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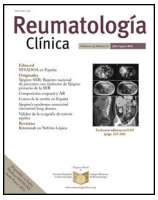

Special Article

Therapeutic options for the management of severe COVID-19: A rheumatology perspective☆

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ABSTRACT

The novel SARS-CoV-2 human coronavirus in Wuhan, China, has triggered a worldwide respiratory disease outbreak (COVID-19). Acute respiratory distress syndrome (ARDS), multiorgan dysfunction and thrombotic events are among the leading causes of death in critically ill patients with COVID-19. The elevated inflammatory cytokines suggest that a "cytokine storm", also known as cytokine release syndrome (CRS), may play a major role in the pathology of COVID-19. In addition to anti-viral therapy and supportive treatment in critically ill patients, unique medications for this condition are also under investigation. Here we reviewed therapeutic options, including the antibody therapy that might be an immediate strategy for SARS-CoV-2 therapy.

Opciones terapéuticas en el manejo de la COVID-19 grave: una perspectiva de Reumatología

Palabras clave:
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Síndrome de liberación de citocinas

RESUMEN

El inicio del nuevo coronavirus humano del síndrome respiratorio agudo grave (SARS-Cov-2) en Wuhan, China, ha desencadenado un brote respiratorio mundial (COVID-19). El síndrome de insuficiencia respiratoria agua (SIRA), el fallo multiorgánico y eventos trombóticos están entre las causas que llevan a la muerte en pacientes críticamente enfermos con COVID-19. Las citocinas inflamatorias elevadas sugieren que una "tormenta de citocinas", también conocida como síndrome de liberación de citocinas (SLC), puede jugar un papel principal en la patología de COVID-19. Adicionalmente al tratamiento anti-viral y la terapia de apoyo respiratorio en pacientes críticamente enfermos, están en investigación medicamentos únicos para esta condición. En esta revisión sintetizamos la evidencia más actual de opciones terapéuticas, incluyendo anticuerpos anti-citocinas como una estrategia intermedia para la terapia de SARS-Cov-2.

Introduction

The degree of disease severity with COVID-19 varies and can become fulminant or fatal. The World Health Organization (WHO) estimates that severe disease can occur in about 13.8% of cases and 6.1% are critical.[1] When cases are fulminant, patients may develop sepsis, acute respiratory failure syndrome (ARDS) or multiple organ failure, which are not exclusive to coronaviruses. Cytokine

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release syndrome (CRS) refers to an uncontrolled and exaggerated release of pro-inflammatory mediators into the activated immune system.[2] This disturbance may be present in various clinical entities, including the rheumatology setting, Still's disease, systemic juvenile idiopathic arthritis, systemic lupus erythematosus and catastrophic antiphospholipid syndrome (APS). CRS is involved in the immunopathogenesis of many pathological processes, such as ARDS, sepsis, Macrophage activation syndrome (MAS), etc., several of which are described in severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and also in the new COVID-19 infection.[3] While treatment directed against the virus is desired, treatment of the systemic response is possibly the most important aspect of patient care and should be viewed aggressively. Finally, patients with COVID-19 who develop a severe condition may have a procoagulant pattern.[4] Therefore, this review synthesizes the evidence related to therapies with an anti-inflammatory role that can play a relevant role in the management of patients with severe COVID-19, briefly mentioning the role of antithrombotic therapy in the treatment of complicated patients.

Glucocorticoids

Glucocorticoids (GC) are some of the most widely used anti-inflammatory agents; they are commonly prescribed in the treatment of patients with COVID-19 (72% in the ICU).[5] However, as mentioned in the Chinese COVID-19 guidelines,[6] physicians must be careful in the use of GCs because of their uncertain benefits in the context of viral respiratory infection. Several studies have reported inferior results in SARS patients treated with GC,[7] due to delayed purging of the virus. Other concerns with GCs are short-term and long-term adverse effects.

Antimalarials (chloroquine and hydroxychloroquine)

Recent publications have drawn attention to the possible beneficial effect of hydroxychloroquine (HCQ) and chloroquine (CLQ) in the treatment of patients infected with the new SARS-CoV-2 coronavirus. It has been observed that the growth of several different viruses (including SARS coronavirus) can be inhibited in cell cultures by both CLQ and HCQ. In addition, these drugs are weak bases that can affect acidic vesicles and inhibit several enzymes. This characteristic enables inhibiting of viral entry into cells when endocytosis is pH dependent. They also inhibit the enzyme glycosyltransferase (inhibition of virus glycosylation), post-transcriptional viral modifications and replication of some viral families. As it is known that COVID-19 infection can on occasion lead to severe pictures with SARS, which can be due in part to the increase of proinflammatory cytokines such as interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α). CLQ is highly effective in combination with remdesivir in controlling SARS-CoV-2[8] in vitro. There is now already some evidence in humans. In an open observational study conducted in France, they evaluated the role of HCQ in combination with azithromycin on respiratory viral load in 20 patients with COVID-19 compared with 16 controls.[9] A significant reduction in viral load was shown (70% at day 7) compared to the controls. When azithromycin was added, more efficient elimination of the virus was found (100% reduction). Gao et al. described results in 100 patients in China where they demonstrated the superiority of CLQ over the control treatment in inhibiting exacerbation of pneumonia, improving lung imaging findings, promoting negative virus conversion, and shortening the course of the disease.[10] However, the details of this study are not known in depth. A recent study reported the results of a retrospective analysis of 368 hospitalized patients with confirmed SARS-CoV-2 infection (U.S. Veterans Health Administration) of evaluation of exposure to HCQ alone or in combination with azithromycin.[11] The mortality rates in the HCQ alone, combined HQC, and no HQC groups were 27.8%, 22.1%, and 11.4%, respectively. Ventilation rates in the HCQ, combined HCQ and no HCQ groups were 13.3%, 6.9% and 14.1%, respectively. In this study, no evidence was found that the use of HCQ alone or combined reduces the risk of mechanical ventilation in hospitalized patients with COVID-19 and that patients receiving HCQ alone had the highest mortality rate. These findings highlight the importance of waiting for the results of the prospective randomized studies that are underway before widely adopting these drugs. There are currently about 14 clinical trials registered to prove the benefit of antimalarials. Although antimalarials are relatively safe drugs, it should be remembered that their most frequent effects are gastrointestinal, pruritus, and dermal changes in 10% of patients. The most serious effects are of low incidence, such as cardiomyotoxicity, neuromyopathy, and irreversible retinopathy (large doses and long term).

Tocilizumab, inleukin-6 inhibitor

There has recently been much interest in the possibility of using tocilizumab, a humanized antibody targeting the IL-6 receptor, on the grounds of preventing or treating the cytokine storm that has been observed in patients that progress to cardiovascular collapse, multiorgan dysfunction, and death.[12] Inflammatory cytokines and chemokines, including IL-6, IL-1β, induced protein 10, and monocyte chemotactic protein-1, have been found to be significantly elevated in Covid-19 patients, and are more often elevated in severe patients than in non-severe patients.[13] In patients with COVID-19, with elevated inflammatory cytokines, post mortem pathology revealed tissue necrosis and infiltrations of macrophages and monocytes in the lung, heart and gastrointestinal mucosa,[14] which suggests an uncontrolled immune response.

Studies have shown that ARDS occurs in some SARS patients despite a reduced viral load, suggesting that an exuberant immune response rather than viral virulence is possibly responsible for the pathology at tissue level. Therefore, antiviral therapy alone may not be sufficient.[15] As previously mentioned, IL-6 is one of the cytokines that plays a role in the pathogenesis in patients with severe COVID-19; it has also been suggested as a biomarker of severe disease,[16] and therefore blockade may be a promising strategy for COVID-19-induced CRS.

IL-6 is essential for the generation of T-helper 17 (Th17) lymphocytes in the interaction between T-lymphocytes and dendritic cells.[17] Therefore elevated IL-6 may explain the excessive Th17 activation observed in patients with COVID-19, as reported by Xu et al.[14] Although no data are available on IL-6 blockade in CRS induced by viral infection, animal studies of SARS-CoV have shown that they inhibit nuclear factor kappa-B, an essential transcription factor of IL-6, increasing animal survival with reduced levels of IL-6.[18] Tocilizumab, which blocks IL-6, binds to the IL-6 receptor in both soluble and membrane-bound forms to inhibit IL-6-mediated signals. This drug has been approved by the Food and Drug Administration for the treatment of CRS associated with CAR T-cell therapy.

Data on the use of this molecule in the treatment of SARS-CoV-2 infection are still preliminary but promising results have prompted the Chinese Health Commission to update its national guidelines, which include tocilizumab for the treatment of severe COVID-19.[19] The Italian guidelines also support the use of tocilizumab (at a dose of 8 mg/kg, with a second dose 12 h after the first and a possible third after 24-36 h, depending on the clinical response), in the event of rapid clinical or radiological worsening, after excluding contraindications to its use (levels of transaminases >5 times the upper limit of normal, neutrophil count <50,000 cells/μl, presence of doc-

umented sepsis complicated by bacteria, diverticulitis/intestinal perforation, skin infection).[20]

There are case reports of improvement in patients with severe COVID-19 after the administration of tocilizumab.[21,22]

Interleukin 1b inhibitors and protein kinase inhibitors JAK1/2 (roxulitinib)

Several laboratory markers related to MAS/ haemaphagocytic lymphohistiocytosis (HLH) are elevated in severe COVID-19.[23] Therefore, treatments aimed at controlling MAS/HLH have been suggested for the management of severe COVID-19. The recombinant human IL-1 receptor antagonist, anakinra, has been used for the treatment of MAS/HLH associated with autoimmune rheumatic diseases.[24] Data from a reanalysis of a phase III controlled trial found that anakinra was associated with significant improvement in the survival of patients with sepsis with concurrent MAS/HLH.[25]

Small molecule inhibiting Janus kinases, such as the JAK1/2 inhibitor ruxolitinib,[26] are capable of blocking signals from IL-6, interferon γ (IFN-γ) and other cytokines involved in MAS/HLH. Therefore, this drug could have potential in the treatment of serious complications in patients with COVID-19. More recently, the use of anti-IFN-γ antibodies has been contemplated in the management of this serious complication.[27]

Intravenous immunoglobulin and plasma from recovered patients ("convalescent plasma")

Individuals with a weakened immune system appear to be at greater risk of developing complications associated with COVID-19. Immunotherapy using IgG in combination with antiviral drugs could be used to treat or prevent SARS-CoV-2 infection and strengthen our immune system against this virus.[28,29] They have also have been administered as anti-infective agents against viruses, bacteria and fungi in experimental models and in humans.[30] IVIGs can modulate the immune response by several mechanisms, including blocking various pro-inflammatory cytokines, Fc receptors, and leukocyte adhesion molecules, suppressing Th1 and Th17 cell subtypes, and neutralizing pathogenic autoantibodies.[31] IVIGs can also expand regulatory T lymphocytes.[32] However, IVIGs have adverse reactions. During the SARS outbreak in 2003, IVIG was used extensively in Singapore. However, some critically ill patients developed venous thromboembolism (VTE) including pulmonary embolism despite the use of prophylactic low molecular weight heparin.[33] This is due to the increased viscosity in hypercoagulable states of SARS patients.

Convalescent plasma samples have been used to treat SARS in Hong Kong and China and may be valuable because, unlike standard IVIG preparations, they have high levels of anti-SARS-CoV antibodies.[34] Pyrc et al. showed that human serum from adult humans inhibited infection by HCov-NL63.[28] Furthermore, they described that IVIGs can also neutralize HCoV-NL63. Boukhvalova et al.[35] demonstrated that, in contrast, the commercially available therapeutic polyclonal IgG products, IVIG obtained from donors with antibodies at high titres against respiratory syncytial virus (RSV), have great potential in improving RSV outcomes in immunocompromised subjects, not only controlling viral replication, but also reducing damage to the lung parenchyma and the epithelial lining of the respiratory tract. The use of convalescent plasma or serum was also suggested by the WHO under the Blood Regulators Network should vaccines and antiviral drugs not be available in an emerging virus. In the current pandemic, there are reports that convalescent plasma has been used in China to treat patients with COVID-19.[36] In a pilot study of 10 patients with severe COVID-19, investigators collected convalescent plasma with neutralizing antibody titres at a dilution of 1:640 or more.[37] The convalescent plasma transfusion resulted in no serious adverse events in the receivers. All 10 patients had improvement of symptoms (e.g., fever, cough, shortness of breath, and precordial pain) within 1-3 days of the transfusion; they also showed radiological improvement in lung lesions. Similarly, an undetectable viral load was found in most of them.

IgG immunotherapy could be used to neutralize the virus causing COVID-19. The efficiency of IgG could be improved if these immune IgG antibodies were collected from patients who had recovered from COVID-19 in the same city, or surrounding areas, as donor subjects who have dealt with the virus.

Plasma interchange

Therapeutic apheresis encompasses a large number of techniques the main basis of which is to process a patient's blood through an extracorporeal device with the aim of eliminating antibodies and preformed immunocomplexes to prevent tissue damage, eliminating inflammation mediators as a complement and cytokines that could contribute to damage, and providing deficiency factors.[38] Among the different types of apheresis, some of the most used are therapeutic plasma exchange (PE) and immunoadsorption. Therapeutic PE is a technique for purifying extracorporeal blood, through which plasma is removed. A variable volume of plasma is removed from the patient and replaced with replacement solutions that maintain volume and oncotic pressure. The term p̈lasmapheresiss̈hould be reserved for situations in which only plasma removal without replenishment is performed, such as plasma donation by apheresis for transfusion or subsequent industrial plasma fractionation. This procedure extracts less plasma (around 600 ml), without replenishment solution, in less time and with simpler separation techniques than those used in PE. The host response to infection has been described and involves a complex interaction of cytokine storm, inflammation, endothelial dysfunction, and pathological coagulation. Plasma exchange is a pathway that offers benefit at multiple levels by removing inflammatory cytokines, stabilizing endothelial membranes, and restarting the hypercoagulable state.

Busund et al.[39] showed a trend towards improving mortality with therapeutic PE as an adjuvant treatment in adults with sepsis and multiple organ failure in a controlled clinical trial, while a meta-analysis by Rimmer also showed benefit in adult patient mortality.[40] Addressing this information, Patel et al.[41] used therapeutic PE during the 2009 A (H1N1) influenza epidemic in 3 paediatric patients with a fulminant condition similar to the current pandemic. All 3 patients developed ARDS with haemodynamic compromise that continued to deteriorate despite rescue treatment for ARDS including inhaled nitric oxide and extracorporeal venous membrane oxygenation. All 3 patients made a full recovery from their disease after receiving rescue PE. Recently, 3 patients were described with COVID-19 in Wuhan, China,[42] characterized by deep inflammation and treated with blood purification therapies, including PE and adsorption. A potent effect on cytokine storm management and pathogenic antibodies was shown. Of these 3 patients, 2 maintained a stable state and could be discharged from the Intensive Care Unit, while one developed disseminated intravascular coagulation (DIC) and died.

Antithrombotic therapy

Severe COVID-19 can often present a marked elevation of D-dimer, thrombocytopenia and coagulation disturbances that are considered to be regulated by various inflammatory cytokines[43,44] and that correlate with mortality. Another biomarker that has been

Table 1
Summary of the consensus on recommendations for antithrombotic therapy during the COVID-19 pandemic.

Patients with mild COVID-19 (outpatient)
For outpatients with COVID-19, increased mobility should be encouraged. Although indiscriminate use of pharmacological VTE prophylaxis should not be pursued, assessment for the risk of VTE and of bleeding is reasonable. Pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk VTE, without high bleeding risk
There is no known risk of developing severe COVID-19 due to taking antithrombotic agents (i.e., antiplatelet agents or anticoagulants). If patients were taking antithrombotic agents for prior known thrombotic disease, they should continue their antithrombotic therapy as recommended
For patients on vitamin K antagonists who do not have recent stable INRs, and are unable to undergo INR testing, it is reasonable to transition the treatment DOACs if there are no contraindications and no problems with drug availability. If DOACs are not approved or available, LMWH (enoxaparin 40 mg/day) can be considered
Patients with moderate or severe COVID-19 without DIC hospitalised
Hospitalized patients with COVID-19 should undergo risk stratification for VTE prophylaxis
For hospitalized patients with COVID-19 and not in DIC, prophylactic doses of anticoagulation should be administered to prevent VTE (enoxaparin 40 mg/day or dalteparin 5000 U daily; subcutaneous heparin 5000 U twice daily may be considered for patients with kidney failure [e.g., creatinine clearance <30 ml/min]). If pharmacological prophylaxis is contraindicated, it is reasonable to consider intermittent pneumatic compression
For hospitalised patients with COVID-19 and not in DIC, there are insufficient data to consider routine therapeutic or parenteral therapeutic doses with LMWH (e.g., enoxaparin 1 mg/kg/day, or enoxaparin 40 mg twice a day) or unfractionated heparin (with an activated PTT target of 50−70)
Routine screening for VTE is not recommended (e.g., bilateral lower extremity ultrasound) for hospitalized patients with COVID-19 with elevated D-dimer
Patients with moderate to severe COVID-19 hospitalised and suspected DIC
For patients with moderate to severe COVID-19 and in DIC but without overt bleeding, prophylactic anticoagulation should be administered
For hospitalized patients with COVID-19 with suspected or confirmed DIC with no overt bleeding, there are insufficient data to consider routine therapeutic-dose parenteral anticoagulation at therapeutic doses with LMWH or unfractionated heparin
For patients with moderate or severe COVID-19 on chronic therapeutic anticoagulation, who develop suspected or confirmed DIC without overt bleeding, it is reasonable to consider the indication for anticoagulation and to weigh with risk of bleeding when making clinical decisions regarding dose adjustments or discontinuation. It is recommended to reduce the intensity of anticoagulation in this clinical circumstance, unless the risk of thrombosis is considered to be exceedingly high
For patients with moderate or severe COVID-19 and an indication for dual antiplatelet therapy (e.g., percutaneous coronary intervention in the past 3 months or recent myocardial infarction) and with suspected or confirmed DIC with no overt bleeding, in the absence of evidence, decisions for antiplatelet therapy need to be individualized. In general, it is reasonable to continue dual antiplatelet therapy (aspirin plus a P2Y receptor inhibitor such as clopidogrel) if platelet count is >50,000, reduce to a single therapy if platelet count is 25,000 and 50,000, and discontinue if platelet count is <25,000. However, these guidelines may be revised depending on the individualized relative risk of thrombotic complications vs. bleeding
For patients who were admitted and are now being discharged for COVID-19 and now discharged, routine screening for VTE risk is reasonable for consideration of pharmaceutical prophylaxis for up to 45 days post-discharge. Pharmacological prophylaxis should be considered if there is elevated risk for thrombotic events, without bleeding risk. Ambulation and physical activity should be encouraged
Patients without COVID-19 who have previously known thrombotic disease
There is no known risk of developing COVID-19 due to the administration of antithrombotic agents. Patients should continue treatment with antithrombotic agent as recommended
To minimize risks associated with health care worker and patient in-person interactions, follow-up with e.visits and telemedicine
Patients without COVID-19 who develop new thrombotic disease
To minimize the risks associated with health care worker and patient in-person interactions, in-home treatment or early discharge should be prioritized with electronic or telemedicine follow-up
Patients without COVID-19 but with comorbid conditions (e.g., prior history of VTE, active cancer, major lung disease) who are homebound
Recommendations include increased mobility, and risk assessment for the risk of VTE and risk of bleeding is reasonable
Administration of pharmacological prophylaxis could be considered after risk assessment on an individual case basis based on their risk for thrombosis and bleeding risk

Source: Bikdeli et al.[48]
DOA: direct oral anticoagulants; DIC: disseminated intravascular coagulation; LMWH: low molecular weight heparin; INR: international normalized ratio; VTE: venous thromboembolism.

found to be elevated in patients with severe COVID-19 is ferritin,[12] which is also impaired in other severe conditions, including APS in its most severe form, catastrophic APS.[45] Recently, a group from China described 3 cases with COVID-19 and antiphospholipid antibodies.[46] Recent statements by the International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH) suggest that all patients hospitalized with COVID-19 should receive thromboprophylaxis or full-dose therapeutic anticoagulation. The efficacy of anticoagulation therapy in patients with COVID-19 was recently evaluated retrospectively. Lower mortality at 28 days was found in patients who used heparin (40%) compared to those who did not (64.2%), mainly in those with sepsis-induced coagulopathy or with a markedly elevated D-dimer.[47] Table 1 summarizes the antithrombotic recommendations for patients with COVID-19.

Conclusions

COVID-19 is a viral infection with potentially serious complications that can increase the risk of death in infected patients. Several of these disturbances are secondary to an uncontrolled immune response where a cytokine storm plays a similarly important role in preventing the thrombotic complications to which these patients are exposed. Although antiviral treatment and respiratory support therapies are essential in the treatment of severe cases, it is necessary to assess the risk-benefit of therapies aimed at controlling the immune response to decrease the mortality rate.

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Conflict of interests

The authors have no conflict of interests to declare

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