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COVID-19 TREATMENT: EVOLUTION AND EVALUATION OF THERAPEUTIC STRATEGIES

Bel Houari M.*[1], Bouhlala N.[1,2], Amezouar A.[1,2], Zhim I.[1,2], Lamsaouri J.[1,2] and Tadlaoui Y.[1,2]

[1]Pharmacy Center of the Mohammed V Military Training Hospital in Rabat.
[2]Faculty of Medicine and Pharmacy of Rabat.

***Corresponding Author: Bel Houari M.**

Pharmacy Center of the Mohammed V Military Training Hospital in Rabat.

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ABSTRACT

At the end of 2019, a new coronavirus emerged in Wuhan, China, quickly causing a severe respiratory syndrome and deadly pneumonia (SARS-CoV-2). The lack of information about this disease and its therapeutic management created an atmosphere of urgency to find an effective treatment. The simplest strategy aims to repurpose existing drugs, which had the advantage of reducing costs and development time. These primarily include drugs that act directly against the causative agent, namely antiretrovirals and monoclonal antibodies against SARS-CoV-2, and also, anti-inflammatory drugs and immunomodulatory agents that help combat the hyperinflammatory state induced by cytokine release have been investigated individually or in combination. Over the course of these three years, numerous randomized controlled trials of known drugs have been conducted in COVID-19 patients, and several Emergency Use Authorizations (EUAs) have been issued by the Food and Drug Administration (FDA). The purpose of this work is to provide a summary of the latest potential therapeutic options proposed, authorized, or approved for clinical use in the management of COVID-19 and included in international protocols for managing the COVID-19 crisis. The objective is to assist physicians and all individuals involved in the fight against the epidemic, improve their decision-making, and help them make the appropriate choices.

KEYWORDS: Treatment, COVID-19, Medications, Protocol, Patient Management.

INTRODUCTION

In late 2019, a new coronavirus emerged in Wuhan, China, rapidly causing severe respiratory syndrome and fatal pneumonia, later designated as severe acute respiratory syndrome 2 (SARS-CoV-2) responsible for the coronavirus disease 2019 (COVID-19) pandemic by the World Health Organization, three months after the start of the epidemic.[1]

At the start of the pandemic, understanding of COVID-19 and its therapeutic management was limited, this state of emergency created a race to find effective treatment to combat this viral disease. The main strategy was to reuse existing drugs, which had the advantage of reducing costs and development time. Following this, numerous randomized controlled trials of known drugs have been carried out in patients with COVID-19.[2,3]

In light of the public health emergency, the Food and Drug Administration (FDA) has issued a number of Emergency Use Authorizations (EUAs) for a variety of medications. Different therapeutic options have been evaluated in the management of COVID-19.[4] including antiviral drugs and anti-SARS-CoV-2 monoclonal antibodies, they remain the most effective in the first stage of COVID-19 disease where replication viral is maximal before or shortly after the appearance of symptoms, but also anti-inflammatory drugs and immunomodulatory agents which help to combat alone or in combination the state of hyperinflammation induced by the release of cytokines.

The aim of this work is to provide a summary of the latest potential therapeutic options proposed, authorized or approved for clinical use in the management of COVID-19 and forming part of the international protocols retained in the management of the COVID 19 crisis. objective is to help doctors all those involved in the fight against the epidemic and to improve their decision-making and help them make the appropriate choices.

1. Antiviral Therapies

1.1. Molnupiravir

Molnupiravir is a direct-acting broad-spectrum oral antiviral agent acting on the RdRp enzyme by inhibiting it and thus causing several errors in the replication of the SARS-CoV-2 RNA virus.[5] Based on a meta-analysis of

available phase 1-3 studies, Molnupiravir was noted to demonstrate a significant reduction in hospitalizations and deaths in mild COVID-19 disease.[6] Results from a double-blind, randomized, placebo-controlled phase 3 trial reported that early treatment with Molnupiravir reduced the risk of hospitalization or death in unvaccinated at-risk adults with mild Covid-19 to moderate, laboratory confirmed.[7]

Moreover, the UK's Medicines regulator and the US FDA have authorized the emergency use of molnupiravir for treating mild-to-moderate COVID-19 in adults.

1.2- Ritonavir/Nirmatrelvir

Ritonavir/Nirmatrelvir is an oral pill combination of two antiviral agents that, in an interim analysis of phase 2-3 data (reported by press release) that included 1219 patients, found that the risk of hospitalization associated with COVID-19 or all-cause mortality was 89% lower in the Ritonavir/Nirmatrelvir group compared to placebo when started within three days of symptom onset.[8] On December 22, 2021, the FDA issued an Emergency Use Authorization (EUA) authorizing the use of Ritonavir/Nirmatrelvir for patients with mild to moderate COVID-19.

On April 22, 2022, a tenth version of the WHO guidelines was published, the use of the combination of Ritonavir and Nitmatrelvir was strongly recommended in patients with non-severe COVID-19 at high risk of hospitalization. This combination should be administered as soon as possible after the onset of symptoms, ideally within 5 days.[9] The Guideline Development Group (GDG) concluded that Nirmatrelvir-Ritonavir represents a superior choice because it may have greater effectiveness in preventing hospitalization than alternatives, has fewer concerns in regarding the harms of Molnupiravir; and is easier to administer than intravenous remdesivir and antibodies. This strong recommendation does not apply to pregnant women, children, or people with possible dangerous drug interactions.

No changes have been made to the Nirmatrelvir-Ritonavir recommendation in this twelfth version of the recommendation.[10]

1.3- Remdesivir

Remdesivir is an adenosine nucleoside analogue that interferes with RNA polymerase. It is a broad-spectrum antiviral agent with antiviral activity. It was initially developed to fight against the Ebola virus.[11] it has previously demonstrated its effectiveness against SARS-CoV-2 in vitro.

Based on the results of three randomized controlled clinical trials that showed remdesivir was superior to placebo in shortening recovery time in adults hospitalized with mild to severe COVID-19, the U.S. FDA approved remdesivir for clinical use in adults and pediatric patients (aged over 12 years and weighing 40 kilograms or more) to treat hospitalized patients with COVID-19.[12,13]

However, results from the WHO SOLIDARITY trial conducted in 405 hospitals in 40 countries involving 11,330 hospitalized COVID-19 patients who were randomized to receive remdesivir (2750) or no drug (4088) found that remdesivir had little or no effect on overall mortality, initiation of mechanical ventilation and length of hospital stay.[14]

A recently published double-blind randomized placebo-controlled trial reported an 87% lower risk of hospitalization or death than placebo when non-hospitalized at-risk patients with COVID-19 were treated with a 3-day course of remdesivir.[15]

The main adverse effects noted with remdesivir are hypotension, sometimes severe, as well as kidney and liver damage. Its administration therefore requires close monitoring.

1.4- Hydroxychloroquine and chloroquine

Since the first wave of COVID-19, hydroxychloroquine and chloroquine have been proposed as antiviral treatments. But in its third version, the WHO guidelines, published on December 17, 2020, recommended against the use of hydroxychloroquine. This decision follows the publication of the WHO SOLIDARITY trial on October 15, 2020, reporting results of treatment with hydroxychloroquine, remdesivir and lopinavir/ritonavir in hospitalized patients with COVID-19.[10] However, data from randomized controlled trials evaluating the use of hydroxychloroquine with or without azithromycin in hospitalized patients did not improve clinical status or overall mortality compared to placebo.[14,16] Data from randomized controlled trials of hydroxychloroquine used as post-exposure prophylaxis did not prevent SARS-CoV-2 infection or symptomatic COVID-19 disease.[17]

Hydroxychloroquine and chloroquine are currently not indicated for the treatment of COVID-19 in patients with COVID-19, regardless of disease severity.[10]

1.5- Lopinavir/Ritonavir

Lopinavir/Ritonavir is a combination antiviral protease therapy or ritonavir may increase the serum concentration of lopinavir in vivo by inhibiting CYP3A-mediated metabolism of lopinavir. This combination is approved by the FDA for the treatment of HIV and was proposed as an antiviral therapy for COVID-19 early in the pandemic. Data from a randomized controlled trial reported no benefit over standard care in patients hospitalized with severe COVID-19.[18] Lopinavir/ritonavir is currently not indicated for the treatment of COVID-19 in hospitalized and non-hospitalized patients.

1.6- Ivermectine

Ivermectin is an FDA-approved antiparasitic drug used worldwide in the treatment of COVID-19 based on an in vitro study that showed inhibition of SARS-CoV-2 replication.[19] The recommendation for Ivermectin was published on March 31, 2021 as the fourth version of the WHO guidelines and in the British Medical Journal as rapid recommendations.[10]

A single-center, double-blind, randomized controlled trial involving 476 adult patients with mild COVID-19 disease. The results demonstrated that receiving Ivermectin 300 mg/kg body weight for five days or a placebo did not achieve significant improvement or resolution of symptoms.[20] The use of Ivermectin is not recommended for the treatment of COVID-19 in hospitalized and non-hospitalized patients except in a clinical trial.[10]

2- Anti-SARS-CoV-2 neutralizing antibody products

People who recover from COVID-19 develop neutralizing antibodies against SARS-CoV-2, and how long this immunity lasts is unclear. Nevertheless, their role as therapeutic agents in the management of COVID-19 is being widely pursued in ongoing clinical trials.

2.1- Convalescent plasma

Convalescent Plasma therapy has been evaluated during the SARS, MERS and Ebola epidemics; however, randomized controlled trials to support its actual effectiveness were lacking. Recommendations for convalescent plasma for patients with non-severe, severe and critical COVID-19 were published on 7 December 2021 as the seventh version of the WHO Living Guidelines and in the British Medical Journal as Rapid Recommendations. No changes have been made to the convalescent plasma recommendations in this twelfth version of the recommendation. The FDA approved convalescent plasma therapy under an EUA for patients with severe, life-threatening COVID-19.[10] Although appearing promising, data from several studies evaluating the use of convalescent plasma in life-threatening COVID-19 have generated mixed results. Data from small randomized controlled trials have shown no significant difference in clinical improvement or overall mortality in patients treated with convalescent plasma compared with standard therapy.[21,22]

Another large study of convalescent plasma conducted in the United Kingdom, involving 11,558 patients, confirmed that treatment with high concentration convalescent plasma did not improve the survival of hospitalized patients with COVID-19.[23]

A retrospective study based on a US national registry reported that among patients hospitalized with COVID-19, not on mechanical ventilation, there was a lower risk of death in patients who received convalescent plasma transfusion with a higher rate However, among the 1,181 participants, 149 were fully vaccinated and the age group over 65 represented only 6.8%.[24]

Other trials are underway, notably the COVID-19 trial and the REMAP-CAP trial, to provide additional evidence on the value of convalescent plasma in the treatment of COVID-19.[25]

2.2- Casirivimab/Imdevimab: REGN-COV2

REGN-COV2 is a non-competing two-antibody IgG1 monoclonal antibody cocktail that targets the RBD on the SARSCoV-2 spike protein that has been shown to decrease viral load in vivo, preventing disease-induced sequelae. the virus when administered prophylactically or therapeutically in non-human primates.[26]

Results from an interim analysis of 275 patients from an ongoing double-blind trial involving non-hospitalized patients with COVID-19 who were randomized to receive placebo, 2.4 g of REGNCOV2 (Casirivimab 1200 mg and Imdevimab 1200 mg) or 8 g of REGN - COV2 (Casirivimab 2400 mg and Imdevimab 2400 mg) reported that the REGN-COV2 antibody cocktail reduced viral load compared to placebo. This interim analysis also established the safety profile of this antibody cocktail, similar to that of the placebo group.[27]

However, a recent study, conducted by Wilhelm et al., reported that the Omicron variant of SARS-CoV-2 was resistant to Casirivimab and Imdevimab, in vitro.[28] Wilhelm A, Widera M, Grikscheit K, Toptan T, Schenk B, Pallas C, Metzler M, Kohmer N, Hoehl S, Helfritz FA, Wolf T. Reduced neutralization of SARS-CoV-2 Omicron variant by vaccine sera and monoclonal antibodies. MedRxiv. 2021 Dec 8:2021-12.

On September 16, 2022 a 12th version of the WHO living guidelines was published, regarding updated recommendations on the use of Casirivimab-Imdevimab neutralizing antibodies for patients with COVID-19. Previously, a conditional recommendation was provided for non-severe COVID-19 patients at high risk of hospitalization and also for patients with severe and critical illness provided they were HIV negative. Following the emergence of currently circulating SARS-CoV-2 variants and sub-variants (e.g. Omicron) that now dominate COVID-19 globally, and the availability of evidence from in vitro neutralization assays of SARS-CoV-2, the GDG issued a strong recommendation against the use of Casirivimab-Imdevimab for all patients with COVID-19 as it did not demonstrate sufficient in vitro neutralization activity against SARS-CoV-2. variant and sub-variants of Omicron.[10]

2.3- Bamlanivimab/Etesevimab (LY-CoV555 or LY3819253 and LYCoV016 or LY3832479)

Bamlanivimab and Etesevimab are potent anti-spike neutralizing monoclonal antibodies. Bamlanivimab is a neutralizing monoclonal antibody derived from convalescent plasma obtained from a patient with

COVID-19. Like REGN-COV2, it also targets the RBD of the SARS-CoV-2 spike protein and has been shown to neutralize SARS-CoV-2 and reduce viral replication in non-human primates.[12]

In vitro experiments revealed that Etésevimab binds to a different epitope than Bamlanivimab and neutralizes resistant variants with mutations in the epitope bound to Bamlanivimab. In phase 2 of the BLAZE-1 trial, Bamlanivimab/Etesevimab was associated with a significant reduction in SARS-CoV-2 viral load compared to placebo at day 11.[29] Phase 3 data from BLAZE-1 are awaiting release, but preliminary information indicates the therapy reduced the risk of hospitalization and death by 87%. In vitro data are available regarding the effect of Bamlanivimab/Etesevimab on new SARS-CoV-2 variants of concern (B.1.1.7; B.1.351) and reveal conserved activity.[25]

2.4- Sotrovimab (VIR-7831)

Sotrovimab is a potent anti-spike neutralizing monoclonal antibody that has demonstrated in vitro activity against the four VOCs Alpha (B.1.1.7), Beta (B.1.351), Gamma(P1) and Delta (B.1.617.2). Results from a planned interim analysis of the multicenter, double-blind, placebo-controlled COMET-ICE trial by Gupta et al., which evaluated the clinical efficacy and safety of Sotrovimab demonstrated that a dose of Sotrovimab (500 mg) reduced the risk of hospitalization or death by 85% in non-hospitalized high-risk patients with mild to moderate COVID-19 compared to placebo.[30] A randomized controlled trial in patients with COVID-19 at high risk of progression showed that early treatment with Sotrovimab compared to placebo may be associated with reduced costs of hospitalization longer than 24 hours and costs healthcare totals for COVID-19 care.[31]

According to the latest update of WHO guideline recommendations, the use of Sotrovimab is strongly discouraged for any patient with non-severe COVID-19.[10]

2.5- Bebtelovimab (LY-CoV1404, 1404)

Bebtelovimab is a neutralizing monoclonal antibody that targets the RBD of the spike (S) protein of the SARS-CoV-2 virus. On February 23, 2022 the US FDA issued an EUA authorizing the use of Bebtelovimab for the treatment of mild to moderate COVID-19 in outpatients (aged ≥ 12 years and weighing ≥ 40 kg) with SARS infection. Laboratory-confirmed CoV-2 and mild to moderate COVID-19 who are at high risk of progressing to severe illness and/or hospitalization or death, and provided that other treatment options for COVID-19 are not accessible or not clinically appropriate.[32,33]

2.6- Tixagevimab/Cilgavimab: AZD7442

Tixagevimab and Cilgavimab are potent, long-acting anti-spike neutralizing monoclonal antibodies obtained from antibodies isolated from B cells of patients infected with SARS-CoV-2 that have demonstrated neutralizing activity against SARS-CoV-2 virus by binding to non-overlapping epitopes of the virus RBD spike protein.[32,34,35]

Results from an ongoing multicenter, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single dose combining these 2 monoclonal antibodies for pre-exposure prophylaxis against COVID-19 in high-risk patients, patients who had an inadequate response to COVID-19 vaccination or were unable to receive vaccines demonstrated the effectiveness of this combination of monoclonal antibodies for the prevention of COVID-19 without any safety concerns.[34]

In December 2021, the United States Food and Drug Administration showed an EUA for emergency use of this monoclonal antibody combination for use in pre-exposure prophylaxis of COVID-19 in adults and the pediatric population (12 years and older weighing at least 40 kg) with no current evidence of SARS-CoV-2 infection and no recent exposure to SARS-CoV-2 positive individuals and AND who have moderate or severe immunosuppression due to multiple types of conditions and treatments OR are on immunosuppressive therapy and may not mount an adequate immune response to COVID-19 vaccination OR in individuals in whom COVID-19 vaccination is contraindicated due to a history of serious adverse reaction to one of the components of the vaccine.

Kertes et al,[36] also showed that the use of AZD7442 in immunocompromised individuals aged 12 years and older can protect against Omicron variant infection and severe disease.

3- Immunomodulatory agents

3.1- Corticosteroïds

Severe COVID-19 is associated with inflammation-related lung injury driven by cytokine release characterized by elevation of inflammatory markers. Early in the pandemic, the effectiveness of glucocorticoids in patients with COVID-19 was not well described. The Randomized Covid-19 Therapy Evaluation (RECOVERY) Trial, which included hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 who were randomly assigned to receive dexamethasone (n=2104) or usual care (n = 4321), showed that the use of dexamethasone resulted in reduced 28-day mortality in patients receiving invasive mechanical ventilation or oxygen support, but not in patients receiving no support respiratory.[37] Based on the results of this landmark trial, dexamethasone is currently considered the standard of care, either alone or in combination with remdesivir depending on disease severity in hospitalized patients who require supplemental oxygen or non-invasive or invasive mechanical ventilation.

Treatment with systemic corticosteroids is strongly recommended in WHO guidelines for patients with severe or critical COVID-19 where their administration has been proven to relatively reduce mortality by 21%.[10]

3.2- Interferon-β-1a (IFN -β-1a): SNG001*

Interferons are cytokines that are essential for mounting an immune response against viral infection, and SARS-CoV-2 suppresses their release in vitro.[38] Results of a randomized, double-blind, placebo-controlled trial showed that the use of inhaled IFN-β-1a had greater chances of clinical improvement and recovery compared to placebo.[39] Another randomized clinical trial showed that the clinical response using inhaled IFN-β-1a was not significantly different from that of the control group. The authors reported that when used early, this agent resulted in a shorter length of hospital stay and a decreased 28-day mortality rate. However, four patients who died in the treatment group before the end of treatment were excluded, making the interpretation of these results difficult.[40]

3.3- Interleukin-1 antagonists

Anakinra is an interleukin-1 receptor antagonist approved by the FDA to treat rheumatoid arthritis.[41] Its off-label use in severe COVID-19 was evaluated in a case-control study trial based on the rationale that severe COVID-19 is driven by the production of cytokines, including interleukin (IL)-1β. This trial found that of the 52 patients who received Anakinra and the 44 patients who received standard care, Anakinra reduced the need for invasive mechanical ventilation and mortality in patients with severe COVID-19.[42] There are no data available regarding the effectiveness of interleukin-1 receptor antagonists on the three new variants of SARS-CoV-2 (B.1.1.7; B.1.351 and P.1). Given the insufficient data regarding this treatment based only on case series, it is currently not recommended for use to treat COVID-19 infection.

3.4- Anti-IL-6 receptor monoclonal antibodies

Interleukin-6 (IL-6) is a proinflammatory cytokine that is considered the main driver of the hyperinflammatory state associated with COVID-19. Targeting this cytokine with an IL-6 receptor inhibitor could slow the inflammation process based on case reports that showed favorable outcomes in patients with severe COVID-19.[43,44]

The FDA has approved three different types of IL-6 receptor inhibitors for various rheumatologic conditions (Tocilizumab, Sarilumab) and a rare disease called Castleman syndrome (Siltuximab).

The recommendation for IL-6 receptor blockers (Tocilizumab or Sarilumab) was published on July 6, 2021 as the fifth version of the WHO guidelines. It follows the publication of the RECOVERY and REMAP-CAP trials in February 2021, and new trial data from 1020 patients randomized head-to-head to either Tocilizumab or Sarilumab in REMAP-CAP, made available to WHO on 1 June 2021.[10]

In the twelfth version of the guideline, WHO updated the strong recommendation for Baricitinib in patients with severe and critical COVID-19, reflecting that IL-6 receptor blockers and Baricitinib can be administered together.[10]

The results of a study conducted by Villaescusa et al., confirm that the administration of Siltuximab downregulates IL-6 levels, thereby reducing the inflammatory process in COVID-19 patients with severe respiratory disease.[45]

3.5- Janus kinase (JAK) inhibitors

The JAK/STAT pathway regulates a number of inflammatory cytokines and growth factors. These cytokines are very important for initiating and controlling innate and adaptive immune responses, but they can lead to excessive or uncontrolled inflammatory reactions and tissue damage in patients with COVID-19.

JAK inhibitors can competitively bind to the adenosine triphosphate binding site of JAKs and interfere with the phosphorylation of STAT proteins, thereby inhibiting the expression of downstream inflammatory genes and growth factors. They have already demonstrated their effectiveness in the treatment of several inflammatory diseases, such as rheumatoid arthritis (RA). The use of these kinase inhibitors in hospitalized patients with COVID-19 has had a significant impact on improving clinical outcomes. By inhibiting hypercytokinemia and virus-induced immune activation.[46]

A- Baricitinib

Baricitinib is an oral selective inhibitor of JAK 1 and JAK 2 currently indicated for patients with moderate to severe active rheumatoid arthritis (RA). It was considered as a potential treatment for COVID-19 due to its inhibitory effect on SARS-CoV-2 endocytosis in vitro and the intracellular cytokine signaling pathway that causes the late-onset hyperinflammatory state, it could also have direct anti-SARS-CoV-2 activity by interfering with viral endocytosis, thereby hindering SARS-CoV-2 entry and infection into susceptible cells.[46]

Its benefit in the treatment of Covid -19 has been the subject of several studies. Indeed, a study demonstrated that the combination of baricitinib with standard care, including corticosteroids, mainly reduced 28-day and 60-day mortality in patients belonging to a population with an ordinal score defined by the Institute National Allergy and Infectious Diseases (NIAID-OS 7); these patients were hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Overall, 28-day all-cause mortality among patients on invasive mechanical ventilation or ECMO at baseline was 58% among those receiving placebo and 39%

among participants receiving baricitinib. Mortality at 60 days was significantly lower in the baricitinib group compared to the placebo group (45% versus 62%, respectively).[47] A meta-analysis of randomized controlled trials shows that treating hospitalized patients with COVID-19 with Baricitinib could significantly reduce the risk of COVID-19-related death by 43%, and lead to a significant reduction in risk of ECMO initiation of 36%.[48]

A multicenter observational retrospective study of 113 hospitalized patients with COVID-19 pneumonia who received Baricitinib combined with lopinavir/ritonavir (Baricitinib arm, n=113) or hydroxychloroquine and lopinavir/ritonavir (control arm, n =78) reported significant improvement in clinical symptoms and 2-week mortality rate in the Baricitinib arm compared to the control arm. Results from the ACTT-2 trial, a randomized, double-blind, placebo-controlled trial evaluating Baricitinib plus remdesivir in hospitalized adult patients with COVID-19 found that Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation.[49] Baricitinib, in combination with remdesivir, has been approved for clinical use in hospitalized patients with COVID-19 under an EUA issued by the FDA.

Following these encouraging results, the FDA issued the first Emergency Use Authorization (EUA) for baricitinib in combination with remdesivir for the treatment of hospitalized adults with COVID-19 and pediatric patients 2 years of age or older requiring assisted invasive mechanical ventilation or ECMO. It can now be used concomitantly with IL-6 receptor antagonists (Tocilizumab or Sarliumab), in addition to corticosteroids in patients with severe or critical COVID-19 for the treatment of adults hospitalized with COVID-19. 19 requiring supplemental oxygen, mechanical ventilation, or ECMO.[10]

B- Ruxolitinib

Ruxolitinib, a selective oral inhibitor of JAK 1 and 2, is indicated for the treatment of myeloproliferative disorders, polycythemia vera and steroid-resistant graft versus host disease.[50] Similar to Baricitinib, it has been hypothesized to have an inhibitory effect on the intracellular cytokine signaling pathway, which could, in fact, represent a potential treatment against COVID-19. Results of a prospective multicenter randomized controlled phase 2 trial evaluating the efficacy and safety of Ruxolitinib reported no statistical differences compared to standard of care. However, most patients demonstrated significant improvement in chest CT and faster recovery from lymphopenia.[51] A randomized, double-blind, placebo-controlled phase 3 trial showed that the use of Ruxolitinib 5 mg twice daily showed no benefit in the overall study population. A larger sample size is needed to determine the clinical importance of the treatment.[52]

C- Tofacitinib

Tofacitinib is another oral selective inhibitor of JAK 1 and JAK3 that is indicated for moderate to severe rheumatoid arthritis, psoriatic arthritis, and moderate to severe ulcerative colitis.[53] Given its inhibitory effect on the inflammatory cascade, it was hypothesized that its use could ameliorate lung injury induced by viral inflammation in patients with severe COVID-19. Results from a randomized controlled trial that evaluated effectiveness involving 289 patients randomized to receive Tofacitinib or placebo showed that Tofacitinib resulted in a lower risk of respiratory failure or death.[54]

3.6- Tyrosine kinase inhibitors

Bruton's tyrosine kinase inhibitors such as Acalabrutinib, Ibrutinib, Rilzabrutinib are tyrosine kinase inhibitors that regulate macrophage signaling and activation currently approved by the FDA for certain hematologic malignancies. Macrophage activation is proposed to occur during the hyperinflammatory immune response observed in severe COVID-19. The results of a study carried out on 19 hospitalized patients with severe COVID-19 who received Acalabrutinib, off-label, highlighted the potential clinical benefit of BTK inhibition.[55] Clinical trials are underway to validate the real effectiveness of these drugs in severe cases of COVID-19.

3.7- Azithromycin

Azithromycin is a macrolide with immunomodulatory effects linked to the induction of INF. It can be used in certain long-term respiratory conditions. It also appears to have antiviral effects in vitro, which are not yet proven.

The Chloroquine-Azithromycin therapeutic option has been evaluated by several studies in the management of COVID-19 by rapid negativation of RT-PCR.[56]

Trials comparing the use of hydroxychloroquine with azithromycin vs chloroquine alone have been reviewed for the treatment of COVID-19. There was no evidence that the addition of azithromycin altered the effect of hydroxychloroquine for any outcome and available retrospective data made no difference in mortality with or without hydroxychloroquine.[57]

Likewise, a randomized controlled study published at the beginning of September 2020 with and without hydroxychloroquine in severe patients did not find any benefit from azithromycin.[58]

Macrolides are well known for a certain number of adverse effects, notably cardiac, the risk of prolongation of the QT segment as well as their inhibitory effect on cytochrome 3A4 which causes several drug interactions.

CONCLUSION

From the start of the pandemic, a multitude of studies were carried out globally, aimed at developing therapeutic strategies against COVID-19. Since then, some have been retained and are now part of international and national care protocols and others have been abandoned. But the almost majority of these therapeutic approaches are based on the reuse or repurposing of various drugs, aiming either to inhibit cellular entry and replication, or to suppress the cytokine storms caused by coronavirus infection. In parallel, a global effort has also resulted in the development of various types of vaccines, which are currently being administered, and encouraging results have been achieved. Therefore, considering the progress made in the field of etiology, drug and vaccine development, we can expect promising results in the near future.

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