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Anti-rheumatic drugs as potential anti-inflammatory, immunomodulatory agents against COVID-19: A systematic review

Reza Sinaei[1], Sara Pezeshki[*2], Ali Asadipour[3], Reza Shiari[4], Roya Sinaei[5], Ali Sinaei[6]

[1]Assistant Professor of Pediatrics Rheumatology, Department of Pediatrics, Kerman University of Medical Sciences, Kerman, Iran; Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran, **Email:** r.sinaei@kmu.ac.ir, **ORCID:** 0000-0002-2702-5836

[2]Assistant Professor of Internal Medicine, Department of Internal Medicine, Kerman University of Medical Sciences, Kerman, Iran; Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran, **Email:** s.pezashki@kmu.ac.ir; sarapezeshki83@gmail.com, **ORCID:** 0000-0001-9795-4713

[3] Professor of Pharmaceutical Chemistry, Pharmaceutical Sciences and Cosmetic Products Research Center, Kerman University of Medical Sciences, Kerman, Iran, **Email:** aliasadipour@kmu.ac.ir, **ORCID:** 0000-0002-1449-2195

[4]Associate Professor of Pediatrics Rheumatology, Department of Pediatric Rheumatology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, **Email:** Shiareza@yahoo.com, **ORCID:** 0000-0002-7712-279X

[5]Pediatrician, Department of Pediatrics, Kerman University of Medical Sciences, Kerman, Iran **Email:** Sinaeiroya866@gmail.com, **ORCID:** 0000-0001-9029-9330

[6]PharmD student, School of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran, **Email:** ali.sinaei@ymail.com, **ORCID:** 0000-0001-9108-9335

[*]**Corresponding Author:** Sara Pezeshki, Department of Internal Medicine, Kerman University of Medical Sciences, Kerman, Iran; Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran, **Email:** s.pezashki@kmu.ac.ir; sarapezeshki83@gmail.com

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 until August 2, 2020, 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.

Keywords: Anti-inflammatory, Immunomodulatory, COVID-19, SARS-CoV2

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)-κB and then pro-inflammatory cytokines. The initiation of immune response is through some cytokines such as IL-1β and TNFα.[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 IL-6 and ferritin are predictors of fatality.[8] Caricchio et al. 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.[6] 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 TNFα 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.

Materials and Method

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 "interlukin-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 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 1-7. 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

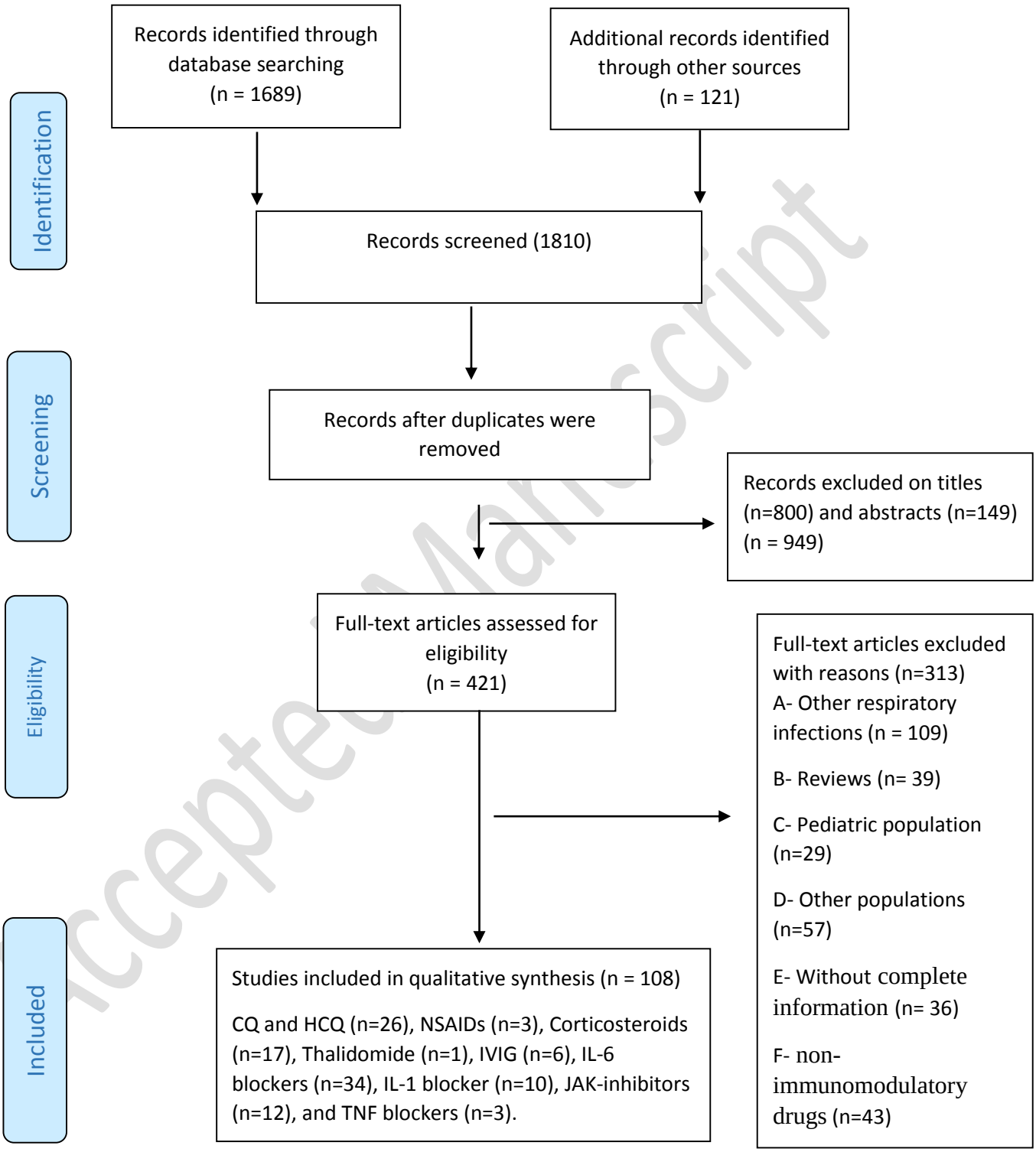

Figure-1. PRISMA flow diagram of studies using anti-inflammatory, immunomodulatory drugs against COVID-19.

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 1-6 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, 96-98 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.

1-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, 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, INFγ, and TNFα, and have antagonistic effects upon TLR7/9.[12, 13]

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 (EC_{50}) of 1.13 μM and a half-cytotoxic concentration (CC_{50}) greater than 100 μM.[18] Liu et al. found a similar CC_{50} for two drugs, but EC50 was more for HCQ than CQ.[19] Furthermore, Yao et al. found that HCQ (EC_{50}=0.72 μM) is more potent than CQ (EC_{50}=5.4 μM) in virus inhibition.[20]

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. found that HCQ in 568 critically ill COVID-19 patients is significantly associated with lower mortality via attenuation of the inflammatory cytokine storm.[25] 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, TNFα, and NF-κB. 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] Wong Y et al. 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. reported that a moderate dose of CS plus Intravenous Immunoglobulin (IVIG) significantly reduced lung injury.[56] 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 (NSAID):

NSAID as cyclooxygenase (cox1/cox2) inhibitors are used clinically for their anti-inflammatory, analgesic, and anti-pyretic properties. COX1 provides PGs for housekeeping, while COX2 is upregulated at sites of inflammation by IL-1, TNFα, 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 IκBα 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-κB that promotes TNFα production. Furthermore, it inhibits phagocytosis, chemotaxis, and reduces the expression of TNFα, IL-1β, and IL-6 mRNA.[13, 81]

One study revealed that thalidomide decreases the expression of IL-1β and IL-6 in human epithelial cells; therefore, it may help prevent emphysema.[82] It can reduce the HIV replication by TNFα 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 TNFα and IL-8 via inhibition of NF-κB.[77] Anti-inflammatory effects of thalidomide in an animal model showed that it decreased the production of IL-1B, IL-6, TNFα, and TGFβ.[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-κB 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]

IVIG:

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 (FcγR), the neonatal Fc receptor (FcRn) and immunomodulation by salivated IgG.[88]

IVIG has been used as an anti-infective in experimental models.[89, 90] Pyrc et al. showed that human sera from healthy people and IVIG can neutralize H-CoV-NL63.[91] 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.[92] 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.[93] In previous studies on SARS and MERS, IVIG exhibited various clinical benefits.[94, 95] 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.[96] Similarly, two retrospective cohort indicated beneficial effects when high-dose IVIG was administrated early in the critical COVID-19 patients .[97, 98]

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. described a couple who were successfully treated with methylprednisolone and IVIG.[65]

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.[99]

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 INFγ production, and may modulate anti-inflammatory effects by inhibiting NF-κB.[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.[100] CsA is considered as an interaction partner of SARS-CoV N-protein.[101] It might exert its effect by inhibiting cyclophilin or even direct inhibitory effect on virus function.[102] It has been reported to inhibit the replication of HIV, vesicular stomatitis virus (VSV), HCV, and influenza-A,[103-106] 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]

2- **Biological anti-rheumatic drugs**

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.[88] 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.[115,116,117]

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. 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.[119] 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 sclerodermia 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-1Rα. It prevents the interaction of the receptor with IL-1 and subsequent signaling. Thus, it is used in R.A, some auto-inflammatory diseases (e.g., S.JIA, CAPS), and HLH.[88] 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-1β 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 series [154-157] and case reports [158-161] 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-1β, 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.[88]

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.[163] Cao et al. 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.[164] Giudice et al. revealed a significant improvement in respiratory symptoms and radiographic lesions and a marked decrease in D-dimer levels with ruxolitinib.[165] Baricitinib had several significant effects on both primary and secondary end points of 113 patients with moderate COVID-19-related pneumonia.[166]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.[167] Another retrospective cohort analysis was carried out on 105 consequent patients with severe COVID-19. 14 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.[168] Also, in a prospective trial, patients receiving ruxolitinib plus SOC (22 of 43) had a faster clinical improvement and a more favorable safety than the control group (21 of 43).[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-1β, and

TNFα, 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]

TNFα inhibitors:

This group (e.g., etanercept) has been now proven in the treatment of some inflammatory and autoimmune conditions (e.g., inflammatory bowel disease).[88]

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-TNFα 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 adjutant 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 TNFα 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 TNFα in SARS- CoV, the use of TNFα 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 TNFα inhibition is harmful in COVID-19 patients, and also there is no strong evidence for their use. Studies utilizing TNFα 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. Although 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.

Authors' contribution

Reza Sinaei: 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.

Sara Pezeshki: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published.

Ali Asadipour: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published.

Reza Shiari: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published.

Roya Sinaei: Acquisition and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the version to be published.

Ali Sinaei: 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.

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Supplementary Table 1. Studies investigating **H (CQ)** in CoV-2 and some other viruses

Country of Study	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[21]	a prospective open-label randomized controlled (RCT) study	Np=48 /Nc=12	CQ (1g on day 1, then 500 mg/d× 9 days; n=18), HCQ (200 mg BID×10 d; n=12) had beneficial effects on median time in days to clinical recovery (TTCR), duration of admission, and findings on lung CT-Scans in moderate illnesses. CQ had a significantly faster TTCR (5.5 d, P=0.019), and HCQ had a non-significantly faster TTCR (6 d, P=0.049) vs the controls (7.5d). The secondary and safety outcome as median time to viral negative by RT-PCR was shorter in CQ (2.5d, P=0.006) and HCQ (2d, P=0.010) groups vs control (7d). Adverse events were more in the CQ group (44.44%) and HCQ (50%) than controls (16.6%), albeit in mild types.	Fair
China[22]	limited case series as a letter	N=100	Refers to CQ that improved COVID-19 pneumonia, images focus, and reduced the course of illness of more than 100 patients.	Fair
China[23]	RCT	Np=31/Nc=31	Adding HCQ (400 mg/d×5 d) in the treatment of 31/62 patients, reduced the TTCR, radiological results, and improved pneumonia (80.6% vs 54.8%). Adverse events happened more in controls (4 vs 2).	Good
China[24]	RT-RCT	Np=10/Nc=12	In 22 admitted cases: CQ 500 mg/BID for 10d and Lopinavir/Ritonavir, 400/100 mg/BID for 10d as control had similar efficacy in treating COVID-19. Controls became virus-negative faster on day 3, while the CQ group was slightly higher on day 7, day 10, and day 14. Patients treated with CQ appear to recover better and are discharged at a much quicker pace. All adverse events were mild and limited to CQ.	Good
China[25]	retrospective clinical trial study	Np=48/Nc=520	HCQ 200 mg/BID for 7-10 d was significantly associated with lower mortality (P<0.001) and lower hospital stay (<0.05), via attenuation of the inflammatory cytokine storm.	Good
France[26]	Open-label non-randomized clinical trial.	Np=20/Nc=36	HCQ (200 mg. TID× 10 d) reduced the viral load in 20 patients (P<0.001)) and its efficacy was enhanced with azithromycin (100%).	Good
France[27]	Pilot observational cohort	N=80	In an observational cohort of 80 relatively mildly infected inpatients treated with HCQ and azithromycin, except 2 old patients, all cases improved clinically and discharged rapidly. 83% were PCR negative on day 7, and 93% on day 8.	Fair
USA[28]	Retrospective cohort	Np=412 (198 [HCQ]+214 [HCQ+ Azithromycin] /Nc=395	HCQ without or with azithromycin did not reduce the risk of mechanical ventilation and mortality although an association of increased overall mortality was seen in those treated with HCQ alone P-0.009).	Good

USA[29]	multi-center retrospective Cohort	N=2541	In the treatment of 2541 confirmed hospitalized patients with HCQ±, azithromycin reduced mortality. HCQ provided a 66% hazard ratio reduction, and their combination 71% compared to neither treatment (P<0.001).	Good
France[30]	Retrospective Cohort	N=1061	Early administration of HCQ 200mg TDS×10d+azithromycin was safe and associated with a very low fatality (n=8; 0.75%) among the 1061 patients. 2.3% mild adverse events (GI, headache, insomnia, and transient blurred vision) were reported.	Good
USA[31]	retrospective cohort with random sampling	N=1438	Those receiving HCQ (400 mg BID then 200 mg BID) ± azithromycin were more likely than others to be without significant effect on mortality.	Good
USA[32]	Observational cohort	N=1446	Observational study on 1446 consecutive patients showed that HCQ 600 mg BID×1d, then 400 mg/d ×median 5d, in admitted patients was not associated with either greatly lower or increased risk of the composite endpoint of intubation or death.	Good
USA[33]	Observational Retrospective cohort	N=2512/with controls from convenience sample	Preprint: HCQ (800 mg od on day 1 and 400 mg on days 2-5) ±azithromycin was not associated with a survival benefit among hospitalized patients. TCZ demonstrated a trend association towards reduced mortality among 134 ICU recipients.	Good
France[34]	limited case series as a letter	N=11	A prospective study of 11 hospitalized patients using HCQ 600 mg/d for 10d and azithromycin, with 1 death, 2 ICU transfers, 1 Long QT interval, had no sufficient beneficial effect.	Fair
China[35]	open label, RCT	Np=75/Nc=75	75 patients were enrolled in each study arm. Adding HCQ to the standard of care (SOC) did not result in a significantly mild to moderate COVID-19. Adverse events were higher in the HCQ recipients.	Good
France[36]	Cohort study.	N=4642	Revealed no evidence for the efficacy of HCQ (600 mg on day 1, then 400 mg/d for 9d) with or without azithromycin (500 mg on day 1 then 250 mg for 4 d) in 29-days mortality. Significantly, higher rates of discharge were observed by HCQ.	Good
France[37]	observational comparative cohort	N=173	The results do not support HCQ (600 mg/d within 2d of admission) in admitted patients requiring O2 comparing no HCQ.	Fair
USA[38]	Cohort study	N=3372	HCQ + azithromycin did not show beneficial effects on mortality or the need for mechanical ventilation compared to the matched cohort.	Fair
Brazil[39]	Multicenter, RT-RCT	N=630 in 3 groups	Among 504 confirmed COVID-19 patients hospitalized with mild to moderate COVID-19, HCQ 400 mg BID ± azithromycin (P=1.00) did not improve clinical status in 15 d compared to SOC. Prolongation of QT and elevation of liver enzymes were more in HCQ groups.	Good

USA & Canada[40]	RCT	N=491	HCQ 800 mg then 600 mg after 6-8 h, then daily for 4 d did not substantially reduce symptom severity in outpatients with early mild COVID-19 (P=0.21).	Good
USA[41]	Quasi-randomized comparative cohort.	Np=32/Nc=31	In 63 hospitalized COVID-19 patients, HCQ was associated with an increased need for escalation of respiratory support. Also, there were no benefits on mortality and lymphopenia in this cohort.	Good
Brazil[42]	Randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study)	N=81	81 patients with SARS-CoV-2 enrolled. High-dose CQ (600 mg. BID for 10 days, or a total dose of 2.7 g) was associated with higher QT prolongation and fatality than low-dose (450 mg. BID stat and then daily for 5 days). Also, there was no difference between treated and non-treated patients in terms of total fatality.	Good
USA[43]	observational retrospective Cohort	Np=21/Nc=13	Preprint: 34 confirmed COVID-19 patients were included in this study. 21 patients received HCQ. HCQ was independently associated with time to negativity test after adjustment for potential confounders in multivariable linear regression analysis.	Good
Spain[44]	observational cohort	N=166	Preprint: in a cohort of 166 patients hospitalized with COVID-19, HCQ with an initial loading dose of 800 mg improved patients' survival when admitted in early stages (P=0.002). There was a non-statistically significant trend towards survival in all groups.	Fair
China[45]	pilot study	N=30	30 patients while one group were given HCQ 400 mg/ day for 5 days and the other group conventional treatment; no significant differences were found in clinical endpoints (viral clearance by day 7 or death).	Fair
USA & Canada[46]	RCT	Np=414/Nc=407	After high-risk or moderate-risk exposure to COVID-19, HCQ did not prevent illness compatible with COVID-19 or confirmed infection when used as post-exposure prophylaxis within 4 d after exposure. Side effects were more in the HCQ group (40.1% vs 16.8%).	Good

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 2. Studies investigating **CS** in CoV-2 and some other viruses.

Country of Study	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[51]	Retrospective observational study (case series)	N=51	The Treatment of 51 COVID-19 patients with the traditional drugs, interferon, lopinavir, ritonavir, and 3-5 days CS (N=10) resulted in the discharge of 50 cases with rapid improvement of clinical and Para clinical parameters (P<0.001). The median hospital stay was 12 d. One patient died.	Fair
China[52]	Observational cohort	N=81	Adding CS (methylprednisolone) for 35 ICU patients resulted in 26 cases discharged from ICU and finally, 16 from the hospital. One died and 2 cases deteriorated	Fair
Canada[53]	limited case series as a letter	N=15	A case series of 15 COVID-19 cases, who received methylprednisolone (60%), or hydrocortisone and dexamethasone revealed a reduction in CRP and O2 and vasopressor need in CRS.	Fair
China[54]	Retrospective cohort	Np=26/Nc=20	26 of 46 patients with severe COVID-19 received methylprednisolone 1-2 mg/kg/day for 5 to 7 days. This was associated with an improvement of the symptoms and chest CT-scan results.	Good
China[55]	Observational study	NP=11/Nc=20	11/31 Covid-19 cases received CS. No association between CS and virus clearance time (HR, 1.26; 95%CI, 0.58-2.74), Hospital stay (HR, 0.77; 95%CI, 0.33-1.78), or duration of symptoms (HR, 0.86; 95%CI, 0.40-1.83) was observed in non-ARDS patients.	Fair
China[56]	Observational study	N=10	Moderate-dose (160 mg/day) methylprednisolone + 20g/day IVIG significantly reduced lung injury and normalized lymphocyte count and CRP levels compared to low dose CS (P<0.05).	Fair
USA[57]	Quasi-experimental prospective cohort	Np=132/Nc=81	An early short course of methylprednisolone 0.5-1 mg/kg/d for 3 d in 132/213 patients with moderate to severe COVID-19 reduced escalation of care, clinical outcomes, and median hospital stay (P<0.001).	Good
Spain[58]	Multicentric, partially randomized, preference, open-label trial	Np=56/Nc=29	Preprint: This open-label trial, of 85 cases, while 56 received 40mg/12h ×3d, then 20mg/12h ×3d methylprednisolone revealed beneficial effects on reducing CRP (0.0003), and outcome, decreasing the risk of composite endpoint of admission to ICU, or death.	Good
UK[59]	RCT	N=6425/Np=2104	Preprint: Dexamethasone 6mg/d reduced 28-d mortality (P<0.001) in those receiving invasive mechanical ventilation, but did not reduce 28-d mortality in those not receiving respiratory support (P=0.14).	Good

China[60]	Case series	N=101/Np=15	This case series of 101 confirmed COVID-19 patients showed that single-pulse methylprednisolone (40-500 mg) had no apparent negative impact on SARS-CoV-2 removal and production of specific IgG while effectively stopping the inflammatory cascade.	Fair
USA[61]	Observational cohort	N=1806/Np=140	CS within 48h of admission was associated with increased risk of mortality or mechanical ventilation in CRP<10 mg/dl (OR, 2.64; 95%CI, 1.39-5.03), and reduced the risk of mortality in CRP>20 mg/dl (odds ratio, 0.23; 95%CI, 0.08-0.70).	Good
China[62]	Multi-centered, retrospective, observational study	Np=43/N=416	In 43/416 COVID-19 patients, CS and concurrent IVIG increased the mortality rate and appear to be useful only in the cases with lower ALCs.	Fair
Japan[63]	case series	Np=7	Methylprednisolone 500 or 1000 mg ×3d, then 1mg/kg×13 d, in 7 mechanically ventilated Japanese patients enabled the doctors to extubate patients within 7d.	Fair
USA[64]	case series	Np=24	3 patients with mild asthma who had received CS before admission represented severe symptoms requiring mechanical ventilation.	Fair
China[65]	Case report	N=2	A couple who were treated with CS and IVIG were successfully discharged in the 2nd week.	Poor
China[66]	Case report	N=1	The treatment of a 45-year-old woman with thalidomide and low-dose methylprednisolone was successful.	Poor
China[67]	Case report	N=1	A 41-year-old man and a 73-year-old man had improvements by CS therapy.	Poor

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 3. Studies investigating **NSAID** in CoV-2 and some other viruses.

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
Israel[78]	retrospective cohort	N=403	A retrospective cohort of 403 confirmed COVID-19 cases showed that ibuprofen was not associated with worse clinical outcomes compared to paracetamol or non-pyretic, while 3 patients died in the ibuprofen group.	Fair
Denmark[79]	A nationwide register-based cross-sectional study	N=1872/Np=46	Among the 1872 COVID-19 patients, 46 were exposed to ibuprofen prior to COVID-19 infection. Patients with ibuprofen exposure tended to have hypertension, COPD, and cancer. However, all of the relationships were insignificant (P>0.05).	Fair
South Korea[80]	A nationwide cohort	N=1824	Preprint: NSAID use among 1824 adult patients was associated with worse outcomes among hospitalized users compared to the non-users. This especially increased the risk of primary outcome (OR 1.65, 95%CI 1.21-2.24) and cardiovascular or renal complications (OR 1.87, 95%CI 1.25-2.8).	Fair

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 4. Studies investigating **Thalidomide** in CoV-2 and some other viruses.

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[66]	Case report	N=1	A 45-years-old woman was successfully treated with thalidomide (100mg/day) and low-dose CS.	Poor

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 5. Studies investigating **IVIG** in CoV-2 and some other viruses.

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[99]	Case series	N=3	They reported 3 severe SARS-CoV2 patients who received high-dose IVIG (0.3-0.5 gr/kg/day) with satisfactory recovery.	Poor
China[56]	Observational study	N=10	CS plus 20 g/d IVIG significantly reduced lung injury & normalized lymphocyte count and CRP levels.	Fair
China[97]	Multicenter retrospective cohort study	Np=174/Nc=151	High-dose (>15 g) IVIG, as early administration had beneficial effects on reducing 60-day mortality in critical types. Only in patients with the critical disease, IVIG could significantly reduce the 28-day mortality, decrease the inflammatory response, and improve some organ functions ($p<0.05$).	Good
China[98]	Retrospective study as editorial	N=58	In a retrospective study of 58 severe or critically ill COVID-19 patients, adjunct therapy with IVIG within 48h of hospitalization reduced hospital stay and ventilator use, and improved 28-day mortality.	Fair
China[62]	Multi-centered, retrospective, observational study	Np=43/N=416	In 416 COVID-19 patients, CS and concurrent IVIG increased the mortality rate and appeared to be useful only in the cases with lower ALCs.	Fair
China[65]	Case report	N=2	A couple were treated with CS and IVIG successfully and discharged in 2nd week.	NA

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 5. Studies investigating **biologics (IL-6** -inhibitors) in CoV-2.

Study Country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[107]	Retrospective observational study	N=21	21 patients with severe or critical criteria of novel-CoV-2 pneumonia enrolled. All patients received TCZ (400 mg. once) +SOC. Within a few days, all symptoms improved and a high percentage of laboratory (e.g. CRP, ALC) and CT-scan findings decreased significantly. Finally, 19 patients were discharged on average 15.1 days after the TCZ.	Fair
Italy[118]	Open-label cohort study	Np=28/Nc=28	A cohort of 28 patients with severe COVID-19 who were treated with sarilumab and 28 contemporary patients received SOC. 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).	Good
Italy[119]	Retrospective case series	N=15	Sarilumab was administered 400 mg SQ, while 3 received 2 doses. Rapid improvement in respiratory parameters and CRP were observed in 10 (67%). A total of five patients died.	Fair
Italy[120]	Editorial case series	N=8	Adding intravenous sarilumab (400 mg) to SOC, caused at least a 30% reduction in oxygen requirement, and increased oxygenation. The secondary endpoint was the evaluation of CRP, serum amyloid-A, IL-6, D-dimer, LDH, and ALC on days 1, 4, 7. Early treatment led to discharge within 14 days of hospitalization.	Fair
Italy[121]	Case series	N=53	A prospective, case series was done in 53 patients with COVID-19 in both ICU and wards. Sarilumab 400 mg IV was administered on day 1, and patients were followed up for at least 14 days. On day 19, 89.7% of patients significantly improved, 70.6% were discharged, and 85.7% no longer needed oxygen therapy. The overall mortality rate was 5.7%.	Fair
Italy[122]	Pilot prospective open, single-arm, multicenter study (Case series)	N=63	A prospective, case series was done in 63 patients with COVID-19, while 34 patients received TCZ (8 mg/kg) IV, and 29 received TCZ (324 mg) SQ. TCZ decreased fever, PaO2/FiO2, CRP, Ferritin, D-dimer, ALC, and the chance of mortality within 6d of treatment (P<0.05).	Fair
Italy[123]	Prospective cohort study	N=100	In 100 consecutive patients admitted with COVID-19, the response to TCZ 8 mg/kg IV 1-3 doses was rapid, sustained, and associated with significant clinical improvement	Fair

USA[124]	Observational study	N=239 (104 were severe)/Np=153	TCZ-treated cases (n=153) comprised 90% of those with severe disease; 44% of non-severe cases received TCZ for evolving Cytokine storm (CRS). TCZ-treated cases with severe disease had similar survival to the non-severe group (83% vs 91%; P=0.11). After the treatment, oxygenation and inflammatory biomarkers improved higher than expected survival.	Good
USA[125]	Case series	N=27	This small compassionate use study revealed that a single 400 mg IV of TCZ reduced oxygen requirements, inflammation, vasopressor support, and mortality.	Fair
Italy[126]	Case series	N=51	They observed in 51 severe COVID-19 patients, after administration of TCZ a rapid beneficial effect on fever, inflammatory markers happened (P<0.001).	Fair
China[127]	Retrospective cohort study	N=15	15 patients with moderate to severe and critical COVID-19 cases all received at least one dose of TCZ (80 to 600 mg) alone (47%) ± methylprednisolone (53%). After 7 days of treatment, 67% were clinically stable and 20% died. The CRP levels rapidly dropped after the TCZ treatment.	Fair
Spain[128]	Retrospective cohort study	Np=77/Nc=94	Patients in the TCZ group had significantly fewer ICU admission (P=0.005), need for invasive ventilation (P=0.001), and lower mortality rates, especially in the early stages of the inflammatory storm	Good

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 7. Studies investigating **biologics (IL-6**-inhibitors**)** (Continued).

Italy[129]	Retrospective cohort study	Np=179/Nc=365	Among a cohort of 544 admitted patients, the 179 patients who received TCZ revealed beneficial effects of TCZ (8mg/kg IV and 162 mg SQ) in the reduction of both invasive mechanical ventilation (IMV) and death in patients with severe COVID-19 (AHR O.61, 95%CI 0.4-0.92; P=0.02).	Good
USA[130]	Retrospective cohort study	Np=28/Nc=23	An American cohort of 51 hypoxic COVID-19 patients revealed that TCZ 8 mg/kg was associated with a significantly shorter duration of vasopressor support. Although not significantly, TCZ reduced the time of clinical improvement and the duration of IMV.	Good
Qatar[131]	Retrospective cohort study	N=25	TCZ was associated with a dramatic decline in inflammatory markers, radiological improvements (68% by day 14), and reduced ventilator support (P= 0.001) requirements. 36% discharged from ICU by day 14.	Fair
Turkey[132]	Retrospective cohort study	Np=21/Nc=22	Earlier use of TCZ was beneficial for survival, length of admission, and oxygen support. 3 of 21 cases who received TCZ were transferred to ICU, and none of them died.	Fair
Poland[133]	Retrospective, multi-center study	N=28	TCZ controlled the symptoms of 28 severe COVID-19 patients by reducing inflammatory responses and rapidly improving the clinical status and lung changes in most patients (P<0.001). Only 2 (7%) patients died.	Fair
USA[134]	Retrospective cohort	Np=78/Nc=76	Preprint: TCZ 8 mg/kg (1-2 doses) among 78/154 mechanically ventilated patients with COVID-19 was associated with a decreased likelihood of death despite the higher superinfection occurrence.	Good
Italy[135]	Observational cohort	Np=62/Nc=23	62 patients received TCZ 400-800 mg IV or 324 mg SQ; (based on availability) with a significantly greater survival rate compared to the control patients (HR of death,0.035; 95% ci, 0.004-0.347; P=0.004). The respiratory function improved in 64.8% of the TCZ group while 100% of controls needed MV.	Good
USA[136]	Multicenter, retrospective cohort	N=145	A retrospective study of 145 COVID-19 patients. Near 85% of cases received one dose of TCZ. It was effective in decreasing MV (P=0.002) and mortality (P<0.001), especially when instituted early in the management of critically ill patients	Fair
Spain[137]	Multicenter Cohort Study	Np=261/Nc=969	A total of 1229 and 10673 persons/ days were analyzed. TCZ was associated with a lower risk of death (AHR 0.34, 95%CI 16%-72%, P=0.005) and ICU admission or death (AHR 0.38, 95%CI 19%-81%, P=0.011) among patients with higher CRP levels (>150 mg/dl).	Fair
Italy[138]	Retrospective cohort.	Np=21/Nc=21/ N=112	TCZ did not reduce ICU admission (OR 0.11,95%CI; 0.00-3.38; P=0.22) or mortality	Good

	Preliminary Results from SMAtteo COvid19 REgistry (SMACORE)		rate (OR 0.78,95%CI; 0.06-9.34; P=0.84) among 21 patients compared to SOC.	
Italy[139]	retrospective cohort study	Np=32/Nc=33	In a retrospective cohort of 65 patients with severe COVID-19, 32 patients were treated with TCZ. On day 28 the clinical findings and mortality rate were not statistically different between the groups (P=0.15).	Good
Italy, Canada, Denmark, UK, USA, Spain, France, Germany ,Netherland[140]	Double-blind, placebo-controlled trial	Np=294/Nc=144	A new trial as COVACTA, which was conducted by Roche, did not meet its primary endpoint of improved clinical status	Good
Italy[141]	retrospective cohort study	N=457/Np=78	Hyperglycemia had negative impacts on TCZ therapy in both diabetic and non-diabetic patients. TCZ, in hyperglycemic, did not attenuate the risks of the severe outcome as did in normoglycemic cases (p<0.009).	Fair
China[142]	Case report	N=1	A 60-year-old male on maintenance therapy for multiple myeloma was admitted with severe COVID-19. He received TCZ and after 3 days chest tightness improved. Finally, a Chest CT scan cleared after 10d and he was discharged.	Poor
France[143]	Case report	N=1	A 42-year-old male with metastatic sarcomatoid clear cell renal cell carcinoma, after two doses of TCZ alongside antivirals and SOC, experienced clinical improvement.	Poor
China[144]	Case report	N=1	A 57-year-old man, despite multi-drug receiving finally received TCZ and gradually improved and was discharged.	Poor
Italy[145]	Case report	N=1	A 54-year-old obese male with COVID-19 and severe respiratory insufficiency whose condition worsened despite antivirals and non-invasive ventilation was successfully treated with TCZ and NIV.	Poor
Turkey[146]	Case report	N=1	A 41-year-old woman with a history of HTN, presented with COVID-19, and after 3d of deterioration, she was given TCZ 400mg/d and methylprednisolone 60 mg/d, and on day 10 improved dramatically.	Poor
UAS[147]	Case report	N=1	A-56-year-old male with ESRD-secondary to IgA- nephropathy undergoing maintenance hemodialysis for 3 years have reported, who developed COVID-19 pneumonia and	Poor

			gastroenteritis. He was successfully treated with HCQ+TCZ+SOC.	
UAS[148]	Case report	N=1	A-68-year-old man with COVID-19 who was initially treated with HCQ and lenzilumab, deteriorated with respiratory symptoms and an increase in inflammatory markers. He was subsequently treated with TCZ, with significant clinical improvement and a decrease in CRP within 48 h.	Poor
UAS[149]	Cautionary case report.	N=2	Radbel et al. have presented 2 cases of COVID-19 induced CRS with elevated IL-6 and progression to HLH. Both developed poor outcomes despite TCZ treatment.	Poor
Switzerland[150]	Case report	N=1	In a 57-year-old woman with systemic sclerosis who developed COVID-19, the treatment with TCZ led to good control of both scleroderma and arthritis. 4 weeks after the last TCZ infusion, the patients presented with COVID-19. Albeit, this case presented with mild symptoms, that may be due to prophylactic effects of TCZ.	Poor

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 6. Studies investigating biologics (**IL-1**- inhibitors) in CoV-2 (Continued)

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
France[152]	Retrospective cohort Study	Np=52/Nc=44	Both groups received SOC. Anakinra: 100 mg SQ BID×3d, followed by 100 mg/d×7d reduced both the need for invasive MV in ICU and mortality(P<0.0001), without significant side-effects.	Good
Italy[153]	Retrospective cohort study	NP=29/Nc=16	All cases had moderate to severe COVID-19. Only the high dose of anakinra (5 mg/kg. IV twice a day) was effective, with a reduction in CRP, a progressive improvement in respiratory function, and survival (P=0.009).	Good
USA[154]	A small retrospective Case Series	N=14/Np=11	Anakinra could be beneficial in CRS when initiated early after the onset of acute hypoxic respiratory failure	Fair
Greece, Netherland[155]	Case series	Np=8/Nc=29	8 severe COVID-19 cases in Netherland with HLH were given anakinra. This led to less need for vasopressor, significant improvement in respiratory function, and lowered H-Score. Although 3 patients died, it was less than historical controls.	Fair
France[156]	Case series	N=9	A single-center small case series of 9 hospitalized patients, revealed a reduction in O2 need, CRP, and CT-Scan findings	Fair
France[157]	Retrospective cohort	Np=12/Nc=10	They retrospectively compared 22 patients in France with stages 2b and 3 COVID19-pneumonia presenting with acute severe respiratory failure and systemic inflammation who received SOC (n=10), or SOC+ anakinra (n=12). Treatment started with 300mg/d^{-1} for 5d, then tapered in 3d. All the patients in the Anakinra group improved clinically (P<0.01), with no death, significant decreases in O2 need (P<0.05), and more days without IMV (P<0.06), compared to controls.	Fair
Italy[158]	Case report	N=1	A 57-year-old man presented with severe COVID-19. Despite administration of Lopinavir/ ritonavir, HCQ+ azithromycin, the respiratory status deteriorated. Treatment with anakinra 100 mg.q6h.SQ ×7 d was introduced. He improved dramatically and was discharged in good condition.	Poor
Italy[159]	Case report	N=1	A 50-year-old healthy man with COVID-19 who was admitted in ICU received off-label anakinra 200 mg IV followed by 100 mg SQ, QID, due to contraindication of TCZ and remdesivir for hepatic involvement. A sharp reduction of inflammatory markers and liver enzymes happened and respiratory parameters	Poor

			improved by day 13, followed by a favorable radiological evolution	
Turkey[161]	Case report	N=1	Anakinra was useful in a 33-year-old man with COVID-19 and pericarditis.	Poor
Italy[162]	Retrospective cohort study	N=10	A retrospective analysis of 10 patients with COVID-19, and respiratory failure, canakinumab, 300 mg. SQ. was safe and associated with a rapid reduction in the inflammatory response and oxygen requirement	Fair

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 6. Studies investigating biologics (**JAK**- inhibitors) (continued)

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.

Supplementary Table 6. Studies investigating **biologics** (JAK and TNFα- inhibitors) in CoV-2 (continued)

Study country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
China[164]	RCT	Np=20/Nc=21	Although no statistical difference was observed, ruxolitinib recipients had a numerically faster clinical improvement. Significant CT improvement (P=0.049) happened on day 14. No death happened in the ruxolitinib group.	Good
Italy[165]	RCT	N=17/Np=7	Ruxolitinib 10 mm BID for 14d, and eculizumab showed significant improvement in respiratory symptoms and radiologic lesions and a decrease in D-dimer levels.	Fair
Italy[166]	Retrospective cohort study	N=191/Np=113	The 2-week case fatality rate was significantly lower in the baricitinib-arm (0 vs 6.4%, P=0.01). ICU admission was 1/113 vs 14/78 (P=0.019) in week-1. The discharge rate was significantly higher in the baricitinib arm at week-1 (P=0.039).	Good
Italy[167]	pilot study	N=12	A pilot study of 12 hospitalized patients with moderate COVID-19 was conducted. Baricitinib tablets added to ritonavir/lopinavir therapy. In the baricitinib-treated group, all clinical characteristics and respiratory functions improved, and CRP levels decreased at week1 and 2 compared to baseline. Discharge in week 2 occurred in 58% of the treated group vs 8% of controls	Fair
Germany[168]	Monocentric, retrospective cohort	N=105/Np=14	14 patients received ruxolitinib due to inflammatory score (CIS) $\geq$ 10 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	Fair
China[169]	Multicenter, single-blind, RCT	Np=22/Nc=21	Severe COVID-19 patients receiving ruxolitinib+ SOC (22/43) had a faster clinical improvement and a more favorable safety than controls.	Good
USA[170]	prospective case series	N=86/Np=62	A prospective case series involving patients with immune-mediated inflammatory diseases who were receiving anti-cytokine biologics, other immunomodulatory agents conducted when developed to COVID-19. 86 cases were enrolled, while 62 of them were receiving biologics or JAK-inhibitors. A smaller proportion of hospitalized patients were taking JAK inhibitors or biologics (76%), but not with a significant difference. They conclude that despite the small sample size, the baseline use of biologics and JAK	Fair

			inhibitors are not associated with worse outcomes.	
Study Country	Type of study	Number of patients (Np)/ Number of controls (Nc)	Investigations and Outcomes	Quality (Assessment of bias)[1]
Italy[171]	Observational, longitudinal trial	Np=20/N=76	Baricitinib 4 mg BID for 2d, then 4mg/d for 7d, demonstrated a marked reduction in serum levels of IL-6, IL-1β, and TNFα, rapid recovery in T& B cell frequencies and an increased Ab-production against SARS-CoV-2 spike protein, reduction in the need to O2.	Good
USA[172]	Multicenter, retrospective cohort	NP=11/N=15	Baricitinib + HCQ was associated with recovery in 11/15 COVID-19 cases. 86.7% of patients had a significant reduction in body temperature and CRP levels, representing 80% survival at the end of the study, with 3 death.	Fair
Italy[174]	Case report	N=1	A 50-year-old man with a previous history of non-Hodgkin lymphoma that was in remission was admitted with COVID-19. After that with severe illness and moderate ARDS baricitinib tablets 4 mg/d was started. Nevertheless, he worsened, with a high IL-6 level of 191 pg/ml. So, CS1mg/kg and TCZ 8mg/kg IV were given, with a drop in IL-6, and he gradually improved in both clinical and CT-scan findings.	Poor
Italy[175]	Case report	N=1	A 71-year-old woman with respiratory failure due to COVID-19, with insufficient response to antiviral, HCQ, and TCZ; treated successfully with baricitinib 4mg/d × 2 week (both respiratory symptoms and CT-Scan findings).	Poor
Italy[176]	Case report	N=1	A favorable course of COVID-19 was observed in an 87-year- old woman despite the underlying RA, while she received baricitinib from 1 year before. This allows speculating that baricitinib had a positive impact on the outcome	Poor
Sout Korea[180]	Case report	N=1	A 53-year-old woman developed COVID-19 during treatment with etanercept and methotrexate for Ankylosing Spondylitis. He had a loss of smell and taste at this time, suggesting that TNFα-inhibitor can delay in dysfunction of smell and taste.	Poor
France[181]	Case report	N=1	The use of Etanercept prior to COVID-19 was not associated with a severe evolution of the COVID-19.	Poor
Germany[182]	cautionary case series	N=7	7 critically ill COVID-19 patients were treated with a single 5 mg/kg infliximab between 0-3 days. A rapid decrease of pro-inflammatory cytokines, and CRP, and LDH was observed, along with clinical improvement in 6 of 7. The 17 cases of the	Fair

			control group showed 35% mortality and prolonged inflammation.	

[1]Assessment of risk of bias using NHLBI tool: Good if they fulfilled 60-100% of the tool items, Fair if 50-59% or Poor if 0-49%.