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The COVID-19 pandemic has resulted in more than 2 million deaths globally. Two interconnected stages of disease are generally recognised; an initial viral stage and a subsequent immune response phase with the clinical characteristics of hyperinflammation associated with acute respiratory distress syndrome. Therefore, many immune modulators and immunosuppressive drugs, which are widely used in rheumatological practice, have been proposed as treatments for patients with moderate or severe COVID-19. In this Review, we provide an overview of what is currently known about the efficacy and safety of antirheumatic therapies for the treatment of patients with COVID-19. Dexamethasone has been shown to reduce COVID-19 related mortality, interleukin-6 inhibitors to reduce risk of cardiovascular or respiratory organ support, and baricitinib to reduce time to recovery in hospitalised patients requiring oxygen support. Further studies are needed to identify whether there is any role for glucocorticoids in patients with less severe COVID-19. Although evidence on the use of other antirheumatic drugs has suggested some benefits, results from adequately powered clinical trials are urgently needed. The heterogeneity in dosing and the absence of uniform inclusion criteria and defined stage of disease studied in many clinical trials have affected the conclusions and comparability of trial results. However, after the success of dexamethasone in proving the anti-inflammatory hypothesis, the next 12 months will undoubtedly bring further clarity about the clinical utility and optimal dose and timing of other anti-rheumatic drugs in the management of COVID-19.

Introduction
The COVID-19 pandemic has resulted in more than 2 million deaths globally. SARS-CoV-2 is highly infectious and, although most individuals with infection are either asymptomatic or have mild-to-moderate symptoms, a substantial proportion have a severe, life-threatening disease course associated with a deleterious host immune response phase. Mortality in SARS-CoV-2 infection is estimated to be 0.5–1.0%.[1] This mortality risk, combined with large population outbreaks, has meant this virus has had a major effect on lives, economies, and health-care systems across the world.

Risk factors associated with poor outcomes include, older age, male sex, diabetes (especially type 2), chronic obstructive pulmonary disease, elevated body mass index, and the presence of cardiovascular comorbidity.[2] Several other adverse prognostic factors include lymphopenia and elevated transaminases, lactate dehydrogenase, D-dimers, ferritin, and soluble interleukin (IL)-2 receptor alpha chain (sCD25). These laboratory measures represent a state of hyperinflammation that largely drives the risk of COVID-19-related acute respiratory distress syndrome (ARDS), multi-organ failure, and mortality.[3]

Although the first vaccines have been approved and vaccination campaigns are underway, much of the research done this far has focused on early therapeutic approaches for SARS-CoV-2 (eg, lopinavir-ritonavir, remdesivir, azithromycin, interferon, hydroxychloroquine). As of February, 2021, only remdesivir has shown any promise in reducing length of hospital stay, and no antiviral approaches have been shown to reduce mortality. Recent reports even question the benefit of remdesivir and the efficacy of interferon therapy.[4]

Rheumatologists use immunomodulators and immunosuppressive drugs in their daily practice to treat rheumatic and musculoskeletal diseases. Many of these therapeutics are also used to treat various hyperinflammation syndromes, and so these therapies have gained substantial global attention for their potential to modulate COVID-19-related hyperinflammation. This Review aims to summarise the evidence on the use of antirheumatic drugs in the treatment of patients with COVID-19 from the start of the pandemic through to February, 2021.

Pathophysiology of COVID-19
SARS-CoV-2 is a single-stranded RNA virus belonging to the Coronavirusidae family that can infect any cell expressing the angiotensin converting enzyme 2 receptor, including pneumocytes, endothelial cells, cardiomyocytes, glia, enterocytes, and epithelial tubular distal cells.[5] Several virus, host, and environment-related factors affect virus-host interactions and, therefore, the clinical manifestations and outcomes of infection.[6] Overall, the underlying pathological mechanisms of COVID-19 are multifaceted and intertwined. Notably, SARS-CoV-2 has been reported to have cytopathic effects (causing apoptosis, autophagy, and pyroptosis events) and to possess potential strategies to evade the immune system by inducing severe lymphopenia, impaireing T-cell exhaustion, CD4–CD8 imbalance, and antibody-dependent cell-mediated cytotoxicity—all of which can potentially enhance infectivity.[7] These processes, alongside the presence of viral structural and non-structural proteins, drive an increased production of proinflammatory cytokines and chemokines (eg, IL-6, IL-1β, and tumour necrosis factor [TNF]) and local infiltration of innate immune cells.[8,9] From the local site of infection and inflammation, this response can spread to the systemic circulation, triggering an accelerated immune response and inducing perturbations in the coagulation system. These responses, coupled with direct infection of endothelial cells and pericytes, results in vascular leakage, microvascular and macrovascular thrombotic events, and tissue hypoxia (figure 1).[5,10]
The disease course of COVID-19 is often described as a sequence of phases. This description is most likely an over simplification and, in reality, the key pathogenic mechanisms occur in parallel and can drive and synergise each other. Consequently, when considering immunomodulating therapy, the specific mechanisms being targeted and the optimal time when such pathology causes clinical outcomes need to be assessed. This assessment is important for interpreting the results of studies and trials, especially those that show no clear benefit, excess harm, or both.

Several pathophysiological mechanisms relevant to COVID-19 severity, such as imbalance in the renin angiotensin system and angiotensin converting enzyme system, have been extensively reviewed. However, evidence suggests that most organ damage in severe COVID-19 is mediated by the immune response to infection, therefore, this Review focuses on use of antirheumatic drugs in patients with COVID-19 and considers the process of immune-mediated pathology.

Hyperinflammation

Much of the mortality associated with COVID-19 is attributable to a hyperinflammatory host immune response that is seen in a substantial proportion of individuals positive for SARS-CoV-2 who require hospitalisation for respiratory distress. Many such patients can rapidly develop ARDS and eventual multi-organ dysfunction that resembles a cytokine storm syndrome. COVID-19-associated hyperinflammation, however, is somewhat unique compared with other cytokine storm syndromes (eg, lower concentrations of serum ferritin and IL-6 in COVID-19). These differences have led investigators to establish criteria for recognising hyperinflammation in the context of COVID-19 (figure 2) which include features of liver dysfunction (eg, elevated transaminases), hypercoagulability (eg, elevated D-dimers), and evidence of hyperinflammation (elevated C-reactive protein, ferritin, and IL-6).

For patients with COVID-19 who have features of hyperinflammation, treatment must be directed to the hyperinflammatory state to improve survival. An array of proinflammatory cytokines has been reported to be elevated in COVID-19, including IL-1, IL-6, and TNF. Despite the distinct pattern of hyperinflammation seen in patients with COVID-19, treatment approaches used in patients with other cytokine storm syndromes have informed therapeutic strategies for patients with COVID-19-related hyperinflammation. Some of the first therapies used in patients with COVID-19 were established for the rare familial form of infantile cytokine storm syndromes, primary haemophagocytic lymphohistiocytosis (HLH). Because primary HLH is fatal if left untreated, aggressive protocols including chemotherapy (with etoposide) and broadly immunosuppressive glucocorticoids (such as dexamethasone), followed by haematopoietic stem cell transplantation were established. This aggressive approach has also been applied to secondary forms of HLH, including cytokine storm syndrome triggered by infections, rheumatic and musculoskeletal diseases, and haematological malignancies in adolescents and adults. Over the past 10–15 years, various targeted approaches to dampening inflammatory cytokines have been explored as effective but less toxic treatments for cytokine storm syndromes.

Antirheumatic drugs for the management of COVID-19

Research on treatments for COVID-19 hyperinflammation has explored approaches used in treating other cytokine storm syndromes, including glucocorticoids and anti-IL-6 drugs. Other therapeutic drugs have also been studied.

Figure 1: COVID-19 disease course and therapeutic windows of opportunity for DMARDs

Schematic depicts the evolution of a severe SARS-CoV-2 infection and therapeutic windows of opportunity for the indicated DMARDs according to the timing of the different ongoing immunopathological processes from the initial viral inoculum to multi-organ failure. (A) SARS-CoV-2 binds to the host receptor ACE2 (yellow and green receptors), and viral docking is eased by TMPRSS2 (blue co-receptor) cleaving viral spike protein (B: C) In the asymptomatic phase, host cell infection, viral diffusion in the human body, and virion production predominate. Mucosal and local innate immunity (natural killer cells, neutrophils and monocyte-macrophages) react to viral replication, causing cytotoxic effects and pro-inflammatory mediators release, and the onset of signs and symptoms occurs. (D) Cellular immunity (B cells, CD4 T cells, CD8 T cells) develop locally and systemically, and symptoms and signs increase in severity. (E) An imbalance between effective and hyper-activated immune responses can result in cytokine storm, which depletes lung injury, precipitating or determining respiratory insufficiency. (F) At this stage, potentially protective neutralising antibodies could also trigger antibody-dependent enhancement and the activation of the classical pathway of complement system, enhancing viral replication and further proinflammatory cytokine release. (G) The imbalance between inflammation and coagulopathy as well as SARS-CoV-2 infection of endothelial cells and pericytes determines concurrent micro- and macro-thrombotic events enhancing organ damage. (H) These uncontrolled processes trigger reinforcing and self-maintaining pathological loops (dashed arrows) that eventually lead to systemic cellular and organ dysfunction resulting in multi-organ failure. ACE2=angiotensin-converting enzyme 2. DMARD=disease-modifying anti-rheumatic drug. TNF=tumour necrosis factor. TMPRSS2=transmembrane protease serine 2.
including hydroxychloroquine, colchicine, Janus Kinase (JAK) inhibitors, anti-IL-1 drugs, anti-TNF drugs, complement inhibitors, and intravenous immunoglobulin (figure 1).25

**Glucocorticoids**

During the COVID-19 pandemic, two separate but linked questions have arisen. First, whether patients on chronic glucocorticoid therapy are at increased risk of developing severe COVID-19; second, whether glucocorticoids have a role in the treatment of patients with COVID-19. The effects of glucocorticoids on the immune system are pleiotropic. Glucocorticoids induce anti-inflammatory and immunosuppressive effects in both primary and secondary immune cells, thereby decreasing production of proinflammatory cytokines (eg, IL-2, IL-6, and TNF) and suppressing activation of T cells, monocytes, and macrophages.

Studies have suggested that chronic glucocorticoid use is associated with complicated COVID-19. A study published in June, 2020, noted that among 117 patients with rheumatic diseases and confirmed COVID-19, 12 (10%) died; seven (58%) of whom were taking more than 30 mg prednisone daily.26 In patients with inflammatory arthritis and COVID-19, hospitalised patients were more likely to be taking glucocorticoids (37% vs 4%, p<0·01).20 The COVID-19 Global Rheumatology Alliance reported that 277 (46%) of 600 patients with rheumatic diseases and COVID-19 were hospitalised; of these, patients taking 10 mg or more of prednisone daily had a higher odds of hospitalisation compared with those not taking glucocorticoids (OR 2·05, 95% CI 1·06–3·96).21 Furthermore, among 390 (10%) of 3729 patients who had died as of July 1, 2020, a prednisolone equivalent of more than 10 mg daily was found to be associated with death (OR 1·69, 95% CI 1·06–2·68).22 The CoDEX trial23 of intravenous dexamethasone in 299 patients treated in an intensive care unit (ICU) found that dexamethasone resulted in more ventilator-free days (mean difference 2·26, 95% CI 0·2–4·38) and a lower mean sequential organ failure assessment score at 7 days (adjusted mean difference –1·16, 95% CI –1·94 to –0·38) compared with standard of care.24 All-cause mortality occurred in 53% of patients in the dexamethasone group, versus 61·5% of patients in the standard of care group.25 The evidence supporting the use of dexamethasone was confirmed by a WHO-initiated meta-analysis.26

Two ICU-based trials27,28 tested the efficacy of hydrocortisone in patients with severe COVID-19. One compared low dose hydrocortisone (n=76) to placebo (n=73);27 the other used an adaptive platform design and randomly allocated patients to receive a fixed, shock-dependent hydrocortisone dose, or no hydrocortisone.28 Neither therapeutic approach met the pre-specified criteria for superiority for the primary outcome of organ-support free days at day 21.29

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### Table 1: COVID-19 hyperinflammation criteria

| Criteria | Value |
|----------|-------|
| Febrile | >38°C |
| Diagnosed COVID-19 | RT-PCR positive |
| Lungs: | by HRCT or chest X-ray |
| Ground Glass Opacities | + |
| Ferritin | >350 µg/L |
| C-reactive protein | >4 mg/dL |
| Albumin | <2.8 g/dL |
| Neutrophil to lymphocyte ratio | ≥10 |
| Neutrophils (absolute) | ≥11 000/mL |
| Lymphocytes (abolute) | ≥1.0 x 10^9/L |
| Lactic dehydrogenase | >416 U/L |
| Troponin I | >1.0 ng/mL |
| Anion gap | >6 mEq/L |
| Chloride | >126 mmol/L |
| BUN | >9 mg/dL |

**Table 2: COVID-19 signs or symptoms**

| Criteria | Value |
|----------|-------|
| Fever | >38°C |
| Signs or symptoms of COVID-19 | Presence of any COVID-19 signs or symptoms |
| Diagnostic test for COVID-19 | RT-PCR positive for COVID-19 |
| HRCT of chest x-ray | (+) Ground Glass Opacities by HRCT or chest X-ray |
| Ferritin | >350 µg/L |
| C-reactive protein | >4 mg/dL |
| Albumin | <2.8 g/dL |
| Neutrophil to lymphocyte ratio | ≥10 |
| Neutrophils (absolute) | ≥11 000/mL |
| Lymphocytes (abolute) | ≥1.0 x 10^9/L |
| Lactic dehydrogenase | >416 U/L |
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| Anion gap | >6 mEq/L |
| Chloride | >126 mmol/L |
| BUN | >9 mg/dL |

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Figure 2: COVID-19 hyperinflammation criteria

AST=aspartate aminotransferase. BUN=Blood urea nitrogen. HRCT=High-resolution CT. RT-PCR=reverse transcriptase PCR. *Criteria are met when patients fulfill all the entry criteria and at least one criterion per each cluster. †A score of two or more criteria met distinguished patients along multiple clinical endpoints: median length of hospital stay, requirement for intensive care unit, requirement for mechanical ventilation, and hospital deaths.
Table 1: Key clinical trials assessing glucocorticoid therapy in the management of COVID-19

| Setting | Intervention vs SOC | Study size | Primary endpoint | Primary result | Comments |
|---------|---------------------|------------|------------------|----------------|----------|
| RECOVERY23 | Patients who are hospitalised | Oral or intravenous dexamethasone 6 mg daily for up to 10 days | Dexamethasone (n=2041); standard of care (n=4321) | 28-day mortality | Age-adjusted rate ratio 0.83 (95% CI 0.75–0.93) | Survival benefit observed in patients on invasive mechanical ventilation and patients on oxygen therapy |
| CoDEX24 | ICU | Intravenous dexamethasone 20 mg daily for 5 days, then 10 mg daily for 5 days or until ICU discharge | Dexamethasone (n=1481); standard of care (n=148) | Ventilator-free days over first 28 days | 6-6 mean ventilator-free days (95% CI 0.80–2.96) vs 4.0 (2.9–5.4); mean difference 2.26 days (95% CI 2.21–2.32) | Dexamethasone all-cause mortality at 28 days was 85 (56–93%) vs standard of care 91 (61–5%); p=0.21 |
| CAPE COVID25 | ICU | Intravenous hydrocortisone 200 mg per day continuous infusion | Hydrocortisone (n=76); standard of care (n=73) | Treatment failure (death, persistent dependency on mechanical ventilation or high-flow oxygen) at day 21 | Median fixed dose 0 (IQR −1 to 15) days; shock dose 0 (−1 to 13) days; standard of care 0 (−1 to 11) days | Study stopped early by data and safety monitoring committee |
| REMAP-CAP26 | ICU | Intravenous hydrocortisone fixed dose (50 mg or 100 mg every 6 h for 7 days); shock dose (50 mg every 6 h when shock was clinically evident) | Fixed dose (n=137); shock dose (n=146); standard of care (n=101) | Organ support-free days (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days | Median fixed dose 0 (IQR −1 to 15) days; shock dose 0 (−1 to 13) days; standard of care 0 (−1 to 11) days | Bayesian probabilities of superiority were 93% (fixed dose), 80% (shock-dependent dosing), compared with standard of care |
| GLUCOID27 | Patients who are hospitalised with COVID-19; pneumonia, impaired gas exchange, and biochemical hyperinflammation | Intravenous methylprednisolone 40 mg twice daily for 3 days, then 20 mg twice daily for 3 days | Methylprednisolone (n=56); standard of care (n=29) | Death, admission to ICU, or requirement of non-invasive ventilation | Combined risk ratio 0.55 (95% CI 0.33–0.91) | Of the 59 participants in the methylprednisolone group, 34 were randomly allocated to the group and 22 were treated by physician choice; 17 participants on methylprednisolone also received tocilizumab (n=10) or anakinra (n=7); four patients on standard of care received tocilizumab |
| MetCOVID28 | Patients who are hospitalised | Intravenous methylprednisolone 0.5 mg/kg twice daily for 5 days | Methylprednisolone (n=194); standard of care (n=199) | 28-day mortality | Methylprednisolone overall 28-day mortality 72 (37%) standard of care 76 (38.2%); HR 0.92, 95% CI 0.67–1.28 | Mortality reduced in patients >60 years (HR 0.63, 95% CI 0.41–0.98) |

HR=hazard ratio. ICU=intensive care unit. *On June 30, 2020, the Data and Safety Monitoring Board recommended suspension of inclusions pending publication of the results of the RECOVERY trial and possible changes in treatment recommendations, considering that it would be unethical to resume a corticosteroid versus placebo trial. †Of the 59 participants in the methylprednisolone group, 34 were randomly allocated to the group and 22 treated by physician choice.

A small trial, studied methylprednisolone in 85 patients with COVID pneumonia, respiratory compromise, and biochemical evidence of hyperinflammation. The composite endpoint of death, admission to ICU, or requirement for non-invasive ventilation was reduced in patients treated with methylprednisolone compared with standard of care (age-adjusted risk ratio 0.55, 95% CI 0.33–0.91), but major limitations of the study include the lack of randomisation (22 of the 56 patients were treated with methylprednisolone were treated because of physician choice), and the more frequent use of other medications, including tocilizumab or anakinra, in the methylprednisolone group compared with the standard of care group. Another trial of methylprednisolone versus placebo in patients hospitalised with COVID-19 found that methylprednisolone reduced 28-day mortality in the subgroup of patients aged 60 years or older, but there was no overall reduction in 28-day mortality.

Based on this evidence, there is an apparent dichotomy that needs to be addressed. Treating patients with moderate-to-severe COVID-19 with glucocorticoids (eg, dexamethasone 6 mg daily) has been shown to be effective. By contrast, the chronic use of maintenance doses of glucocorticoids (eg, prednisolone ≥10 mg daily) seems to be associated with an increased risk of COVID-19-related hospitalisation and mortality. Therefore, the value of glucocorticoids in COVID-19 might relate to the stage of disease, and these drugs might be more effective once the immune response overtakes the viral replication stage as the major driver of symptoms and complications. Since dexamethasone has minimal mineralocorticoid effects, it might be that the glucocorticoid effect exerts much of the benefit. Additionally, data from the REMAP-CAP trial suggests that glucocorticoids are beneficial through mechanisms other than the treatment of shock. Further trials accessing the role of corticosteroids in patients in ICUs with and without ARDS are needed.

Baricitinib
AP2-associated protein kinase 1 (AAK1) is a regulator of endocytosis; therefore, the disruption of AAK1 might...
hydroxychloroquine and antivirals (lopinavir–ritonavir) baricitinib was added to standard of care, which included COVID-19-modifying drug. Therefore, baricitinib has been suggested as a potential proinflammatory cytokines such as IL-6 and IL-26;30 baricitinib was identified. Moreover, baricitinib inhibits JAK1 and JAK2 signalling via intracellular regulation of AAK1,31,32 avert the entrance of the virus into cells and the subsequent intracellular viral replication. In a study that aimed to identify compounds with high affinity to AAK1, baricitinib was identified. Moreover, baricitinib inhibits JAK1 and JAK2 signalling via intracellular regulation of proinflammatory cytokines such as IL-6 and IL-26;30 therefore, baricitinib has been suggested as a potential COVID-19-modifying drug.

Four studies31–34 using baricitinib have been published and, as of Feb 1, 2021, eleven further studies are recruiting.35 In three of the published studies,31–33 baricitinib was added to standard of care, which included hydroxychloroquine and antivirals (lopinavir–ritonavir combination therapy). One study compared 4 mg daily baricitinib (n=133) with hydroxychloroquine (n=78) in patients with mild-to-moderate COVID-19 and found that baricitinib was associated with a reduction in ICU admission and mortality.32 Similarly, in patients with moderate to severe COVID-19, treatment with baricitinib (2 mg or 4 mg) plus intravenous methylprednisolone (median dose 500 mg thrice daily, followed by prednisolone 30 mg per day) resulted in greater improvement of respiratory function (oxygen saturation ratio) than placebo plus remdesivir and placebos (median dose 500 mg thrice daily, followed by prednisolone 30 mg per day) resulted in greater improvement of respiratory function (oxygen saturation ratio) than placebo plus remdesivir and placebos.8

IL-6 inhibition

Early observations from China reported an increased risk of death in COVID-19 patients with elevated IL-6 concentrations,14 which were frequently reported in patients with COVID-19-related hyperinflammation. Therefore, anti-IL-6 strategies were explored in patients with severe COVID-19.35–37 An open-label study showed that tocilizumab could be safe and effective in patients in hospital with severe COVID-19, especially when applying strict selection criteria on the basis of clinical and laboratory inflammatory profiling, such as C-reactive protein, D-dimer, ferritin and lactate dehydrogenase concentrations.38 Further data from systematic reviews and meta-analyses, including retrospective case-control studies and single-armed studies,39 supported the addition of tocilizumab to standard of care to reduce mortality in severe COVID-19 cases.

However, three of four large RCTs have not confirmed these early observations (table 2).39–41 The trials from the RCT-TCZ-COVID48 study group and the CORIMUNO-1949 collaborative group did not meet their primary endpoints.

| Inclusion criteria | Study size | Primary endpoint | Primary result |
|--------------------|------------|------------------|---------------|
| Salvadori et al48 | >18 years, ARDS (with PaO2–FiO2 ratio 200–300 mmHg), and fever (>38°C for 2 days) or CRP elevation | Tocilizumab (n=60); standard of care (n=66) | Composite outcome was entry into the ICU with invasive mechanical ventilation, death from all causes, or PaO2–FiO2 ratio <150 mmHg (clinical aggravation) | No benefit on disease progression compared to standard care |
| Hermine et al50 | Group 1: moderate or severe pneumonia WHO CPS score of ≥5; group 2: critical pneumonia and WHO CPS score of ≥6 | Tocilizumab (n=64); standard of care (n=67) | WHO CPS scores > 5 on day 4 and survival without need of ventilation (including non-invasive ventilation) at day 14 | Tocilizumab did not reduce WHO CPS scores ≤5 at day 4; at day 14, fewer patients needed non-invasive ventilation or mechanical ventilation, or died in the tocilizumab group; no difference in mortality on day 28 |
| Stone et al51 | Two of three criteria from: fever (>38°C within 72 h), pulmonary infiltrates, supplementary oxygen-demand to SpO2 >92%, plus one of four criteria: CRP >50 mg/L, ferritin >500 ng/mL, D-dimer >1000 ng/mL, lactate dehydrogenase >250 U/L | Tocilizumab (n=161); placebo (n=81) | Intubation or death, assessed in a time-to-event analysis | No benefit in preventing intubation or death |
| Rosas et al52 (COVACTA) | SARS-CoV-2 positive PCR, chest x-ray or CT positive for infiltrates, and SpO2 >93% or PaO2–FiO2 ratio <300 mmHg | Tocilizumab (n=224); placebo (n=180) | Clinical status assessed using WHO Ordinal Scale (time frame day 28) | No benefit in improving clinical status or mortality; potential benefits in time to hospital discharge and duration of ICU |
| Salama et al53 (EMPACTA) | SARS-CoV-2 positive PCR, positive radiographic evidence for infiltrates SpO2 < 94% | Tocilizumab (n=249); placebo (n=127) | Cumulative proportion of participants requiring mechanical ventilation by day 28 (time frame day 28) | Benefit in reducing the likelihood of progression to requiring mechanical ventilation or death |

All RCTs were done in patients with COVID-19 who are hospitalised. ARDS=acute respiratory distress syndrome. CPS=Clinical Progression Scale. CRP=C-reactive protein. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory coronavirus 2.

Table 2: Comparison of the inclusion criteria and main outcomes for available and ongoing RCTs on tocilizumab (anti-IL-6 receptor) in patients with COVID-19.
Similarly, in the COVACTA trial\textsuperscript{10} tocilizumab did not improve clinical status or mortality. However, some potential benefits were reported in time to hospital discharge and duration of ICU stay. Conversely, in the EMPACTA trial,\textsuperscript{22,23} tocilizumab was superior to placebo in reducing the likelihood of progression to requiring mechanical ventilation or death in non-ventilated patients hospitalised with COVID-19 pneumonia. These trials mainly use clinical inclusion criteria, which might be applied variably in different hospitals and, therefore, might not specifically target the therapy to patients with hyperinflammation. In the COVACTA trial,\textsuperscript{13} the inclusion criteria included at least one index of inflammation together with a clinical parameter, but this resulted in a wide range of disease severities, including patients with mild symptoms. Unsurprisingly, tocilizumab was found to be not effective for preventing invasive ventilation or death in these patients with moderately severe COVID-19.\textsuperscript{13} Inclusion criteria of the ongoing RCTs are shown in the appendix (pp 1–2).

However, a retrospective study examining the effects of glucocorticoids alone and in several combinations with anti-cytokine regimens showed that glucocorticoids plus tocilizumab was the most effective treatment for patients with moderate to severe COVID-19.\textsuperscript{24} Similarly, a beneficial effect of tocilizumab has been shown in the REMAP-CAP trial,\textsuperscript{27} in which patients in the ICU with severe suspected or confirmed COVID-19 and receiving either respiratory or cardiovascular support were randomly allocated to receive tocilizumab (n=353) or standard of care (n=402). Most patients (exact number not specified) also received corticosteroids because of the RECOVERY\textsuperscript{28} trial results, which changed the standard of care after June 17, 2020. Median organ-support free days was greater with tocilizumab (median 10 days [IQR –1 to 16] vs 0 [–1 to –15]), with an adjusted odds ratio (OR) of 1.64 (95% CI 1.25–2.14). In-hospital mortality was also reduced with tocilizumab (27.0% vs 36.0%, median adjusted OR 1.64, 95% CI 1.14–2.35).

The challenge now is to understand whether a specific subset of patients might benefit from anti-IL-6 therapy, on the basis of either the timing of the therapy, identification of the relevant inflammatory state of the patient, or both. More RCTs of tocilizumab in COVID-19 are ongoing,\textsuperscript{31} and results from these studies might provide information on the role of this drug in COVID-19 management.

Sarilumab is an anti-IL-6 receptor antibody that was initially investigated in an open-label trial of 28 patients with COVID-19 pneumonia, in which no differences in deaths or clinical improvement compared with standard of care were reported.\textsuperscript{25} By contrast, a study of 53 patients with severe COVID-19 pneumonia found that after a median follow-up of 19 days, up to 90% of patients substantially improved, and 71% were successfully discharged after treatment with sarilumab.\textsuperscript{25} Another retrospective cohort also showed potential benefit,\textsuperscript{26} and the results of the REMAP-CAP\textsuperscript{27} trial suggest effect on mortality and ICU course albeit only 48 patients received sarilumab treatment.

**Colchicine**

Colchicine has potent anti-inflammatory effects via inhibition of microtubule polymerisation and the NLRP3 inflammasome, thereby suppressing the release of IL-1β, IL-18, and downstream IL-6.\textsuperscript{59} The NLRP3 inflammasome seems to play an important role in the COVID-19 inflammatory response.\textsuperscript{60} Currently, more than a dozen clinical trials are investigating colchicine as a treatment for COVID-19, with early findings from one observational study\textsuperscript{61} and three clinical trials\textsuperscript{59,62,63} showing potential benefits. In a single-centre prospective cohort study of 33 patients hospitalised with COVID-19, the day-28 mortality was 9% (n=3) in colchicine-treated patients and 33% (n=11) in patients not treated with colchicine (OR 0·20, 95% CI 0·05–0·80). However, colchicine was initiated 72 h after admission in more than 30% of patients, thereby introducing an immortal time bias.\textsuperscript{64}

In an open-label, randomised trial of 105 patients hospitalised with COVID-19, fewer patients treated with colchicine had clinical deterioration compared with standard of care as defined by the WHO’s Ordinal Scale for Clinical Improvement (1 patient [1·8%] vs 7 patients [14·0%], OR 0·01–0·96).\textsuperscript{65} The difference in peak high-sensitivity troponin concentrations (the co-primary endpoint) was similar between groups.

Another open-label non-randomised trial of patients hospitalised with COVID-19 showed higher day 21 survival among 122 patients treated with colchicine compared with 140 patients treated with standard of care alone (84·2% vs 63·6%, p=0.001). In a multivariate analysis, colchicine treatment was associated with decreased mortality (HR 0·15, 95% CI 0·06–0·37), although there were notable limitations, including an imbalance in glucocorticoid use between groups (colchicine patients received more glucocorticoids), an absence of information on the time from symptoms onset to colchicine administration, and a likelihood of immortal time bias.\textsuperscript{66}

Results from the double-blind COLCORONA trial\textsuperscript{67} of colchicine versus placebo in 4488 non-hospitalised patients with COVID-19 diagnosed by PCR testing or clinical criteria were published on Jan 27, 2021, as a preprint. Risk of hospitalisation or death was reduced in patients treated with colchicine (0·5 mg twice daily for 3 days and once daily thereafter for 30 days) but this did not reach statistical significance (4·7% in the colchicine group vs 5·8% in the placebo group, OR 0·79, 95% CI 0·61–1·03); overall mortality was very low in this outpatient population (0·2% deaths in the colchicine group vs 0·4% in the placebo group, OR 0·56, 95% CI 0·19–1·66). Based on a pre-specified sub-group analysis of patients with PCR-confirmed COVID-19, approximately 71 patients (95% CI 36–200) would need to be treated with this regimen to prevent one hospitalisation...
or death. Serious adverse events were 4-9% in the colchicine group and 6-3% in the placebo groups (p=0.05), but pulmonary emboli were increased in the colchicine group (0.5% vs 0-1%, p=0.01). Overall, the potential benefit of colchicine on mortality in patients with COVID-19 remains unclear.

**IL-1 inhibition**

High concentrations of IL-1, particularly IL-1β, are detected in the serum of patients with COVID-19 and provide a rationale for studying IL-1 inhibition in this context. Some studies have suggested improvement in clinical outcomes with anakinra (an IL-1 receptor antagonist) in patients with COVID-19. However, these data need to be interpreted with caution. Available studies on anakinra differ with regard to the protocols used and patient populations studied, ranging from high-dose intravenous anakinra for COVID-19-related ARDS and hyperinflammation in the first published study to low doses or subcutaneous administration in patients with less severe disease in subsequent studies (table 3).

The multicentre open-label CORIMUNO-ANA-1 study, which compared anakinra treatment plus standard of care to standard of care alone in patients with mild-to-moderate COVID-19 pneumonia, was terminated early because of futility, which was based on an interim analysis of 116 patients (59 in the anakinra group and 57 in the usual care group). No significant difference was found between the groups in 4-day improvement, 14-day ventilation requirement, or mortality, suggesting that anakinra treatment did not improve clinical outcomes in patients with mild-to-moderate COVID-19. The study was later criticised for its inclusion criteria in that it did not include parameters indicative of hyperinflammation.

By contrast, an analysis of 5776 patients from New York City (NY, USA) noted that patients treated with anakinra

| Study descriptor | Inclusion criteria | Study size (n) | Intervention | End-points | Primary result |
|------------------|-------------------|---------------|--------------|------------|----------------|
| Cavalli et al⁶⁵ | Retrospective cohort | ≥18 years, SARS-CoV-2 positive PCR, moderate-to-severe ARDS, hyperinflammation (CRP ≥100 mg/L or ferritin ≥900 ng/mL) | 29 | Intravenous (5 mg/kg twice a day [high dose]) or subcutaneous (100 mg twice a day [low dose]) anakinra | Survival, mechanical ventilation-free survival, changes in CRP, respiratory function, and clinical status within 21 days | High-dose anakinra was associated with clinical improvement including overall survival and ventilation-free survival |
| Huet et al⁶⁵ | Prospective cohort | SARS-CoV-2 PCR positive or typical lung infiltrates on a lung CT scan and SpO₂ <93% with >oxygen 6 L/min; or aggravation (SpO₂ <93% with oxygen 3 L/min) with a loss of 3% of SpO₂ in ambient air over the previous 24 h | 52 | Subcutaneous anakinra (100 mg twice a day for 7 days) | Composite of either admission to the intensive care unit for invasive mechanical ventilation or death | Benefits in reducing both need for invasive mechanical ventilation in the ICU and mortality |
| Cauchois⁶⁴ | Case control | Respiratory symptoms, CT scan confirmed pneumonia, CRP above 110 mg/L, rapidly deteriorating condition (increased oxygen requirement of >4 L/min within the previous 12 h), with or without fever higher than 38.5°C | 12 | Intravenous anakinra (over 2 h as a single daily dose of 300 mg for 5 days then tapered to 200 mg for 2 days and then 100 mg for 1 day) | Clinical improvement (NEWS score at day 7 and the number of days with oxygen flow less than 3 L/min at day 20) | All of the patients treated with anakinra improved clinically, with no deaths, significant decreases in oxygen requirements, and more days without invasive mechanical ventilation |
| Balkhair et al⁶⁸ | Prospective, open-label, interventional study | Aged >18 years, severe COVID-19 pneumonia, and either respiratory rate >30 breaths per min and SpO₂ <90%, or SpO₂ <93% under oxygen ≥6 L/min, or acute respiratory distress syndrome | 45 | Subcutaneous anakinra (100 mg twice daily for 3 days, followed by 100 mg daily for 7 days) | Need for mechanical ventilation and in-hospital death | Endpoints met compared to a historical control group |
| Bozzi et al⁶⁷ | Prospective observational cohort | Aged >18 years, evidence of pneumonia, ferritin ≥1000 mg/mL, or CRP >10 mg/dL respiratory failure | 65 | Subcutaneous anakinra (200 mg every 8 h for 3 days, then 100 mg every 8 h up to day 14, plus methylprednisolone tapering) | 28-days survival rate | Risk of death was substantially lower for treated patients compared with controls |
| Navarro-Millán et al⁶⁶ | Case series | SARS-CoV-2 PCR positive, fever, ferritin >1000 mg/mL, plus another laboratory marker of hyperinflammation acute hypoxic respiratory failure | 11 | Subcutaneous anakinra (100 mg every 6 h gradually decreasing frequency to every 8, 12, or 24 h according to clinical response, maximum 20 days treatment) | Prevention of mechanical ventilation | The seven patients receiving IL-1 blockade ≤36 h after onset of respiratory failure met the primary outcome, the four patients treated after 4 days required mechanical ventilation and one died |

ARDS=acute respiratory distress syndrome. CRP=C-reactive protein. ICU=intensive care unit. NEWS=National Early Warning Score.

Table 3: Comparison of the main characteristics of studies on IL-1 blockade in patients who are hospitalised with COVID-19.
combined with glucocorticoids had improved survival compared with patients receiving standard of care treatment alone or anakinra alone.22 Although the heterogenous outcomes with anakinra across studies might have resulted from differences in dosage, time to treatment, and route of administration, the question of whether IL-1 targeted approaches have a role in COVID-19 management remains open. The results of the phase 3 CAN-COVID23 trial of canakinumab in COVID-19 were announced via press release in November, 2020.24 Canakinumab, a long-acting anti-IL-1β monoclonal antibody, failed to meet its primary endpoint of improved survival without the need for invasive mechanical ventilation compared with standard of care.24 Notably, whereas anakinra blocks the IL-1 receptor, thereby blocking signalling in response to both IL-1α and IL-1β, canakinumab exclusively blocks IL-1β and thus might be less effective in blunting the downstream effects of IL-1 signalling. Inhibition of IL-1 can also result in at least partial suppression of IL-6, which is induced by IL-1. The most important aspect for the use of anti-IL-1 therapy remains the adequate selection of patients who display clear signs of hyperinflammation. To be eligible for enrolment in the CAN-COVID study23 patients had to have C-reactive protein concentrations of 20 mg/L or more, or ferritin concentrations of 600 µg/L or more, which would not be considered hyperinflammation by some clinicians (figure 2). Overall, the impression remains that IL-1 inhibition has a therapeutic rationale in selected patients with COVID-19 and clear evidence for hyperinflammation.

Hydroxychloroquine

Early in the COVID-19 pandemic, hydroxychloroquine was proposed as a therapeutic drug because of its effect on several cellular processes that might affect viral replication. Early in vitro studies using SARS-CoV-2 infected cells suggested that hydroxychloroquine (and chloroquine) showed antiviral activity.25 Subsequently, some observational clinical studies reported a beneficial effect of hydroxychloroquine alone or in combination with azithromycin in patients with COVID-19, whereas other studies did not find evidence of efficacy.26 The RECOVERY trial27 randomly assigned patients hospitalised with COVID-19 to receive hydroxychloroquine (n=1561) and found no benefit over standard of care (n=3511) on the primary outcome of 28-day mortality.27 Another RCT included 479 patients who were randomly assigned to receive hydroxychloroquine (n=242) or placebo (n=237) and showed no difference in clinical status at day 14 (adjusted OR 1·02, 95% CI 0·73–1·42) nor in mortality at 28 days (10·4% vs 10·6%; absolute difference –0·2%, 95% CI –5·7% to 5·3%; adjusted OR 1·07, 95% CI 0·54–2·09).27

Whether hydroxychloroquine can result in prolongation of the corrected QT interval when used for COVID-19 has also been a subject of concern. A systematic review including 5652 patients who received hydroxychloroquine (or chloroquine) at various dosing regimens (400–1200 mg daily), often in combination with azithromycin, showed a substantial risk of corrected QT prolongation.28 These doses are higher than those used in routine management of patients with rheumatic and musculoskeletal diseases (200–400 mg hydroxychloroquine daily). In the RECOVERY trial, there were no significant differences between groups in the frequency of supraventricular tachycardia (7·6% vs 6·0%), ventricular tachycardia or fibrillation (0·7% vs 0·4%), or atrioventricular block requiring intervention (0·1% vs 0·1%).27

There are also conflicting results on whether patients taking hydroxychloroquine for the treatment of their rheumatic diseases are more likely to be infected with SARS-CoV-2.29,30 A population-based cohort study including 30569 patients with rheumatoid arthritis or systemic lupus erythematosus identified from a UK national primary care database (OpenSAFELY)31 showed no difference in COVID-19-related mortality amongst hydroxychloroquine users versus non-users (HR 1·03, 95% CI 0·80 to 1·33).31 Overall, the data do not support use of hydroxychloroquine in the context of COVID-19.

TNF blockade

Observational data suggests a role for TNF in the hyper-inflammatory response seen in patients with COVID-19.32 This hypothesis has been supported by observational studies of patients already taking anti-TNF drugs who developed COVID-19. In the Surveillance Epidemiology of Coronavirus Under Research Exclusion-IBD33 database—an international, paediatric, and adult database to monitor and report on outcomes of COVID-19 occurring in patients with inflammatory bowel disease—a reduced prevalence of severe and complicated cases of COVID-19 was reported among patients treated with anti-TNF drugs compared with patients treated with steroids. This observation has also been noted in patients with rheumatic and musculoskeletal diseases.34,35 However, these studies should be interpreted with caution because patients with rheumatic and musculoskeletal diseases might be more likely to adopt measures to avoid infection.36 A phase 2 trial of infliximab in patients hospitalised with COVID-19 is underway (NCT04425538) as is the AVID-CC trial37 of adalimumab in community-treated patients with COVID-19.

Intravenous immunoglobulin

Intravenous immunoglobulin is derived from pooled plasma of healthy donors and is widely used in patients with rheumatic diseases. The rationale for the use of intravenous immunoglobulin in patients with COVID-19 is that the immunoglobulins competitively bind to the Fcγ receptor, thereby reducing viral replication and reducing antibody-dependent enhancement of the immune response. Furthermore, studies suggest further anti-inflammatory effects through the presence of anti-idiotypic antibodies binding to antiviral antibodies, and
antibody binding of proinflammatory cytokines, although data are sparse.  
Intravenous immunoglobulin has also been reported to be effective for cytokine storm syndromes in the context of infections. In a retrospective multicentre study of 325 patients with COVID-19 in southern China, mortality was reduced in patients treated with intravenous immunoglobulin (n=174) compared with those who received standard of care (n=151).  
However, a systematic review noted variable outcomes and the scarcity of adequately powered RCTs.  
In a subsequent RCT of 59 patients with COVID-19, hypoxia, positive high-resolution CT, and inadequate response to standard of care (antivirals and one chloroquine class drug), intravenous immunoglobulin was associated with significantly reduced mortality (20% in the intravenous immunoglobulin group vs 48% in the standard of care group, adjusted OR 0·003, 95% CI 0·001–0·815, p=0·042).  
Other trials are underway and these results could help us understand whether intravenous immunoglobulin has a role as a treatment option in moderate-severe COVID-19.

**Anti-complement therapy**

ARDS and microvascular thrombosis are two major causes of mortality in COVID-19. Complement activation is centrally involved in the development of acute lung diseases induced by virus invasion. C3a, C4a, C5a (anaphylatoxins), are active, proinflammatory forms of the respective complement components that affect inflammatory and non-inflammatory cells, causing tissue damage. Anaphylatoxins also activate endothelial cells, platelets, and monocytes, leading to thrombophilia.  
Complement activation is also known to be important in thrombotic diseases, including antiphospholipid syndrome and hypocomplementaemia, and COVID-19 thrombosis shares a number of pathophysiologic mechanisms with thrombotic antiphospholipid syndrome. Several case reports describing off-label use of eculizumab, a C5a inhibitor, for patients with COVID-19 and ARDS have been published; one reported recovery of all four patients treated with eculizumab and standard of care in an ICU setting.  
Another study—a non-randomised proof-of-concept trial of 80 patients with COVID-19 who were severely ill and in the ICU, treatment with eculizumab (n=35) resulted in significantly lower day-28 mortality versus standard of care (51·1% [95% CI 36·5–65·7%] vs 80·0% [66·8%–93·3%]).  
A phase 2 trial of IFX-1 (vilobelimab), another C5a inhibitor, also reported trends towards less progression in oxygen requirements, lower day-28 mortality, and fewer severe pulmonary embolisms (13% vs 41%) in patients treated with IFX-1 compared with best supportive care.  
Therefore, therapies directed against C5a and the complement cascade could have the double advantage of treating both inflammation and thromboembolic risk in patients with COVID-19.

Biomarkers that are capable of identifying the optimal candidate for this challenging therapy are urgently needed.

**Conclusions & perspective**

The drugs we use to manage patients with rheumatic and musculoskeletal diseases have gained increasing attention in the treatment of COVID-19 hyperinflammation. Globally, their clinical efficacy across all stages of the disease is the subject of a large number of clinical trials, some of which are still ongoing. Dexamethasone has now been shown to reduce COVID-19-related mortality in hospitalised patients who require respiratory support; further studies are needed to identify if there is any role for glucocorticoids in patients with less severe COVID-19, particularly considering that immune suppression during the early viral replication phase might be harmful. There is emerging evidence supporting roles for baricitinib, tocilizumab, and sarilumab in addition to standard of care in patients requiring ICU admission, although further evidence is needed. Colchicine might also reduce the risk of COVID-19-related hospital admission or COVID-19-related death in non-hospitalised patients.

Evidence on the use of other anti-rheumatic drugs, including C5a inhibitors and intravenous immunoglobulin, suggest some potential benefit, but large adequately powered clinical trials are urgently needed. It is also now clear that the use of hydroxychloroquine in patients with COVID-19 is not associated with any benefit.

Given the diverse and complex pathogenesis that drives moderate or severe COVID-19 and the associated hyperinflammatory syndromes, it is unrealistic to expect that any single antirheumatic drug will be effective for all patients with COVID-19. Additionally, heterogeneity in dosages and the absence of uniform patient inclusion criteria used in the clinical trials are likely to have affected the results; therefore, further studies to understand whether inhibition of IL-6 or IL-1 pathways is beneficial in subsets of patients with distinctive COVID-19 characteristics are also urgently needed. Efforts to develop criteria to identify COVID-19 patients with hyperinflammation who could benefit from specific targeted approaches are underway.  
Finally, now that dexamethasone, a potent glucocorticoid, is part of standard of care for many patients with severe disease, the efficacy of other drugs will need to be carefully assessed regarding the benefits they deliver over and above dexamethasone. All future trials will need to be designed and powered to account for dexamethasone.

The development of vaccines against SARS-CoV-2 has moved swiftly, with 10 candidate vaccines approved for clinical trials and more than 100 vaccines in preclinical stages.  
Several countries have already started their vaccination programmes, but unknowns remain about the durability of vaccine responses and what the true rate of vaccine uptake will be. Meanwhile, potentially more transmissible SARS-CoV-2 variants (B.1.1.28.1 and B.1.351) have been detected in many countries, including South Africa, Brazil, UK, and the USA, raising un-
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certainties regarding vaccine efficacy, which are already compounded by vaccine hesitancy.97 It should be noted that a many therapeutic targets other than the ones discussed above are also being tested, including interferon therapy to restrict viral replication, suppression of oxidised phospholipids known to promote acute lung injury via Toll-like receptor 4 signalling, inhibitors of angiogenesis such as anti-vascular endothelial growth factor (bevacizumab), and other cytokine and chemokine inhibitors and danger-associated molecular pattern antagonists.98,99 For example, nebulised interferon-b1a reduced the risk for developing severe disease in 79% of treated patients in a phase 2 trial.100 Approaches to directly target the virus or block viral entry with neutralising antibodies are also being tested. Convalescent plasma has been used for treating severe cases,101 and a randomised phase 2 trial has shown that a neutralising monoclonal antibody, LY-CoV555 (bamlanivimab), reduced disease progression (3% vs 10% with standard of care).102 Prophylactic bamlanivimab also reduced symptomatic disease and death among 965 nursing home residents (NCT04497987). There are over 70 ongoing cell-based clinical trials (eg. stem cell from different sources) for treating COVID-19. Mesenchymal stem cells, for example, have been shown to prevent hyperinflammation and are associated with regenerative properties for treating pulmonary damage.103

In 2020, the COVID-19 pandemic has challenged the scientific community profoundly and yet the speed of scientific progress in the past year has been nothing short of extraordinary. Many challenges remain and one of the biggest is the need to establish viable and cost-effective treatments for patients most at risk of developing hyperinflammation and associated severe outcomes.

Contributors
CBN, SS, and KSch conceptualised the Review. CBN and KSch wrote the summary, introduction, and section on hydroxychloroquine. RQC and MT wrote the section on the pathophysiology of SARS-CoV-2 and created the figures. INB wrote the section on steroids and created table 1. CBN and OH wrote the section on baricitinib. DR and SS wrote the section on IL-6 inhibition, IL-1 inhibition, and TNF blockade. EV wrote the section on colchicine. TA wrote the section on anti-complement therapy. KSch and KSta wrote the section on intravenous immunoglobulin. CBN, KSch, and DA wrote the conclusion and perspectives section. All authors participated in the editing process and all authors have read the last version.

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Search strategy and selection criteria
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