonavir increases its plasma half-life.

This drug has shown *in vitro* activity against SARS-CoV-1 and was used during the MERS epidemic, demonstrating efficacy in terms of clinical and radiological improvement and reduction of viral load[13].

Despite its initial compassionate use, clinical trials have shown lack of efficacy against SARS-CoV-2.

The RECOVERY clinical trial is one of the largest studies conducted to date. It included 26 hospitals in the United Kingdom, and has studied the efficacy and safety of various drugs against COVID-19 (hydroxychloroquine, azithromycin, dexamethasone and lopinavir/ritonavir). In this study, 1616 patients were randomized to receive lopinavir/ritonavir *vs* 3424 patients receiving the standard treatment at that time. This study confirmed lack of efficacy of this drug in terms of mortality reduction, clinical improvement or time to discharge, concluding with a recommendation against its use in COVID-19 patients[14].

Hyperimmune plasma

Convalescent plasma (hyperimmune plasma, with active antibodies against SARS-CoV-2) has been proposed as a treatment for COVID-19 due to its direct antiviral neutralizing effect, its ability to modulate viral activity in the acute moment and its ability to indirectly activate antiviral functions of the immune system such as the complement cascade, NK cells, *etc.* Hyperimmune plasma has been successfully used for the treatment of influenza pneumonia and, more recently, for SARS-CoV-1. The RECOVERY group has assessed mortality at 28 d with hyperimmune plasma in comparison with standard of care, concluding that there are no significant differences; neither when analysing by subgroups. They propose as a limitation for the study that only hospitalized patients are included, so most are not in the viral replication phase, where theoretically hyperimmune plasma would have more effect[15].

Piechotta *et al*[16] made a review of 20 studies comparing hyperimmune plasma and standard of care. In a preliminary analysis, they did not find any benefit in terms of mortality, death time or improvement of clinical symptoms, concluding that there is insufficient evidence on efficacy and safety[16].

Plitidepsin

The antiviral activity of plitidepsin is mediated by the inhibition of eukaryotic translation initiation factor 1, establishing it as a possible drug target. Thus, as observed both *in vitro* and *in vivo* in the article by White *et al*[17], plitidepsin can reduce viral replication by two orders of magnitude and lung inflammation *in vivo*, showing clinical potential against COVID-19. Clinical studies are needed to see if it is effective in human patients.

TREATMENTS IN THE INFLAMMATORY PHASE

Corticosteroids

Corticosteroids have been proposed as a possible treatment for COVID-19 due to their anti-inflammatory and immunosuppressive properties, being able to reduce the systemic damage produced in the inflammatory phase. In the systematic review by Budhathoki *et al*[18], 83 articles were included. It attempted to assess which patients would benefit the most from corticosteroid treatment according to the severity of the disease. It was observed that severely ill patients were more likely to receive corticosteroids in their treatment, with the groups receiving corticosteroids presenting a longer hospitalization and higher mortality; without being able to rule out bias because of the non-randomization of the patients[18].

The RECOVERY group assessed mortality from all causes at 28 d, comparing standard of care with the daily administration of dexamethasone 6 mg for 10 d. It demonstrated that mortality was lower in patients who received dexamethasone. In addition, they saw that this benefit was greater in those patients requiring oxygen therapy, with or without positive pressure therapy, and in those patients recruited after more than 7 d of symptoms. Likewise, it was observed in those patients with oxygen therapy that the administration of dexamethasone decreased their risk of needing invasive mechanical ventilation (IMV) and increased their possibility of IMV withdrawal if they were already receiving it[19].

Finally, it should be noted that a WHO work group has published a meta-analysis. Out of 1703 randomized patients, 678 received corticosteroids and 1025 received conventional treatment, showing an absolute risk of mortality at 28 d of 32% and 40% respectively. Also, mortality was lower in those patients who received low doses of corticosteroids (29%) than in those who received high doses (36%). No increase in adverse effects was perceived in the group receiving corticosteroids.

The Food and Drug Administration, WHO, European Medicines Agency and National Institutes of Health recommend the use of corticosteroids for the treatment of COVID-19 in patients requiring oxygen therapy. The WHO also established that a corticosteroid regimen should be part of the standard treatment of critically ill patients [20].

Tocilizumab

Hypoxia and severe respiratory failure that occurs in patients with COVID-19 infection have been related to a disproportionate increase in acute phase reactants and pro-inflammatory cytokines such as Interleukin-6 (IL-6) or IL-1[21].

Therefore, it is believed that specific immunomodulatory substances against these cytokines could stop the mentioned inflammatory cascade and slow down the clinical deterioration of these patients.

Tocilizumab is a monoclonal antibody used in rheumatological diseases such as Rheumatoid Arthritis. It blocks the IL-6 membrane and soluble receptors, with the consequent reduction of the associated inflammatory response[22].

Its efficacy in patients with COVID-19 infection is still uncertain. To date, multiple clinical trials have been conducted, with disparate results.

In October 2020, Stone *et al*[23] published the results of its randomized clinical trial, conducted in 7 hospitals in the city of Boston (United States). They included a total of 243 patients with moderate COVID-19 infection (who did not require mechanical ventilation), randomized with a 2:1 ratio to receive conventional treatment *vs* placebo, or a single dose of 8 mg/kg of tocilizumab (maximum 800 mg). This study did not demonstrate any beneficial effect on the use of tocilizumab in mortality, IMV requirements or decrease in clinical deterioration. It should be noted that, at the time of this study, the results of the RECOVERY study on the efficacy of dexamethasone had not been published, so corticosteroids were not included as standard treatment [23].

In February 2021, Malhotra's group published the results of its phase 3 clinical trial. This was carried out in 61 centers between the United States and Europe, in patients with severe COVID-19 infection, randomized with a 2:1 ratio to receive tocilizumab 8 mg/kg *vs* placebo. In this study, no results were obtained that demonstrated an additional benefit of tocilizumab on mortality, or improvement in clinical status according to the ordinal severity scale (Table 1) at 28 d. It suggests a possible reduction in hospitalization time and ICU stay time in the treatment group, but more extensive research is needed[24].

Salama *et al*[25] conducted a phase 3 trial in 6 countries, with 389 patients of different age groups and ethnicity. This trial has demonstrated a decrease in the progression of the clinical deterioration and the need for IMV, mainly in patients with moderate or severe disease without mechanical ventilation. No reduction in mortality was demonstrated compared to the placebo group.

The RECOVERY group has recently published the results of the randomized trial carried out in the United Kingdom, with the participation of 131 hospitals belonging to the National Health System. The trial included 4116 patients who were randomized to receive tocilizumab *vs* standard treatment. The results of this study have shown a significant decrease in mortality at 28 d in the group randomized to receive tocilizumab and in patients with hypoxia and elevated acute phase reactants. It also improved the odds of hospital discharge before 28 d and a lower rate of progression toward IMV. In this study, the use of corticosteroids was included as standard medical treatment against COVID-19, also suggesting a possible benefit of the synergy of these two drugs[26].

Table 1 Coronavirus disease 2019 treatments

Drug	Mechanism of action	Recommendation	Posology	Benefits
Remdesivir ¹	RNA replication inhibition	Hospitalized patients in the first 10 d of infection requiring supplementary oxygen, without mechanical ventilation or extracorporeal oxygenation	Loading dose of 200 mg, followed by 100 mg daily for 5 d	Reduction in recovery time compared to placebo (10 d <i>vs</i> 15 d)
Corticosteroids ¹	Anti-inflammatory and immunosuppressive effects	Hospitalized patients requiring oxygen therapy. Also beneficial in patients with higher requirements of respiratory support	Dexamethasone 6 mg daily for 10 d	Reduction of mortality at 28 d. Decrease the risk of IMV and days of IMV
Tocilizumab ¹	Antagonist of IL-6 receptor. Immunomodulatory effect	Hospitalized patients with hypoxia and elevated acute phase reactants	8 mg/kg in a single dose (maximum of 600 mg). A second dose might be administered if lack of effect	Reduction of mortality at 28 d. Reduce progression to IMV
Anakinra ²	Antagonist of IL-1 receptor. Immunomodulatory effect	Not clear recommendations. Hospitalized patients with hypoxia and elevated acute phase reactants	-	Some data show some effect on clinical improvement in patients with NIMV requirements.
Sarilumab ²	Antagonist of IL-6 receptor. Immunomodulatory effect	Not clear recommendations. Hospitalized patients with hypoxia and elevated acute phase reactants	-	It might reduce mortality in critical patients (unclear data)
Baricitinib ²	Janus kinase (JAK) 1/2 inhibitor. In-vitro activity against SARS-CoV-2, given its inhibitory effect on cytokine release and its inhibition of virus entry into pneumocytes	Not clear recommendations. Hospitalized patients with moderate-severe COVID-19 infection	-	In combination with corticosteroid, it improves SpO ₂ /FiO ₂
Colchicine ²	Lipid soluble alkaloid, with anti-inflammatory effect	Not clear recommendations. Non-hospitalized patients with COVID-19	-	Some data show reduction of mortality and hospitalization in patients with mild infection.
Otilimab ²	Monoclonal antibody, anti-granulocyte macrophage colony-stimulating factor	Not clear recommendations. Hospitalized patients with severe disease	-	Might have beneficial effects in elderly patients with severe disease
Plitidepsin ²	Inhibition of eef1a, reduce viral replication	More studies needed, not clear recommendations	-	-
Hydroxychloroquine ³	RNA replication inhibitor	Not recommended	-	-
Azithromycin ³	Immunomodulatory effect	Not recommended	-	-
Lopinavir-Ritonavir ³	Protease inhibitor.	Not recommended	-	-
Hyperimmune plasma ³	Convalescent plasma with active antibodies against SARS-CoV-2	Not recommended	-	-

¹Recommended ones.²Need more evidence.³Not recommended treatments. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; IMV: Invasive mechanical ventilation.

Anakinra

Anakinra is an antagonist of the IL-1 receptor, with the ability to inhibit the pro-inflammatory activity of IL-1 alpha and beta. This drug is approved for the treatment of rheumatologic diseases such as Still's disease or familial Mediterranean fever. It is believed that it could be a therapeutic target against the inflammatory cascade produced by COVID-19, and especially against macrophage activation syndrome[27].

So far, this drug has shown effectiveness in patients with sepsis criteria and signs of hyperinflammation[28].

In the retrospective study carried out by Cavalli *et al*[29], they analyzed 29 patients admitted to the San Raffaele hospital in Milan with NIMV requirements. This showed a certain improvement of the clinical status of the patients, without finding a reduction in mortality.

The CORIMUNO-ANA-1 clinical trial included 153 patients across France with moderate-severe COVID-19 infection, without mechanical ventilation (category 5 on the WHO severity scale). It did not demonstrate any beneficial effect of anakinra, indicating the need for further studies in other groups of patients with greater severity [30].

Therefore, according to the literature, so far there is no clear evidence that supports the use of anakinra in any specific group of patients. Currently, there are ongoing clinical trials with this drug in different subgroups of patients.

Sarilumab

Several studies prove that elevated levels of interleukin-6 are related to greater severity of COVID-19 infection and higher mortality [31].

Sarilumab is a recombinant monoclonal antibody against the IL-6 receptor (soluble and membrane), approved for rheumatoid arthritis [32].

Many publications and trials have shown a benefit with the use of IL-6 antagonist drugs on severe COVID-19 infection. The study carried out by the REMAP-CAP group on 895 patients with COVID-19 demonstrated a reduction in mortality and a higher clinical improvement in critically ill patients randomized to receive an IL-6 antagonist. However, it should be noted that in this trial only 48 patients received sarilumab, while 366 patients received tocilizumab [33].

The results of the clinical trial carried out by Lescure *et al* [34] for the Sarilumab COVID-19 Global Study Group were recently published. In this Phase 3 trial, 431 patients with severe SARS-CoV-2 pneumonia (categories 5, 6 or 7 on the WHO severity scale) were randomized. This trial compared the use of sarilumab (200 or 400 mg) *vs* placebo. Sarilumab did not show to be effective in reducing mortality, improving the clinical severity scale, or reducing the length of hospital stay.

Baricitinib

Baricitinib is another drug used in rheumatology as a Janus kinase 1/2 inhibitor. Multiple *in vitro* studies have been carried out with this molecule. The results of these studies suggest *in vitro* activity against SARS-CoV-2, given its inhibitory effect on cytokine release and its inhibition of virus entry into pneumocytes [35].

Studies in animal models show a significant reduction in cytokine production by alveolar macrophages, which translates into a reduction in the local inflammatory cascade and neutrophil recruitment [36].

The Oxford study, carried out by Rodriguez-Garcia *et al* [37], suggests a beneficial effect of the combined use of baricitinib with corticosteroids in patients with moderate-severe COVID-19 infection, by observing an improvement in lung function measured by SpO₂/FiO₂. It might produce a certain lung protective effect, as lower D-dimer values are observed in this group of patients.

The study carried out by Kalil *et al* [38] suggested a benefit from the combination of baricitinib together with remdesivir in patients with COVID-19 infection. In this clinical trial, 1033 patients were randomized to receive remdesivir in combination with baricitinib or placebo. The results demonstrated a greater benefit with the association of the two drugs in terms of improvement in clinical status and in the days to recovery, with a greater benefit in patients requiring high-flow therapy or NIMV at the beginning of treatment.

Right now, there are multiple ongoing studies about the efficacy of this drug, alone or combined with others.

Colchicine

Colchicine is a lipid soluble alkaloid that accumulates in granulocytes and monocytes. It reduces chemotaxis of inflammatory cells, blocks the expression of E-selectin, responsible for leukocyte binding to endothelial cells, and it is also in charge of the inflammasome activation and superoxide production. It has shown anti-inflammatory activity in pathologies such as pericarditis or gout.

McEwan *et al* [39] conducted a systematic review of the infectious complications of the use of colchicine and the use of colchicine for the treatment of infectious diseases, concluding in the case of COVID-19 that mortality at 21 and 28 d was lower in the colchicine group than in the standard treatment group. However, it is unknown whether this potential benefit is due to the antiviral or anti-inflammatory action of colchicine.

Likewise, the preliminary results of the COLCORONA study (Tardif *et al* [40]) were recently published confirming that in non-hospitalized patients with COVID-19, colchicine reduces mortality and hospitalization.

Otilimab

This monoclonal antibody that inhibits granulocyte macrophage colony-stimulating factor (anti-GM-CSF) is currently under investigation in patients with severe SARS-CoV-2 infection.

The OSCAR clinical trial, which is about to start Phase 3, has shown promising results in Phase 2, ensuring the safety goals and suggesting a benefit in groups with older patients[41].

OTHER TREATMENTS

Hydroxychloroquine

Hydroxychloroquine has shown *in vitro* antiretroviral activity against several viruses, including SARS-CoV-2, it has an acceptable adverse effect profile and is inexpensive. It has not shown clinical efficacy in animals, but there are several studies that have suggested clinical benefits from the association of azithromycin with hydroxychloroquine.

The Oxford RECOVERY group compared all-cause mortality at 28 d in two groups, one of which received hydroxychloroquine ($n = 1561$) and the other, standard treatment ($n = 3155$). The risk of progression to non-invasive mechanical ventilation was found to be higher in the group taking hydroxychloroquine. Likewise, mortality was higher in the group taking hydroxychloroquine, determining that hydroxychloroquine is not an effective treatment for COVID-19. In addition, there is a risk of cardiovascular toxicity, which is exacerbated by co-administration with azithromycin [42].

Tleyjeh *et al*[43] studied the cardiovascular risk of the use of chloroquine and hydroxychloroquine in patients with COVID-19, establishing a significant risk of drug-induced QT prolongation and increased incidence of Torsades de pointes, ventricular tachycardia and cardiac arrest. Therefore, they do not recommend this treatment by routine for COVID-19.

The meta-analysis by Kashour *et al*[44] establishes with moderate certainty that hydroxychloroquine, with or without azithromycin, does not reduce short-term mortality in hospitalized patients with COVID-19 or the risk of hospitalization in patients treated on an outpatient basis.

Fiolet *et al*[45] also analysed the mortality of hydroxychloroquine alone, hydroxychloroquine and azithromycin, and standard treatment, showing that hydroxychloroquine alone does not modify mortality over standard treatment. However, when it is combined with azithromycin, mortality increases.

Azithromycin

Once the benefit of the use of corticosteroids in COVID-19 had been evaluated, it was assessed whether other treatments that suppress or modulate the immune system could be effective against the disease. Azithromycin, besides being an antibiotic of the macrolide family, has shown an immunomodulatory effect by reducing the production of pro-inflammatory cytokines and inhibiting the activation of neutrophils.

The RECOVERY group studied mortality at 28 d, the time to discharge and the need for invasive mechanical ventilation in hospitalized COVID-19 patients. No significant differences between the azithromycin group and the standard treatment group were observed, nor were significant differences in subgroup analysis. Thus, they consider that azithromycin is not an effective treatment in hospitalized patients with COVID-19 and should be reserved for those who have an indication of azithromycin for antibiotic purposes[46].

Verdejo *et al*[47] conducted a systematic review on the use of macrolides in COVID-19, evaluating articles in which they are used alone or in combination with other drugs such as hydroxychloroquine. They evaluated all-cause mortality, the need for invasive mechanical ventilation and extracorporeal membrane oxygenation, hospitalization time, respiratory failure, serious adverse events, and SARS-CoV-2 PCR time to negativize. Although the quality of the evidence for most of the results was low, they concluded that macrolides do not show any beneficial effect compared to standard treatment.

Anticoagulation and thromboprophylaxis

So far, there is wide evidence that confirms a higher risk of thromboembolic events in patients with severe COVID-19. For this reason, despite not being a direct COVID-19 treatment, the use of anticoagulation in these patients has been a controvert topic.

These thrombotic events are caused by the infection itself, but also by the proinflammatory response, the hypoxia and the critical illness. Some of these mechanisms are still unknown.

Most of the recent guidelines recommend keeping a high level of suspicion of thromboembolic events in hospitalized patients, monitoring laboratory parameters such as D-dimer and blood count. It is important to point out also the risk of haemorrhage in some patients, with its consequent implications. Tools like Wells score and IMPROVE-bleeding score could be useful to predict the risk of thrombosis and bleeding.

According to the article published by Skeik *et al*[48], patients with low or no suspicion for VTE calculated by Wells score (0 for deep vein thrombosis or < 2 for pulmonary embolism), they recommend regular antithrombotic prophylaxis. In patients with higher risk, imaging should be considered. If the result is negative, or imaging is not available, we should consider the bleeding risk. If this one is high, also regular thromboprophylaxis is recommended; if it is low, we should consider anticoagulation. In patients with high suspicion of VTE (Wells > 2 for VDT or 6 for PE) and without imaging available, the anticoagulation is also recommended according to the bleeding risk. Direct oral anticoagulants are usually preferred[48].

Guidelines like the CHEST Guidelines or the American College of Cardiology also recommend thromboprophylaxis in hospitalized patients depending on the thrombotic and bleeding risk of each patient. More studies are still needed.

CONCLUSION

Currently, multiple pharmacological studies continue to be carried out. For the moment, the evidence recommends treating patients with remdesivir in the viral phase and with dexamethasone, tocilizumab or baricitinib in the inflammatory phase. Nevertheless, we are sure that in the following months we will be able to have more therapeutic weapons to tackle COVID-19.

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