

Anti-inflammatory, immunomodulatory agents as potential strategies against COVID-19: A systematic review

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Abstract

Aim: SARS-COV-2 infections are causing substantial morbidity and mortality, especially due to “exuberant cytokine storm”. In this study we review effectiveness of anti-inflammatory and immunomodulatory drugs in this situation. **Methods:** Ovid MEDLINE, PUBMED, Google Scholar and Cochrane library searched for anti-inflammatory and immunomodulatory drugs against COVID-19 including: Anti malaria agents, non-steroidal anti-inflammatory drugs, steroids, cyclosporine, thalidomide, IVIG, interleukin-6 blockade, IL-1 blockade, tumor necrosis factor- α blockade, and Janus kinase inhibitors. **Results:** We included 95 studies. Unlike preliminary positive results, the effect of Chloroquine is questionable. Thalidomide has been shown to be effective in some studies but not be proved yet. Low dose Corticosteroids may be effective in the early phases of SARS-CoV-2 as a bridge. There is neither evidence of benefits or adverse outcomes for the use of NSAIDs, nor is there evidence indicating that target therapies (IL-1, TNF α and JAK inhibitors) and also cyclosporine are effective. In some cases and clinical trials, interleukin-6 blockade is useful in critically ill patients. Finally, the high dose IVIG reversed the deterioration of patients in most clinical trials. **Conclusion:** Unlike preliminary positive results, Hydroxychloroquine seems ineffective. Thalidomide is effective in some cases. Although, low dose CS may be effective in the early phases of illness, administration of NSAIDs and steroids is controversial. The effectiveness of more target therapies including IL-1, TNF- α , and JAK inhibitors, also cyclosporine is less clear. Tocilizumab can be used in severe situations, where other drugs are ineffective. IVIG can be used at least as a bridge therapy in deteriorating patients.

Introduction

The emergence of the novel coronavirus (nCoV-2), which causes severe respiratory infections, has become a global health concern [1]. About 80% of patients’ experience mild to moderate disease and fatality rate is about 2.3% [2]. As disease progressed, a series of complications tend to develop, it is important to consider both the severity of disease and response capacity of health systems in the management strategies. At this setting, also for decision to hospitalization, bacterial colonization and secondary bacterial infections should be considered [3-5]. Given the rapid spread of COVID-19 and high mortality of severe disease, understanding the disease immunopathogenesis and inflammatory response is obligatory. According to the evidence, the SARS-COV-2 enter cells via receptor mediated (probably ACE2) endocytosis [6]. After recognition of virus by TLRs, signaling pathways activate NF- κ B and then pro-inflammatory cytokines. The initiation of immune response is through some cytokines like IL-1 β and TNF α [7, 8]. Recently, structure analysis of the spike protein of CoV-2 showed that this protein binds weaker to the ACE2 receptor on human cells [9], so probably several mechanisms are involving in pathogenesis, both environmental and cell entry. A cytokine profile like hemophagocytic lymphohistiocytosis (sHLH) is associated with COVID-19 severity [10]. Hyper inflammatory state including elevated IL-6 and ferritin are predictors of fatality [11].

Due to complexity of pathogenesis, as of this time, there is no effective antiviral treatment, so several potential rheumatic drugs as anti-inflammatory and immunomodulatory agents are candidates [12, 13].

Although, there have been no significant relapses of rheumatic disease in SARS-CoV-2 infection [14], the relation between them and viral infectious is very complex and even, a simple scenario of fever and arthritis may be challenging to differentiate between infectious and reactive arthritis [13,15]. These relatively low relapses, along with the historical background of using the rheumatic drugs in infectious diseases [12], justifies the hypothesis of their use in COVID-19.

This review focuses on the effects of some proposed rheumatologic drugs as their anti-inflammatory and immunomodulatory effects while ignoring or paying attention to some of their immunosuppressive effects.

Methods

Study Design

We aimed to include all scientific papers without limitations, which evaluated the anti-inflammatory, immunomodulatory agents against COVID-19. We excluded public health agencies or institutes recommendations because their frequent renewal. The PRISMA guideline was followed for study design, search protocol, screening and reporting.

Search strategy

A systematic review carried out with searching OVID MEDLINES, PUBMED, Google Scholar and Cochrane library databases from inception up to April 8, 2020 and updated on April 12, 2020. No language and status (abstract or full text) limitation were imposed. The following terms used in titles, abstracts and keywords: “COVID-19”, “SARS-CoV-2”, “Coronavirus”, “2019-nCoV infection”, “2019-nCoV disease”, “2019 novel coronavirus disease”, “MERS-CoV”, “SARS-CoV”, “severe acute respiratory syndrome”, and “anti-inflammatory agents”, “immunomodulatory agents”, “antiviral agents”, “cytokine storm”, “inflammatory state”, “drugs”, “treatment”, “Antimalarial”, “Chloroquine (CQ)”, “Hydroxychloroquine (HCQ)”, “NSAIDs”, “Glucocorticoids”, “Thalidomide”, “Cyclosporine A”, “TNF α blocker (inhibitors)”, “Tocilizumab”, “interleukin-6 (IL-6) blocker”, “Janus kinase (JAK) inhibitor”, “anakinra”, “IL-1 blocker”, “cyclosporine”, “IVIG”.

Appraisal of the selected articles

Two authors and one high experienced librarian, extract articles independently, by providing information on the efficacy and safety of anti-inflammatory and immunomodulatory drugs in COVID-19. The first step consisted in the screening of titles and abstracts of all retrieved references and then proceeded to cross check the results. Due to rarity, we increased the references with using an additive snowballing technique. So additional relevant articles were identified.

Results

The initial search identified 521 results among total 1389 sources, of which a total of 95 relevant articles deemed suitable were included for 10 drug groups separately including, CQ and HCQ (21), NSAIDs (9), Corticosteroids (20), Thalidomide (7), IVIG (8), Cyclosporine (7), IL-6 blockers (11), IL-1 blocker (4), JAK-inhibitors (4), and TNF blockers (4). In addition, 14 recommendations including one national guideline recommendations alongside expert consensus were included. We excluded public health agencies or institutes recommendations because their frequent renewal. We did not enter ongoing clinical trials and systematic reviews.

Antimalarial agents (CQ and HCQ):

Both immunomodulatory agents have been used in auto-inflammatory and Rheumatic diseases (e.g. Lupus, RA). They inhibit chemotaxis, nitric oxide production and phagocytosis. Also, may antagonize the action of prostaglandins (PGs), interfere with production of IL-6, IL-1, INF γ and TNF α , and has antagonistic effects upon TLR7/9 [16, 17].

Studies: In vitro studies have suggested that CQ inhibits replication of MERS and SARS-CoV [18, 19]. Moreover, two studies revealed that these broad spectrum effects occur by both increasing endosomal pH

and blocking replication; also, interfering with glycosylation of ACE-2 receptors of SARS-CoV [19, 20]. Moreover, the effects of CQ has been found during post entry stages via inhibition of viraPLpro [21].

One study revealed that QC can inhibit nCoV-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 [22]. Liu et al., found a similar CC50 for two drugs, but EC50 was more for HCQ than CQ [23]; Also, Yao et al., found that HCQ (EC50=0.72 μ M) is more potent than CQ (EC50=5.4 μ M) for virus inhibition [24]. Gao and colleagues revealed a significant improvement in the course of COVID-19 pneumonia and images focus of more than 100 patients with using CQ [25]. Another cohort of 62 patients revealed similar results with additional using of HCQ (400 mg/d for 5-days) [26]. An open-label non randomized controlled trial showed that HCQ (600 mg/d for 10 days) reduces viral load in most COVID-19 patients specially in combination with azithromycin [27]. There are several issues with this study, including small sample size, lack of randomization, no qRT-PCR data and drop out of multiple HCQ treated patients who clinically deteriorated. In a cohort of 30 patients while one group were given HCQ 400 mg per day for 5 days and the other group were given only conventional treatment; no significant differ were found in clinical end points [28]. Sahraei and colleagues suggested that HQ is preferred due to less adverse effects and availability [29]. In contrast, in a recent cohort of 63 hospitalized CoV-2 patients, HCQ was associated with an increase need for escalation of respiratory support [30]. Also, a prospective study of 11 hospitalized patients reported no benefits from using HCQ and azithromycin [31]. In a parallel, double blind, randomized trial, high dose CQ (600 mg BID for 10 days, or a total dose 2.7 g) was with higher QT prolongation and fatality than low dose (450 mg BID stat and then daily for 5 days). Overall fatality had no difference with similar non treated patients [32].

Some has suggested that CQ can administered with a dose of 500 mg twice a day for 7-10 days [33, 34], additionally, it can administer for prophylactic effects [35-37]. Also, HCQ can administer at a dose of 400 mg BID stat, then 200 mg BID [24], or with an alternative dose of 600 mg daily in another recommendation [38].

Dong et al, also recommended like the national health commission of China (NHC) that published on March 3, 20. It suggested to treat patients with CQP (500 mg BID, first and then daily) for 3-7 days [39, 40]. Nicastry et al. published similar recommendation with HCQ 400 mg (or CQ 500 mg) daily in combination with antivirals [41].

All previous studies have some limitations.

Although in a new cohort, HCQ was associated with an increased risk for escalation of respiratory support; the use of CQ and HCQ should be adhere to MEURI frame work. For ethical reasons and due to first results, alongside scatter experiences, the authors suggest using these drugs as therapeutic agents and even for prophylaxis especially in health workers.

Systemic corticosteroids (CS) :

CS reduce inflammation by inhibition of arachidonic acid, IL1, TNF α and NF- κ B. Their effects on immune system mediated mainly via T cells [16].

Studies: No in vitro studies were found on cytopathic effects of them alone against SARS-COV. Early studies have shown that inhibition of inflammation improved the outcomes in animal models infected with, SARS and MERS [42, 43]. Some other previous studies have shown that CS for treatment of SARS and MERS CoVs were associated with prolonged viremia and worse outcomes [44-46]. In another study, in the CoV infected pigs, prolonged administration of dexamethasone enhanced viral replication [47]. In a 2019 meta-analysis of CS using in SARS patients, four studies indicated harm effects including diabetes, psychosis, Avascular necrosis (AVN) and prolonged viremia [45, 48-50]. A review of patients with SARS of any cases revealed that, insufficient evidence exists to recommend the use of CS [51]. High dose CS in early stage of SARS-CoV had beneficial effects in two cohorts [52, 53]. In a retrospective cohort of patients with SARS- CoV and sepsis, CS in 147 of 249 noncritical patients, reduced mortality and duration of admission, whereas 121 of 152 critical patients received CS and 25 patients died [54].

In this regard, a Cochrane review revealed an overall association between CS using and increased mortality in influenza patients, although the association among patients with CoVs was unclear [55].

In contrast, at least in two studies, CS were associated with lower duration of admission in COVID-19 patients [56, 57]. Wong Y et al., reported 46 patients with COVID-19 that reduced their symptoms and chest CT-scan results with 5 to 7 days methylprednisolone [58]. Also, in a retrospective cohort of 201 COVID-19 patients, CS was associated with lower mortality rate [59]. Zhou and colleagues, reported that moderate dose CS plus Intravenous Immunoglobulin (IVIG) significantly reduced lung injury [60]. Contrariwise, one study with a total 416 COVID-19 patients revealed that CS increased the mortality rate and appeared to be useful only in the cases with lymphopenia [61]. Although, CS have been used in combination therapies in three other case studies of 278 patients with COVID-19, their effects and adverse effects remain unclear [3, 62, 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 another cohort, as a preprint yet, 11 of 31 COVID-19 patients who received CS within 24h of admission, had more complains and radiological abnormalities, that revealed CS was related to the presence of more symptoms at early presentation [65]. In contrast, analyzing of 89 existing MERS, SARS-CoV and SARS-CoV2 suggested that CS may be beneficial in the early acute phase of infection [66]. Nevertheless, clinical use of CS for SARS-CoV2 pneumonia with the interaction of regulatory cytokine production and avoiding lung injury should be avoided [67, 68], and may stimulate the hypothalamic axis, drive lymphopenia and promote the inflammatory responses [69].

Zheng et al., described a couple that treated with methylprednisolone and IVIG in addition to antiviral drugs successfully [70]. Also, Chen et al., reported a 45 years old woman who treated with Thalidomide and methyl prednisolone [71].

In two guidelines that published on March, 2020 for critically ill patients, in adult receiving mechanical ventilation who do not have ARDS, routine use of CS is suggested against (weak recommendation, LQE). In those have ARDS, use of CS is suggested (weak recommendation, LQE) [72, 73]. Also, NHC (7th version) recommended low dose CS in a short time for deteriorating patient [40].

Thereafter, the use of CS, is still questionable, because of potential inhibition of viral clearance, increasing the duration of viremia and some evidence of disease progression. CS may be beneficial in the early acute phase of illness especially in low dose. Also, CS might serve as a bridge [74] to more specific antiviral therapies for covid-19. Although, its use in severe septic shock is doubtful, In HLH and hyper inflammatory storm may be more useful in an adequate point.

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 up regulated at sites of inflammation by IL-1, TNF α , endotoxins and growth factors [16].

Studies: Experience from in vitro studies for the use of NSAID, on COVID-19 is lacking. An in vitro study revealed that Ibuprofen and Naproxen, inhibited Ab production at pharmacologic doses [75]. A dramatic antiviral effect of Indomethacin was found in a model of feline coronavirus infected cells, also against Canine-CoV, by inhibiting virus replication and protecting the host cell from virus induced damage [76]. Also, one study [77] discussed on crucial mechanism of broad-spectrum anti-influenza virus activity of Naproxen including binding to nucleoproteins, both in vitro [78], and in vivo in animal model [79] assigned to nCoV. Antiviral efficacy of Indomethacin was determined by evaluating virus titers in CoV-infected dogs; also in one human study [80, 81]. Concerns about Ibuprofen seem to be from increasing an over expression of ACE2 in diabetic rats and diabetic patients [82, 83]. So, this effect may worsen the clinical course and even susceptibility to COVID-19 infection theoretically [84]. Also, concerns about Ibuprofen invigorated from an unpublished idea of a French physician who indicated that four patients with COVID-19 after using NSAIDs developed severe illness [85]. 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 [85, 86].

A clinical review of chemotherapeutic strategy for severe COVID-19 pneumonia, pointed that Celecoxib and Thalidomide can modulates $\text{I}\kappa\text{B}\alpha$ degradation and phosphorylation [87]. A team of King's College analyzed 89 existing studies cause by SARS viruses including SARS-CoV-2, and found no evidence for or against the use of NSAIDs [66].

Totally, till this moment the most comprehensive data is from analyzing of 89 existing studies. The researchers found no evidence for or against the use of NSAIDs in COVID-19 patients. While, we have more effective repositioning drugs, the use of NSAIDs is not rational.

Thalidomide:

This major teratogen agent has been used due to antiemetic, analgesic, anxiolytic and sedative properties or in template of some malignancies, autoimmune and infectious diseases [16]. It suppresses activated NF- κ B that promote $\text{TNF}\alpha$ production. Also, inhibits phagocytosis, chemotaxis, and reduces the expression of $\text{TNF}\alpha$, IL-1 β , and IL-6 mRNA [16, 88].

Studies: One study revealed that Thalidomide decreases the expression of IL-1 β and IL-6 in human epithelial cells, so may helpful in preventing emphysema [89]. It can reduce the HIV replication by $\text{TNF}\alpha$ in human macrophages in vitro [90]. Moreover, it may express immunomodulatory effects in cell cultures, especially in combination with Celecoxib and suppress the production of $\text{TNF}\alpha$ and IL-8 via inhibition of NF- κ B [87]. Anti-inflammatory effects of Thalidomide in an animal model showed that it decreased production of IL-1B, IL-6, $\text{TNF}\alpha$, and TGF β [91]. It attenuates inflammation, oxidative stress and pulmonary fibrosis in mice lungs [92]. Also, Antifibrotic effects against bleomycin induced pulmonary fibrosis, were seen in rats [93]. In H1N1 influenza induced pulmonary injury in mice thalidomide dramatically inhibited the activated P-NF- κ B p6 and reduced the inflammation [94]. However, the beneficial effects of Thalidomide (100mg/day) in combination with low dose CS were shown in a 45 years old woman with COVID-19 [71].

Briefly, Thalidomide in addition to its ability to inhibit cytokine surge, and immunomodulation effects, could be helping the patients to reduce oxygen consumption, and relieve digestive symptoms in COVID-19 patients. So, may shed new light as a subsidiary treatment strategy. In combination with low dose CS, it clearly reduces the pulmonary symptoms and shorten the hospital stay. However, it is not able to deal with the very severe symptoms. Therefore, despite lack of strong evidence from large studies, we suggest it in the setting of treatment, from mild to severe cases in combination with other drugs, at this time.

Intravenous Immunoglobulin (IVIG):

IVIG is prepared from pooled human plasma. It administers mainly for autoimmune and auto inflammatory conditions and recently has been used as an anti-infectious agent [1, 95]. Its Fab mediated functions include suppression of cytokines, auto antibodies and complements, targeting of specific immune cell surface receptors, expression of Treg cells by induction of COX2 dependent PGE2 in Dendritic cells, and blockade of leukocyte adhesion molecule binding. Also some FC dependent activities include blockade of Fc- γ receptor (Fc γ R), FcRn and immunomodulation by salivated IgG [95, 96].

Studies: IVIG has been used as an anti-infectious in experimental models [97, 98]. Pyrc et al. showed that human sera from healthy people inhibited HCoV-NL63 infection. Moreover, they reported that IVIG can also neutralize H-CoV-NL63 [99]. In another study, IVIG that obtained from donors with higher Abs against RSV had significant potential to improve the outcome of RSV infection in immunocompromised subjects, not only by controlling viral replication, but also by reducing damage to lungs [100]. A murine model of induced colitis revealed that IVIG reduced intestinal inflammation by suppression of IL6, also inhibited growing of some microorganisms in the gut of mice [101]. In previous studies of SARS and MERS, IVIG has exhibited various clinical benefits [102, 103]. The clinical data of 10 patients with COVID-19 receiving short term corticosteroid (160 mg/day) plus IVIG (20 gr/day) were conducted. This combination significantly reduced SpO₂, lung lesions and normalized ALC and CRP levels [60]. Also administration of the high dose IVIG reported on 3 patients with COVID-19. It started just at the time of initiation of respiratory distress, with

significant improvement in clinical symptoms and radiological findings [104]. Contrariwise, in one study with a total 416 COVID-19 patients that received CS and concurrent IVIG, the use of IVIG was not rescuer [61]. Zhang et al., described a couple that treated with methylprednisolone and IVIG successfully [70].

However, the efficacy of IVIG would be better if the immune IgG Abs will be specific against COVID-19 by boosting the immune response in newly infected patients, especially when it collected from patients recovered from COVID-19 in the same city or surrounding area [1].

IVIG seems to be golden 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 lungs.

Cyclosporine (CsA):

CsA has had a major impact on prevention of solid organ transplant rejection. Also, has potential effects for treatment of immunologically mediated diseases. CsA inhibits calcineurin, so inhibits the early phase of T cell activation and IL2-4, IL15 and INF γ production, and may modulate anti-inflammatory effects by inhibiting of NF- κ B [16].

Studies: Although Low micromolar, non-cytotoxic concentration of CsA strongly affected the replication of some viruses in cell culture, more concentration is need to block coronaviruses; suggesting that coronaviruses are less sensitive to CsA treatment [105]. CsA is considered as interaction partner of SARS-CoV N-protein [106]. It might exert its effect by inhibiting cyclophilin or even direct inhibitory effect on virus function [107]. It has been reported to inhibit the replication of HIV, vesicular stomatitis virus (VSV), HCV and influenza-A [108-111], but in vivo studies on CoVs family especially CoV-2 infection is required. The patients who fulfill the HLH criteria may benefit from the use of related chemotherapeutic agents like CsA [10, 62].

We cannot suggest CsA as a first line therapeutic agent at this time, but it should be noted that it can be prescribe in HLH as a potentially effective drug.

IL-6 blockers:

Tocilizumab is a humanized monoclonal Ab to the soluble IL-6 receptor that can inhibit intracellular signaling that originates from IL-6. It administers in some auto-inflammatory and autoimmune diseases [95]. Since IL-6 and GM-CSF are key cytokines, which may result in lung injury [112], tocilizumab might be have therapeutic role for severe and critical COVID-19 [113].

Studies: The findings suggest that overexpression of IL-6 and IL-2R are useful for estimating the severity of COVID-19 [114]. At least two animal models have been shown association between IL-6 level and SARS-CoV severity [115,116]. In contract, there was no significant difference in cytokine levels in the presence of SARS symptoms in 14 adult CoV patients [117]. This discrepancy has been justified in some studies with delayed inflammation [118], Imbalance between LI-6 and IL-10 [119] or the presence of another mechanism, such as gamma interferon related cytokine storm [120]. At least, it has been shown that 4 potential CoV therapeutic target (ADAM17, DUSP1, P38MAPK, GU-rich ssRNA) are related to IL-6 regulator [69,121,122]. In a review of 69 severe patients with COVID-19, the base line IL-6 was related to the maximal body temperature, CT findings and also related to the high base line levels of CRP, LDH, Ferritin and D-dimer. After treatment with drugs other than tocilizumab there was a marked decrease in IL-6 level and chest CT findings [123]. In another cohort, 21 patients with severe or critical criteria of nCoV pneumonia enrolled. All patients received tocilizumab (400 mg. once) in addition to routine therapies. Within a few days, all symptoms improved and high percentage of laboratory (including CRP, ALC) and CT scan findings decreased significantly. Finally, 19 (90.5%) patients have been discharged on average 13.5 days after receiving tocilizumab [113]. A 65 years old male on a maintenance therapy for multiple myeloma admitted with severe COVID-19. He received tocilizumab and after 3 days chest tightness improved. Finally, Chest CT scan cleared after 10 days and discharged [124].

It is recommended that in patients with extensive lung lesions and severe illness with increased IL-6,

tocilizumab can be administered for 1-2 dose [40].

Generally, the results are promising and tocilizumab has been used especially on severe and critical cases with beneficial effects. Because the peak level of IL-6 is associated with severity of pulmonary complications, tocilizumab can be used in this situation, where other drugs are ineffective. More studies are needed to determine that this target therapy has beneficial effects.

IL-1 blockade:

Anakinra is a human recombinant form of IL-1R α . It prevents the interaction of the receptor with IL-1 and subsequent signaling. Thus, it uses in R.A, some auto-inflammatory disease (e.g., S.JIA, CAPS) and HLH [95]. The nCoV might be bind to TLRs which activate production of pro IL-1 that mediates the inflammation of lungs, fever and fibrosis [8].

Studies: Although one study showed no difference in IL-1 β levels in patients with COVID-19 in any severity and general population [114], some others have been shown the beneficial effects of steroids in reducing IL-1 in SARS patients [53,125]. One animal model has been shown beneficial results for an IL-1 receptor antagonist in rat [126].

All patients with COVID-19 should be screened for hyper-inflammation, using laboratory tests and H score for needing to immunosuppressant like anakinra and tocilizumab [10,127].

Overall, large studies are need to evaluate the efficacy and safety of anakinra, as a target therapy. At this time, we suggest it, only in the situation of inflammatory storm that 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 has yield promising results in many systemic, cancerous and cutaneous disease [95].

Studies: No published clinical trial evidence for JAK inhibitors as a treatment for COVID-19 is available at this time. But, one study suggested that baricitinib has potential beneficial effects to reducing both viral entry via receptor and also inflammation in COVID-19 [128]. A retrospective in vitro study using past SARS-COV and MERS-COV data reported that, baricitinib has shown no inhibitory activities against SARS-COV-2 at concentration of 3 μ M or 3.2 μ M [129]. The combination of sunitinib and erlotinib display potent activity against HCV, Dengue virus, Ebola virus [130]. Another class, the cellular tyrosine kinase inhibitors (e.g. imitinib), inhibited replication of MERS and SARS-CoVs in cellular culture cells and reduced overall mortality in a mouse model [131].

Although, these group historically can reduce viral infectivity, viral replication and the aberrant host inflammatory state; at this time no imperative conclusion can be made on efficacy and safety of them on COVID-19.

TNF α inhibitors:

This group (e.g., Etanercept, Adalimumab) have been now proven in the treatment of some inflammatory and autoimmune conditions (e.g., RA, inflammatory bowel disease) [95].

Studies: These inhibitors produced a dramatic reduction of overall illness severity of virus-specific lung immunopathology in mice without interfering with viral clearance [132]. Etanercept has been reported to be effective for treatment of a non-infectious pulmonary syndrome like SARS pneumonia in one report [133]. A recent research letter suggested that, TNF α blockade could have a potential role to reduce the lung damage during SARS-CoV infection [134]. In contrast, Etanercept alone was not sufficient to ameliorate disease in the virus-endotoxin mediated model of respiratory disease in pigs [135].

In conclusion, due to elevated TNF α in SARS- CoV, the use of TNF inhibitors, has a potential role to suppress the inflammatory cascade and ameliorating the severe alveolar damage. Also, these group can modulate biologic responses that are mediated by TNF or even induce immunosuppressive Treg cells (especially Adalimumab). Nevertheless, there is no evidence indicating that TNF α blockade is harmful in COVID-19 patients, and also there is not strong evidence for the use of them. Studies utilizing TNF α blocker for CoV-2 infection would be prudent.

Conclusion

Despite the collective wisdom, decision-making about treatment of COVID-19 especially in severe condition is challenging problem. Howbeit, several anti-inflammatory, immunomodulatory repositioning drugs have been candidate, their definite effects are unknown, and each one belongs to a time situation; where CS may be useful in the early acute phase of infection especially in low dose, and IVIG may help for all patients with moderate to severe disease just when their pulmonary symptoms begin. Because the peak level of IL-6 is associated with severity of pulmonary complications, tocilizumab can be used in severe and critical cases with beneficial effects, where other drugs are ineffective.

Unlike preliminary studies, HCQ was associated with an increased risk for escalation of respiratory support. Never the less, for ethical reasons and due to first results, alongside scatter experiences, the authors suggest using these drugs as therapeutic agents and even for prophylaxis especially in health workers. Also, thalidomide may shed new light on an adjunctant treatment strategy for its potentially anti-viral effects. Therefore, despite lack of strong evidence from large studies, we suggest it in the setting of treatment, from moderate to severe cases in combination with other drugs. At this time, there is no evidence for or against the use of NSAIDs in COVID-19 patients. Using NSAIDs confronting to the virus function and replication does not logical when we have more effective and acceptable drugs. Also, we cannot suggest CsA as a first line therapeutic agent, but it should be noted that it can be prescribe in HLH as a potentially effective drug. Finally, large studies are need to evaluate the efficacy and safety of IL-1 and TNF α blockade as a target therapy. At this time, we suggest anakinra, only in the situation of inflammatory storm that IL-6 is not high or in HLH /macrophage activation syndrome. Although, JAK inhibitors, can reduce viral infectivity, viral replication and the aberrant host inflammatory state, historically; further in vitro and in vivo studies require to confirm their therapeutic effects.

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