



Review

Anti-Rheumatic Drugs as Potential Anti-inflammatory, Immunomodulatory Agents against COVID-19: A Systematic Review

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Abstract

Background: The effective responses of both innate and adaptive immunity are crucial in combating novel coronavirus-2 infection. An excessive response may lead to cytokine storm, which is a challenging problem in therapeutic strategies.

Methods: A systematic review was carried out by searching Ovid MEDLINE, PubMed, Google Scholar, and Cochrane library databases from inception, for anti-inflammatory and immunomodulatory drugs against coronavirus disease 2019 (COVID-19).

Results: The results of the effectiveness of Hydroxychloroquine are just like a sinusoidal diagram and in a state of ambiguity. Thalidomide was effective in some cases but has not yet been proven. Low-dose Corticosteroids may be effective in the early stages of the illness as a bridge. There is no evidence of benefits or adverse outcomes for the use of non-steroidal anti-inflammatory drugs and Cyclosporine-A. In some critically ill patients, Interleukin-6 (IL-6) and IL-1 blockers and to some extent, Tumor-Necrosis-Factor- α and Janus-Kinase inhibitors are useful. Finally, high-dose intravenous immunoglobulin reversed the deterioration of patients in most trials.

Conclusion: One strategy behind the treatments for COVID-19 is based on breaking the cytokine storm. Although avoiding the suppression of anti-viral immunity is crucial by choosing the weaker and more selective anti-inflammatories, some strategies are kept for hyper-inflammatory situations. Scheduling of treatment is also important. Although low-dose steroids may be effective in the early stages of the illness, "Tocilizumab" is more effective in severe situations, when the IL-6 level is high and other drugs are ineffective. Therefore, consideration should be given to each patient separately.

Introduction

The emergence of the novel coronavirus, which causes severe respiratory infections, has become a global health concern. About 80% of patients experience mild to moderate disease and the fatality rate is about 2.3%.¹ Excessive immune responses to infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been incriminated in both respiratory distress and multi-organ failure that is seen more in some patients.² Considering both the severity of the disease and the response capacity of health systems is important in the management strategies. In this setting, secondary bacterial infections should be noted.^{1,3} Due to the rapid spread of COVID-19 and high mortality of the severe disease, understanding the disease immunopathogenesis and

inflammatory response is obligatory. According to the evidence, Angiotensin-Converting Enzyme-2 (ACE-2) is the enzyme that acts as the receptor, allowing SARS-COV-2 to enter the cells.⁴ After the recognition of the virus by Toll-like Receptors (TLR), signaling pathways activate nuclear factor (NF)- κ B and then pro-inflammatory cytokines. The initiation of immune response is through some cytokines such as IL-1 β and TNF α .^{1,5} A sizeable number of patients develop a severe hyper immune response characterized by a cytokine storm.⁶ Just like hemophagocytic lymphohistiocytosis (sHLH) and macrophage activated syndrome (MAS), there is a cytokine profile that is also responsible for the COVID-19 severity.⁷ Hyper inflammatory markers including elevated

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IL-6 and ferritin are predictors of fatality.⁸ Caricchio *et al.*⁶ developed new predictive criteria for COVID-19 cytokine storm, met when patients meet all the entry criteria (signs/symptoms of COVID-19, positive molecular test, ground-glass opacity, ferritin > 250 ng/ml, C-reactive protein (CRP) > 4.6 mg/dl) and one variable from each cluster. The first cluster included decreased levels of albumin, lymphopenia, along with increased absolute neutrophil count. The second cluster included the increased levels of both alanine and aspartate aminotransferases, D-dimers, Lactate dehydrogenase, and Troponin-I. The third cluster included the decreased anion gap, and increased levels of chloride, potassium, and blood urea nitrogen: creatinine ratio. Although these criteria need further validation, they can be readily used in practice to determine the need for an early therapeutic regimen, blocking the hyper-inflammatory response, and thereby reducing mortality. However, several potential anti-inflammatory and immunomodulatory agents are candidates. Although there have been no significant relapses of rheumatic disease in SARS-CoV-2 infection, the relationship between these agents and viral infections is very complex and even a simple scenario of fever and arthritis may be challenging to differentiate between infections and reactive arthritis.^{1,9,10} These, along with the historical background of using the rheumatic drugs in infectious diseases,¹ justify the hypothesis of their use in COVID-19. However, a variety of both biological and non-biological agents are candidates. Blocking the inflammatory cascade by some traditional or milder anti-inflammatory or immunomodulatory drugs such as anti-malarial agents, or stronger suppression of hyper-inflammatory states in some situations by IL or TNF α inhibition is of great importance. This review focuses on the effects of some proposed anti-inflammatory and immunomodulatory drugs, noting some of their immunosuppressive effects.

Methods

Study protocol

We aimed to include all scientific papers, which had evaluated the anti-inflammatory and immunomodulatory agents against COVID-19, without limitations. The PRISMA guideline for a systematic review was followed for study design, search protocol, screening, and reporting (Figure 1). Searching databases, selecting studies, evaluating the quality of studies, and extracting data were done by two researchers. Whenever there was a discrepancy between them, the subject was consulted with and considered by a third reviewer. The protocol is available at PROSPERO (CRD42020221700).

Inclusion and exclusion criteria

Inclusion criteria for the studies were as follows: 1. RCTs, case series, case-controls, and cohort studies, investigating the effect of anti-inflammatory, immunomodulatory agents in the management of COVID-19 (Due to paucity of information especially in some class drugs, all scientific

articles even case reports were included.); 2. Articles in which the study population were more than 18 years with both confirmed and suspected COVID-19. We excluded articles without complete information, with low quality, letters to the editor without case presentation, and public health agencies or institutes recommendations, alongside expert consensus, because of their frequent renewal. In addition, we did not include ongoing clinical trials and reviews. In vitro studies were cited in the text only to supplement insufficient information. We excluded trials evaluating traditional Chinese medicines and non-immunomodulatory drugs. The planned primary outcomes, which were selected based on their clinical usefulness, included time to hospital stay and severity characterized by requirements for invasive mechanical ventilation. Secondary outcomes included time to clinical improvements, the adverse events related to the treatment, overall mortality, and 28-day mortality.

Information databases and search strategy

A systematic review was carried out by searching OVID MEDLINE, PUBMED, Google Scholar, and Cochrane library databases from inception up to August 2, 2020. No language and status (abstract or full text) limitations were imposed. Keywords selection was done based on Mesh terms using “OR” and “AND” operators and included the following terms used in titles, abstracts and keywords: [“COVID-19”; OR “SARS-CoV-2 infection”; OR “Coronavirus”; OR “2019-nCoV infection”; OR “2019-nCoV disease”; OR “2019 novel coronavirus disease”; OR “COVID-19 drug treatment”; OR “Middle East Respiratory Syndrome Coronavirus”; OR “SARS Virus”; OR “severe acute respiratory syndrome”], AND [“anti-inflammatory agents”; OR “Immunomodulation”; OR “antiviral agents”; OR “Cytokines”; OR “Acute-Phase Reaction”; OR “Pharmaceutical Preparations”; OR “Therapeutics”; OR “Antimalarial”; OR “Chloroquine (CQ)”; “Hydroxychloroquine (HCQ)”; OR “Anti-Inflammatory Agents, OR Non-Steroidal”; OR “Glucocorticoids”; OR “Thalidomide”; OR “Cyclosporine”; OR “Tumor Necrosis Factor-alpha”; OR “Tocilizumab”; OR “Sarilumab”; OR “interleukin-6”; OR “anti-IL-6”; OR “Janus kinase inhibitors”; OR “Interleukin 1 Receptor Antagonist Protein”; OR “Interleukin-1”; OR “Canakinumab” OR “Immunoglobulins, Intravenous”; and some other non-Mesh terms [All Fields] of “IVIG”; OR “IL-6 blocker”; OR “NSAID”]. Correlated references of the selected studies were searched manually.

Selection of studies and data extraction

Two authors and one highly experienced librarian extracted articles independently by providing information on the efficacy and safety of anti-inflammatory and immunomodulatory drugs in COVID-19. The first step included the screening of titles and abstracts of all retrieved references and then cross-checking the results. Due to rarity, we increased the references using an

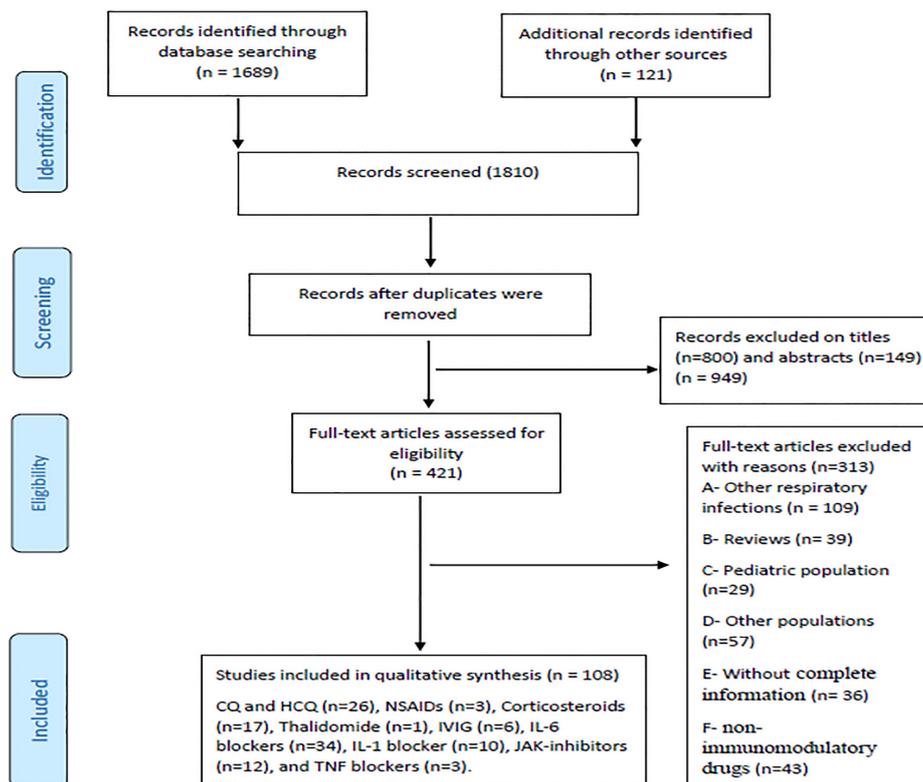


Figure 1. PRISMA flow diagram of studies using anti-inflammatory, immunomodulatory drugs against COVID-19.

additive snowballing technique (n=121). The information extracted from the articles were summarized in the data extraction form as first author, publication date, country of study, journal, type of study, and PICO as population, type of interventions, number of people in the control and intervention groups, mean age of patients in each group and outcomes. The EndNote X5 Resources Management Software was utilized for categorizing, studying the titles and abstracts, and identifying duplicate cases. When studies did not report an effect size (HR, OR, or RR) for outcomes including mortality risk, we used the number of deaths per group. The quality of the included articles was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools. The various papers were evaluated by two independent authors assessing the trustworthiness, relevance, and results irrespective of their risk of bias rating.¹¹

Assessment of risk of bias in included studies

National heart, lung, and blood institute (NHLBI) tool was used to assess the risk of bias for observational studies, case series, and each eligible trial illustrated in Tables S1-S8 in supplementary data. The quality was considered as rates of good, fair, and poor if they fulfilled 60-100%, 50-59%, and less than 49% of the tool items, respectively. The included case reports were considered poor due to the low sample sizes of the case series.¹²

Statistical analysis

Due to heterogeneity between the results and paucity of papers, multiple errors in several systematic reviews seem relevant to the subject resulting in not feasibility to perform a suitable meta-analysis to combine the results.

Results

The initial search identified 1810 results. Following the removal of duplications, screening and full-text review, of which a total of 108 relevant articles deemed suitable were included for 10 drug groups separately. Tables S1-S8 in supplementary data, summarize the identified results of the articles' characteristics and outcomes. In vitro articles were only included in the text as supplementary issues, but not included in the tables. More relevant included articles in these supplementary tables were 21-46 in HCQ, and CQ group (N=26), 51-67 in CS group (N=17), 78-80 in NSAID group (N=3), 66 in thalidomide group (N=1), 56, 62, 65, 103-105 in IVIG group (N=6) as non-biologic disease-modifying anti-rheumatic drugs, and 107, 118-150 in IL-6 blockers (N=34), 152-159, 161-1 62 in IL-1 blockers (N=10), 164-172, 174-176 in JAK and Tyrosine kinase inhibitors group (N=12), and finally 180-182 in TNF blocker group (N=3), as biologic categories. Risk of bias assessment of the retrieved studies identified several limitations and highlighted a number of biases. Following a formal risk of bias assessment, 40 (37%), 47 (43.5%), and 21 (19.5%) studies were rated as good, fair, and poor, respectively.

Non-biologic disease-modifying anti-rheumatic drugs Antimalarial agents (H(CQ))

Both immunomodulatory agents have been used in auto-inflammatory and Rheumatic diseases (e.g. Lupus, Rheumatoid arthritis (RA)). They inhibit chemotaxis, nitric oxide production, and phagocytosis. Moreover, they may antagonize the action of prostaglandins (PGs), interfere with the production of IL-6, IL-1, INF γ , and TNF α , and have antagonistic effects upon TLR7/9.¹³⁻¹⁴

In vitro studies suggested that HCQ inhibits SARS-CoV2 replication.¹⁵ These broad-spectrum effects occur by both increasing endosomal PH, blocking replication, as well as interfering with glycosylation of ACE-2 receptors of SARS-CoV. Moreover, the effects of CQ were found during the post-entry stages via inhibition of viraPLpro.^{16,17}

One study revealed that CQ can inhibit the novel-CoV-2 replication with a half-maximal effective concentration (EC₅₀) of 1.13 μ M and a half-cytotoxic concentration (CC₅₀) greater than 100 μ M.¹⁸ Liu *et al.*¹⁹ found a similar CC₅₀ for two drugs, but EC50 was more for HCQ than CQ. Furthermore, Yao *et al.*²⁰ found that HCQ (EC₅₀=0.72 μ M) is more potent than CQ (EC₅₀=5.4 μ M) in virus inhibition. A prospective cohort of 48 moderate COVID-19 cases was conducted. CQ (1000 mg on day one, then 500 mg/daily for nine days; n=18), HCQ (200 mg BID for 10 days; n=12) had beneficial effects on clinical recovery, duration of hospitalization, and Lung CT scan findings in moderate illnesses.²¹ Several other cohorts revealed similar beneficial results with Hydroxy-(CQ)²²⁻²⁵ alone or in combination with azithromycin.²⁶⁻³⁰

Yu *et al.*²⁵ found that HCQ in 568 critically ill COVID-19 patients is significantly associated with lower mortality via attenuation of the inflammatory cytokine storm. Several other studies showed that HCQ alone or in combination with azithromycin reduced mortality.^{29,30} However, in a retrospective analysis of 807 laboratory-confirmed patients with COVID-19 in the US, HCQ with (n=214) or without (n=198) azithromycin no significant reduction in mortality or the need for mechanical ventilation was identified although an association of increased overall mortality was observed in those treated with HCQ alone.²⁸ In a retrospective multicenter cohort of 1438 hospitalized COVID-19 patients, those who received HCQ with or without azithromycin were similar without significant differences in mortality,³¹ coinciding with no beneficial effects in other observational studies in both moderate and severe illness courses,^{23,32-38} and even mild to moderate inpatients,³⁹ as well as outpatient recipients.⁴⁰ In contrast, in a cohort of 63 hospitalized CoV-2 patients, HCQ was associated with an increased need for escalation of respiratory support.⁴¹ However, most studies had a moderate risk of bias due to their small sample sizes and methodological process.

A French parallel, double-blind, randomized trial suggested that a higher dosage of CQ is not recommended for critically ill patients, especially in combination with azithromycin or oseltamivir.⁴²

Some controlled studies utilized 800-1200 mg,^{32,35,41,43,44} as loading dose, and a doses of 200-800 mg/day^{25,26,34,37,42,44-46} as maintenance therapy from 5 days^{23,45} to 2-3 weeks.³⁵ Anyway, HCQ within 4 days post-exposure prophylaxis of 821 participants revealed no beneficial effect.⁴⁶

Systemic corticosteroids (CS)

CSs reduce inflammation by inhibiting arachidonic acid, IL1, TNF α , and NF- κ B. Their effects on the immune system are mediated mainly via T cells.¹³

Studies: No in vitro studies were found on cytopathic effects of them alone against SARS-COV. Several studies including animal models have shown that CS for treatment of SARS- CoVs were associated with prolonged viremia and worse outcomes.^{47,48} In contrast, high dose CS in the early stage of SARS-CoV had beneficial effects in previous cohorts.⁴⁹ Furthermore, in a retrospective cohort of patients with SARS-CoV and sepsis, CS in 147 of 249 noncritical patients, reduced mortality and the duration of admission, whereas 121 of 152 critical patients received CS and 25 patients died.⁵⁰

In several studies, CSs were significantly associated with lower duration of admission in COVID-19 patients.⁵¹⁻⁵³ Wang *et al.*⁵⁴ reported 46 patients with COVID-19 whose symptoms and chest CT-scan results were improved with 5 to 7 days administration of methylprednisolone.⁵⁴ In a case series of 15 COVID-19 patients, CS decreased the need for vasopressors and improved the oxygenation, CRP levels, and reduced the hospital stay.⁵³ Moreover, in a retrospective cohort of COVID-19 patients, CSs were associated with a lower mortality rate. The authors found no association between therapy and outcomes in patients without ARDS.⁵⁵ Zhou *et al.*⁵⁶ reported that a moderate dose of CS plus Intravenous Immunoglobulin (IVIG) significantly reduced lung injury. In addition, an early short course of methylprednisolone in moderate to severe cases of COVID-19 reduced the escalation of care and improved clinical outcomes in two studies.^{57,58} Recently, in a randomized, controlled, open-label trial of COVID-19 hospitalized patients, dexamethasone 6 mg/day reduced 28-day mortality among those receiving respiratory support.⁵⁹ In a case series of 101 confirmed COVID-19 patients, a single-dose pulse of methylprednisolone had no apparent negative impact on virus removal, while effectively stopped the inflammatory cascade.⁶⁰ Also, in a recent observational study including 1806 hospitalized COVID-19 patients, early use of CS in 140 patients was not associated with mortality or mechanical ventilation, especially in those whose CRP levels were more than 20 mg/dl.⁶¹ Contrariwise, a cohort of 416 COVID-19 patients revealed that CS increased the mortality rate and appeared to be useful only in the cases with lymphopenia.⁶² Moreover, in a Japanese case series of 7 patients with COVID-19, high dose, short term methylprednisolone enabled extubation of the patients within 7 days.⁶³

In a case series of 24 COVID-19 patients, three patients with asthma who had received CS before admission

represented with severe symptoms requiring mechanical ventilation.⁶⁴

In addition, there is evidence of successful treatment with CS in combination with IVIG, thalidomide, or standard of care in some reports.⁶⁵⁻⁶⁷

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAID as cyclooxygenase (cox1/cox2) inhibitors are used clinically for their anti-inflammatory, analgesic, and antipyretic properties. COX1 provides PGs for housekeeping, while COX2 is upregulated at sites of inflammation by IL-1, TNF α , endotoxins, and growth factors.¹³

There is a lack of in vitro studies on the use of NSAID on COVID-19. An in vitro study revealed that ibuprofen and naproxen were inhibited the Ab production at pharmacologic doses.⁶⁸ A dramatic antiviral effect of Indomethacin was found in a model of feline coronavirus infected cells, as well against Canine- CoV as, by inhibiting virus replication and protecting the host cell from virus-induced damage.⁶⁹ Antiviral efficacy of indomethacin was determined by evaluating virus titers in CoV-infected dogs, and also in one human study.^{70,71} Concerns about ibuprofen seem to be due to the increase in an over expression of ACE2 in diabetic rats and diabetic patients.^{72,73} Therefore, this effect may worsen the clinical course and even susceptibility to COVID-19 infection theoretically.⁷⁴ Also, concerns about ibuprofen invigorated from an unpublished idea of a French physician who claimed that four patients with COVID-19 developed a severe form of the illness after using NSAIDs.⁷⁵ Several studies suggest that the use of NSAIDs before or during admission with pneumonia including viral infection may be associated with an increased risk of empyema.^{75,76}

A clinical review of chemotherapeutic strategy for severe COVID-19 pneumonia pointed out that celecoxib and thalidomide can modulate I κ B α degradation and phosphorylation.⁷⁷

In a retrospective cohort of 403 confirmed cases of COVID-19, ibuprofen was not associated with worse clinical outcomes.⁷⁸ The association between ibuprofen and severity among 1872 patients with COVID-19 was insignificant, albeit with a trend towards increased disease severity risk.⁷⁹ In contrast, in another study, NSAID was associated with worse outcomes among hospitalized users.⁸⁰

Thalidomide

This major teratogen agent has been used due to antiemetic, analgesic, anxiolytic, and sedative properties or in the template of some malignancies, autoimmune, and infectious diseases.¹³ It suppresses activated NF- κ B that promotes TNF α production. Furthermore, it inhibits phagocytosis, chemotaxis, and reduces the expression of TNF α , IL-1 β , and IL-6 mRNA.^{13,81}

One study revealed that thalidomide decreases the expression of IL-1 β and IL-6 in human epithelial cells; therefore, it may help prevent emphysema.⁸² It can reduce

the HIV replication by TNF α in human macrophages in vitro.⁸³ Moreover, it may express immunomodulatory effects in cell cultures, especially in combination with celecoxib, and suppress the production of TNF α and IL-8 via inhibition of NF- κ B.⁷⁷ Anti-inflammatory effects of thalidomide in an animal model showed that it decreased the production of IL-1B, IL-6, TNF α , and TGF β .⁸⁴ It attenuates inflammation, oxidative stress, and pulmonary fibrosis in mice lungs.⁸⁵ Also, antifibrotic effects against bleomycin-induced pulmonary fibrosis were seen in rats.⁸⁶ In H1N1 influenza-induced pulmonary injury in mice thalidomide dramatically inhibited the activated P- NF- κ B p6 and reduced the inflammation.⁸⁷ However, the beneficial effects of thalidomide (100mg/day) in combination with a low dose of CS were shown in a 45-year-old woman with COVID-19.⁶⁶

Cyclosporine (CsA)

CsA has had a major impact on the prevention of solid organ transplant rejection. Also, it has potential effects on immunologically mediated diseases. CsA inhibits calcineurin, therefore, it inhibits the early phase of T cell activation and IL2-4, IL15, and INF γ production, and may modulate anti-inflammatory effects by inhibiting NF- κ B.¹³

Although Low micromolar, non-cytotoxic concentration of CsA strongly affected the replication of some viruses in cell culture, more concentration is needed to block coronaviruses, suggesting that coronaviruses are less sensitive to CsA treatment.⁸⁸ CsA is considered as an interaction partner of SARS-CoV N-protein.⁸⁹ It might exert its effect by inhibiting cyclophilin or even direct inhibitory effect on virus function.⁹⁰ It has been reported to inhibit the replication of HIV, vesicular stomatitis virus (VSV), HCV, and influenza-A,⁹¹⁻⁹⁴ but in vivo studies on CoVs family especially CoV-2 infection are required. The patients who meet the HLH criteria may benefit from the use of related chemotherapeutic agents like CsA.⁷

Biological anti-rheumatic drugs

IVIG

Intravenous immunoglobulin (IVIG) is prepared from pooled human plasma. It is mainly administered for autoimmune, auto inflammatory conditions and has been used as an anti-infectious agent. Its Fab-mediated functions include suppression of cytokines, auto antibodies and complements, targeting of specific immune cell surface receptors, expression of regulatory T-cells by induction of COX2 dependent PGE2 in dendritic cells, and blockade of leukocyte adhesion molecule binding. Moreover, some FC-dependent activities include blockade of fragment crystallizable- γ receptor (Fc γ R), the neonatal Fc receptor (FcRn) and immunomodulation by salivated IgG.⁹⁵

IVIG has been used as an anti-infective in experimental models.^{96,97} Pyrc *et al.*⁹⁸ showed that human sera from healthy people and IVIG can neutralize H-CoV-NL63. In another study, IVIG obtained from donors with higher Abs against RSV had significant potential to improve

the outcome of respiratory syncytial virus infection in immunocompromised subjects, not only by controlling viral replication but also by reducing damage to the lungs.⁹⁹ A murine model of induced colitis revealed that IVIG reduced intestinal inflammation by suppression of IL6, also inhibited the growth of some microorganisms in the gut of mice.¹⁰⁰ In previous studies on SARS and MERS, IVIG exhibited various clinical benefits.^{101,102} The clinical data of 10 patients with COVID-19 receiving short-term corticosteroid (160 mg/day) plus IVIG (20 gr/day) were collected. This combination significantly reduced SpO₂ and lung lesions and normalized ALC and CRP levels.⁵⁶ Furthermore, the administration of the high-dose IVIG on 3 patients with COVID-19, just at the time of initiation of respiratory distress, significantly improved clinical symptoms and radiological findings.¹⁰³ Similarly, two retrospective cohort indicated beneficial effects when high-dose IVIG was administrated early in the critical COVID-19 patients.^{104,105}

Contrariwise, in a cohort of 416 COVID-19 patients who received CS and concurrent IVIG, the use of IVIG was not a rescuer.⁶² Zhang *et al.*⁶⁵ described a couple who were successfully treated with methylprednisolone and IVIG. However, the efficacy of IVIG would be better if the immune IgG Abs was specific against COVID-19 by boosting the immune response in newly infected patients, especially when it is collected from patients recovered from COVID-19 in the same city or surrounding area.¹⁰⁶

IL-6 blockers

Tocilizumab (TCZ) and sarilumab are humanized monoclonal antibodies to the IL-6 receptor that can inhibit intracellular signaling originating from IL-6. They are administered in some auto-inflammatory and autoimmune diseases.⁹⁵ Since IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) are key cytokines, which may result in lung injury, they might play a therapeutic role in severe and critical COVID-19.¹⁰⁷ Apart from the anti-inflammatory role of TCZ, it might be hypothesized that the beneficial effects of TCZ on the coagulation abnormalities associated to COVID-19 are also relevant.¹⁰⁸ The findings suggest that the overexpression of IL-6 and IL-2R is useful for estimating the severity of COVID-19.¹⁰⁹ Animal models showed an association between IL-6 level and SARS-CoV severity.¹¹⁰ However, there was no significant difference in cytokine levels in the presence of SARS symptoms in 14 adult CoV patients.¹¹¹ This discrepancy has been justified in some studies with delayed inflammation,¹¹² imbalance between IL-6 and IL-10,¹¹³ or the presence of another mechanism such as gamma interferon-related cytokine storm.¹¹⁴ At least, it has been shown that four potential CoV therapeutic targets (ADAM17, DUSP1, P38MAPK, GU-rich ssRNA) are related to IL-6 regulator.¹¹⁵⁻¹¹⁷

In a cohort of 28 patients with severe COVID-19 who were treated with sarilumab and 28 contemporary patients receiving standard of care alone; on day 28, overall clinical

improvement and mortality were not significantly different between the two groups. Sarilumab was associated with faster recovery in a subset of patients showing minor lung consolidation at baseline (P=0.01).¹¹⁸ Montesarchio *et al.*¹¹⁹ in a case series of 15 patients with COVID-19 treated with sarilumab, revealed a rapid improvement in respiratory parameters and a reduction in CRP levels in 67%, while 34% of patients died. In a clinical series of eight patients, early treatment with sarilumab led to progressive reduction in CRP and earlier discharge.¹²⁰ Similarly, the investigation of 53 patients with severe SARS-CoV-2-related pneumonia in both medical ward and ICU who received sarilumab in addition to other drugs revealed beneficial effects.¹²¹

A prospective case series was performed on 63 patients with COVID-19. TCZ decreased fever, PaO₂/FiO₂, CRP, ferritin, D-dimer, ALC, and the chance of mortality within six days of treatment.¹²² Similarly, in a prospective series of 100 consecutive patients admitted with COVID-19 in Italy, the response to TCZ was rapid, sustained, and associated with significant clinical improvements.¹²³ Several other studies showed the beneficial effects of TCZ in the reduction of both clinical symptoms and inflammatory markers,^{33,107,124-133} emphasizing on reduction of the mortality,^{33,124,125,128,129,133-136} especially when instituted early in the management of critically ill patients.^{128,136} In a large cohort study, a total of 1229 and 10673 person/ days were analyzed. TCZ was associated with a lower risk of death and ICU admission, albeit among patients with higher CRP levels.¹³⁷

In contrast, in a retrospective analysis of 112 severe COVID-19 patients in Italy, TCZ did not reduce ICU admission or mortality rate among 21 patients.¹³⁸ Also, in a retrospective cohort of 65 patients with severe COVID-19, while 32 patients were treated with TCZ; on day 28 the clinical findings and mortality rate were not statistically different between groups.¹³⁹ A new trial as COVACTA, which was conducted by Roche, did not meet its primary endpoint of improved clinical status.¹⁴⁰

In a retrospective analysis of 457 COVID-19 patients, hyperglycemia had negative impacts on TCZ therapy in both diabetic and non-diabetic patients.¹⁴¹

Several beneficial effects of TCZ have been reported in case reports of COVID-19 patients, with or without underlying diseases.¹⁴²⁻¹⁴⁸ Conversely, two cases of COVID-19 induced CRS with elevated IL-6 levels and progression to HLH developed poor outcomes despite TCZ treatment.¹⁴⁹

In a 57-year-old woman with systemic sclerosis who had developed COVID-19, the treatment with TCZ led to good control of both scleroderma and arthritis. Four weeks after the last TCZ infusion, the patients presented with COVID-19. Albeit, this case presented with mild symptoms that may be due to the prophylactic effects of TCZ.¹⁵⁰

IL-1 blockade

Anakinra is a human recombinant form of IL-1Ra. It prevents the interaction of the receptor with IL-1 and subsequent signaling. Thus, it is used in RA, some auto-

inflammatory diseases (e.g., systemic juvenile idiopathic arthritis (sJIA), cryopyrin-associated periodic syndrome (CAPS)), and HLH.⁹⁵ The nCoV might be bind to TLRs which activate the production of pro-IL-1 that mediates the inflammation of lungs, fever, and fibrosis.¹

Although one study showed no difference in IL-1 β levels in patients with COVID-19 in any severity and the general population,¹⁰⁹ one animal model has shown beneficial results for an IL-1 receptor antagonist in rats.¹⁵¹

A small prospective cohort compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra, and 44 historical controls showed that Anakinra for 7 days reduced both the need for invasive MV and mortality.¹⁵² Also, in a retrospective cohort of 29 moderate to severe COVID-19 patients, only the high dose of anakinra (5 mg/kg, IV twice a day) was effective, with a reduction in CRP and a progressive improvement in respiratory function.¹⁵³ Other small case series¹⁵⁴⁻¹⁵⁷ and case reports¹⁵⁸⁻¹⁶¹ have reported anecdotal evidence of improvement in outcomes. In a retrospective analysis of ten patients with COVID-19, and respiratory failure, canakinumab, a human monoclonal Ab against IL-1 β , 300 mg, SQ, was safe, and associated with a rapid reduction in the inflammatory response and oxygen requirement.¹⁶²

Overall, large studies are needed to evaluate the efficacy and safety of anakinra, as targeted therapy. To date, due to promising results, we suggest that only in the situation of the inflammatory storm IL-6 is not high or in HLH / macrophage activation syndrome.

JAK inhibitors

The therapeutic inhibition aspects of intracellular Janus kinase/ signal transducer and activator of transcription (JAK-STAT) pathway have yielded promising results in many systemic (e.g. RA), cancerous, and cutaneous diseases.^{95,163}

Baricitinib that selectively inhibits the JAK1/2 has potentially beneficial effects on reducing both viral entry via receptors and also inflammation in COVID-19 patients.¹⁶⁴ Cao *et al.*¹⁶⁶ in a prospective, multicenter randomized clinical trial revealed the beneficial effects of ruxolitinib in CT-Scan improvement (P=0.049), faster clinical improvement, and a good profile of safety. Giudice *et al.*¹⁶⁶ revealed a significant improvement in respiratory symptoms and radiographic lesions and a marked decrease in D-dimer levels with ruxolitinib. Baricitinib had several significant effects on both primary and secondary end points of 113 patients with moderate COVID-19-related pneumonia.¹⁶⁷ A pilot study of 12 hospitalized patients with moderate COVID-19 was conducted. In the baricitinib-treated group, all clinical characteristics and respiratory functions improved, and CRP levels decreased at week1 and 2 compared to the baseline.¹⁶⁸ Another retrospective cohort analysis was carried out on 105 consequent patients with severe COVID-19. Fourteen patients received ruxolitinib due to an inflammatory score (CIS) of 10 or more out of 16 points. A total of 12 achieved a significant reduction of

CIS, on day 7 with sustained clinical improvement in 11 cases, without prominent side effects.¹⁶⁹

A prospective case series of 86 patients involved with immune-mediated inflammatory diseases (e.g. RA, psoriasis) who were receiving anti-cytokine biologics and other immunomodulatory agents were conducted when developed COVID-19. Despite the small sample size, the baseline use of biologics and JAK inhibitors were not associated with worse outcomes.¹⁷⁰ Another cohort revealed that baricitinib demonstrated a marked reduction in serum levels of IL-6, IL-1 β , and TNF α , rapid recovery in T and B cell frequencies, and an increased antibody production against SARS-CoV-2 spike protein.¹⁷¹ In a small cohort of 15 patients with COVID-19, baricitinib plus HCQ was associated with recovery in 11 cases.¹⁷² Interestingly, silibinin as a direct inhibitor of STAT3 has been noted as a dual targeting of host CRS and virus replication.¹⁷³ In addition, several beneficial effects of JAK inhibitors have been reported in case reports of COVID-19 patients.^{174,175} A favorable course of COVID-19 was observed in an 87-year-old woman, despite the underlying RA, while she received baricitinib from one year before. This allows speculating that baricitinib had a positive impact on the outcome.¹⁷⁶

TNF α inhibitors

This group (e.g., etanercept) has been now proven in the treatment of some inflammatory and autoimmune conditions (e.g., inflammatory bowel disease).⁹⁵

These inhibitors produced a dramatic reduction of overall illness severity of virus-specific lung immunopathology in mice without interfering with viral clearance.¹⁷⁷ Etanercept has been reported to be effective for the treatment of a non-infectious pulmonary syndrome like SARS pneumonia in one report.¹⁷⁸ In contrast, etanercept alone was not sufficient to ameliorate the disease in the virus-endotoxin mediated model of respiratory disease in pigs.¹⁷⁹ Several studies reported that the use of anti-TNF α prior to COVID-19 infection was not associated with a severe evolution of the COVID-19.¹⁸⁰⁻¹⁸²

Discussion

All previous studies have some limitations. Unlike preliminary studies, HCQ was associated with no gross effects on the need for respiratory support. Most studies revealed no significant differences in mortality among hospitalized patients with severe illness. Nevertheless, for historical reasons alongside scattered experiences of clinical benefits, the authors suggest using these drugs in early phases or post-exposure conditions. In some studies, H (CQ) had some beneficial effects on clinical recovery, duration of hospitalization, lung CT-Scan findings in moderate illnesses, and even mortality among patients with severe illness. Although CS administration is questionable due to the potential inhibition of viral clearance, increase in the duration of viremia, and some evidence of disease progression, there is increasing evidence of beneficial effects. CS may be beneficial in the early acute phase of

illness, especially in low doses. Although its use in severe septic shock is doubtful, it may be more useful in HLH and hyper-inflammatory storm in an adequate time. At this time, there is no evidence for or against the use of NSAIDs in COVID-19 patients. Using NSAIDs to confront the virus function and replication is not logical when we have more effective and acceptable drugs. Additionally, thalidomide may shed new light on an adjuvant treatment strategy due to its potentially anti-viral effects, but there are inconsiderable articles regarding its effectiveness. It may be effective as a subsidiary treatment strategy, especially in combination with low-dose CS. Briefly, thalidomide in addition to its ability to inhibit cytokine surge, and immunomodulation effects, could help patients to reduce oxygen consumption, and relieve gastrointestinal symptoms. Also, we cannot suggest CsA as a first-line therapeutic agent, but it should be noted that it can be prescribed in HLH as a potentially effective drug. IVIG seems to be a golden repurposing drug in deteriorating patients, where it can be used at least as a bridge therapy. Patients might not receive much benefit when systemic damage has already taken place. It acts not only by controlling viral replication but also by reducing damage to the lungs. However, it remains in critical cases, just in the early stages of deteriorating. Generally, despite the recent Phase-III COVATA fail consequences, the results are promising and TCZ has been used especially on severe and critical cases with beneficial effects. Since the peak level of IL-6 is associated with the severity of pulmonary complications, TCZ and sarilumab can be used in the early stages of the inflammatory storm, where other drugs are ineffective. Large studies are needed to evaluate the efficacy and safety of IL-1 and TNF α blockade as targeted therapy. At this time, we suggest anakinra, as a promising repurposing strategy only in the situation of an inflammatory storm that IL-6 is not high or in HLH /macrophage activation syndrome. However, due to elevated TNF α in SARS-CoV, the use of TNF α inhibitors has a potential role to suppress the inflammatory cascade and ameliorating the severe alveolar damage. Also, these groups can modulate biological responses that are mediated by TNF or even induce immunosuppressive Treg cells (especially Adalimumab). Nevertheless, there is no evidence indicating that TNF α inhibition is harmful in COVID-19 patients, and also there is no strong evidence for their use. Studies utilizing TNF α blockers for COVID-19 would be prudent. Although JAK or tyrosine kinase inhibitors could reduce viral infectivity, viral replication, and the aberrant host inflammatory state historically, further studies are required to confirm their therapeutic effects.

Conclusion

Despite the collective wisdom, decision-making regarding the management of COVID-19 especially in severe conditions is a challenging problem. Although several anti-inflammatory and immunomodulatory drugs are candidates, their definite effects are unknown. The results for repurposing therapies are contradictory allowing

humans to make several choices. Although cytokine suppression seems essential in cytokine storm as a possible way to save the patient's life, this method in non-hyper-inflammatory conditions may endanger the patient's life. The timing of treatment is also important. Low-dose steroids may be effective in the early phases of illness, IVIG may be served to deteriorating patients or to block antibodies and immune complexes elsewhere. Moreover, tocilizumab is more effective in severe situations when the IL-6 level is high and other drugs are ineffective. We suggest that decisions should be taken for each patient, separately. However, more studies are needed to decipher the therapeutic secrets of this dilemma.

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Author Contribution

RS: Substantial contributions to the conception and design of the study; acquisition, analysis, revising the manuscript critically for important intellectual content, and interpretation of data, drafting the manuscript, final approval of the version to be published. SP: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published. AA: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published. RS: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published. RS: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published. AS: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published.

Conflict of Interest

The authors did not report any (financial or otherwise) conflict of interest.

Supplementary Data

Tables S1-S8 are available on the journal's web site along with the published article.

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