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Review Article

Effects of colchicine, interferon β, IVIG, tocilizumab and corticosteroids on COVID-19 patient survival from all presently available published clinical trials: A narrative review

Kobra Bahrampour Juybari (PhD) [1]
Manzume Shamsi Meymandi (PhD) [2, 3]
Hamideh Bashiri (PhD) [2, 3*]

1. Immunogenetics Research Center, Mazandaran University of Medical Sciences, Sari, Iran
2. Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
3. Department of Physiology and Pharmacology, Afzalipour School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

*** Correspondence:**
Hamideh Bashiri, Neuroscience Research Center, Institute of Neuropharmacology, Department of Physiology and Pharmacology, Afzalipour School of Medicine, Kerman University of Medical Sciences, P. O. Box 76169 13555, Kerman, Iran

E-mail: bashiry_h@yahoo.com, H.bashiri@kmu.ac.ir
Tel: +98 3431325700

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Abstract

One of the deadliest diseases in the world, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the ongoing global pandemic known as COVID-19. COVID-19 symptoms range from undetectable to deadly, hyper-inflammatory response and the overproduction of pro-inflammatory cytokines or hypercytokinemia are key factors in the pathophysiology of severe COVID-19. However, no specific and effective treatment was available, anti-inflammatory drugs have been vastly used for treating patients. The goal of this narrative literature review (2020–2022) was to elucidate the connection between anti-inflammatory medications and COVID-19 outcomes, such as safety and survival rate. Overall, these studies are consistent in presenting that anti-inflammatory drug can be advised to target the host immune response in patients and have been beneficial in reducing the mortality rate. This is revealed in current recommendations from prominent global public health authorities, which support anti-inflammatory drug use for a decrease of cytokine storm during COVID-19.

Keywords: COVID-19, Colchicine, Interferon β, IVIG, Tocilizumab, Corticosteroids, Anti-inflammatory drugs

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The 2019-novel coronavirus disease (COVID-19) is a contagious acute respiratory disease caused by a new type of beta-coronavirus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) containing a non-segmented positive-sense RNA (1). The first known cases affected by COVID-19 infection were recorded in Wuhan, China in December 2019. It then spread at an alarming rate throughout the world to the extent that the World Health Organization (WHO) announced the breakout of COVID-19 as a pandemic on March 11, 2020 (2). The common symptoms of COVID-19 disease include fever and cough as the principal symptoms, difficulty breathing, excessive mucous production, sore throat, chills, fatigue, and headache much like the flu, rhinosinusitis, or a cold. Also, up to five percent of cases with COVID-19 manifest gastrointestinal signs such as throwing up and watery diarrhea (3-7). The syndrome most commonly occurs in elderly patients or those with primary health conditions such as chronic obstructive pulmonary disease (COPD), cardiovascular complications, diabetes, and hypertension. Other symptoms include coagulation dysfunction, metabolic acidosis, and septic shock which may result in death (5, 8-12). COVID-19 development can be separated into three different steps as follows: (1) early contagious stage, which is characterized by virus infiltration in the lung parenchyma of host cells, (2) pulmonary stage, which is associated with SARS-CoV-2 dissemination, pulmonary damage, and activation of host immune responses, and (3) a severe hyper-inflammation stage, which is initiated by molecular patterns accompanying with virus (i.e., viral RNA) and host-derived danger-associated molecular patterns (i.e., the release of cytosolic substances during pyroptosis) (13).

Exhibition of hyper-inflammatory response as a result of invasion of SARS-CoV-2 and excessive secretion of pro-inflammatory cytokines, which is also known as hypercytokinemia, explain the essential role of inflammation in the pathophysiology of severe COVID-19 (14). Systemic inflammatory syndromes are fatal to the hosts and caused by drugs, infectious and noninfectious diseases. It is characterized by fever, multiorgan failure, and, in a few cases, crystal-induced arthritis (15, 16) and is thought to be involved in the severe acute lung injury observed in the disease COVID-19 (17). Laboratory findings verify many immunological disturbances including: (1) increased levels of inflammatory factors such as interleukin (IL)-18, IL-6, and IL-1β and tumor necrosis factor (TNF-α) (18) (2) elevation of nonspecific biomarkers such as C-reactive protein (CRP), D-dimer, ESR, ferritin, and fibrinogen (19) (3) uncommon neutrophilia and lymphopenia (20, 21); neutrophil extracellular traps (NETs), which is released by neutrophils, are toxic to airway epithelial cells in vitro experiments (22) (4) NOD-LRR protein family and NLRP3 inflammasome (pyrin domain-containing protein 3) activation may play an important role in certain antiviral immune responses (23) (5) stimulation of B, T, and NK cells by activated IL-1β and IL-18 (24). Therefore, early recognition and appropriate clinical management are crucial to minimize of COVID-19-related mortality and morbidity (25, 26).

Finding medication with potent anti-inflammatory activities and beneficial effects against COVID-19 infection is one of the grand challenges that researchers have ever faced (2). These characteristics have led many researchers to consider the potential role and safety of some inflammatory agents such as colchicine (27), interferons (28), corticosteroids (29), tocilizumab (30), and intravenous immunoglobulin G (31) in the modulation of inflammatory cytokine storm induced by SARS-CoV-2 virus. On this subject, we sought to review and summarize the current findings of the possible mechanisms, efficacy, clinical outcomes, and safety concerns of some repurposed inflammatory agents that are being used in the management of cases hospitalized for moderate to severe COVID-19. In the event of such an emergency, collecting and summarizing the clinical trial data may provide new insights into understanding the outcomes as well as indicating promising therapeutic options.

Colchicine

Colchicine is an old and well-known anti-inflammatory alkaloid isolated from Colchicum autumnale (32), which has been traditionally used for more than 2000 years in herbal preparations to manage acute gout flares. Colchicine has Food and Drug Administration (FDA) approval for alleviation and prevention of acute gout and treatment of familial Mediterranean fever (FMF) in oral products (capsule/tablet/liquid). In addition, colchicine is used off-label for several clinical settings including Behcet's disease, primary biliary cirrhosis, amyloidosis, calcium pyrophosphate deposition disease (pseudogout), pericarditis, and other inflammatory conditions (33). Several reasons have been proposed to clarify the advantageous effects of this medication in the management of patients with COVID-19. Colchicine can influence a variety of fundamental cellular processes by preventing microtubule formation. The function of microtubules has been proven to be critical for coronavirus to construct intracellular vacuoles in vitro and cause infection (14). Colchicine may also prevent cell entry and replication of SARS-CoV-2, which are dependent on the microtubule network, by targeting tubulin polymerization. Furthermore, colchicine at low prophylactic concentrations can diminish the expression of selectins on neutrophils and endothelial cells, thereby preventing the adhesion of cytokine-mediated vascular endothelium to neutrophils induced by E-selectin (34). In patients with COVID-19, leukocytes such as neutrophils have a critical function in cytokine storm progression. The elevated levels of neutrophil-to-lymphocytes ratio (NLR) have been linked to poor prognosis and higher mortality in COVID-19-infected patients (35).

Additionally, colchicine can decrease the formation of pro-inflammatory cytokines by suppressing excessive NLRP3 inflammasome activation. Blocking inflammasome activation leads to a reduction in IL-1β production, which in turn inhibits the generation of TNF-α and IL-6 and subsequently reduces additional macrophage and neutrophil recruitment (13). Excessive cytokine levels can result in extensive lung damage, which has been observed in severe COVID-19-infected cases (36). Therefore, the potential role of colchicine in alleviating cytokine production may help to reduce increased mortality and poor prognosis in COVID-19-infected patients.

Colchicine in COVID-19 clinical trials

Despite having pleiotropic mechanisms of action, clinical trials have shown that colchicine may inhibit the development of moderate (inflammatory activation) to severe (hyper-inflammation) stages of COVID-19 infection. Colchicine is not an immune-suppressing drug and is less potent to lower cytokine storm compared to the biologic agents such as tocilizumab (anti-interleukin-6). However, the possible efficacy of colchicine is recommended to be elevated if it is administered in the early stage of COVID-

19 infection especially in advance of inflammatory activation, such as in cases with slight-to-moderate clinical presentation of COVID-19 (13). Several clinical trials were conducted to consider the potential benefit of colchicine in patients influenced by COVID-19 infection. A Greek open-labeled, randomized, prospective trial evaluated the effect of colchicine on myocardial injury or inflammatory parameters and clinical effectiveness in early inpatients infected with COVID-19 compared to the usual care. In this clinical trial study, 50 patients were randomly separated into the control group (standard medical treatment) and 55 to the intervention group (colchicine with standard medical treatment). Clinical data analysis showed a significant increase in clinical primary endpoint rate in the group with the usual care contrast to in the colchicine group, and the time to clinical deterioration was significantly decreased in patients who took colchicine in comparison to the control arm. Moreover, patients in the colchicine arm showed a smaller increase in D-dimer levels in the colchicine vs control arm (37). A cohort study with a single center and propensity score matching of 66 hospitalized patients having a verified infection of SARS-CoV-2 demonstrated an increased rate of discharge from the hospital in the colchicine arm. The authors also noticed that treatment with colchicine prior to the progression into acute respiratory, especially within 72 h, was linked to a lower death rate by day 28 in individuals with severe COVID-19 (38).

In a double-blind, randomized, placebo-controlled clinical trial by Lopes et al., COVID-19 patients with moderate to severe illness who received colchicine were compared to those who received a placebo; Seventy-five individuals (37 in the placebo group and 38 in the colchicine group). The research found that individuals in the colchicine arm required a lower median time of supplemental oxygen therapy (6% vs 39%) and hospital stay (94% vs 83%). In addition, patients receiving colchicine experienced a greater reduction of serum C-reactive protein (CRP) than the placebo arm. Two patients died during the trial, but deaths were observed only in the placebo group. However, clinical studies including a sizable patient population are required to conclude the effects of colchicine on the mortality rate in moderate to severe coronavirus disease 2019 (39). Scarsi et al. directed a single-center cohort research to investigate the effect of colchicine on improved survival of hospitalized individuals suffering from pneumonia and COVID-19 acute respiratory distress syndrome. In this study, colchicine was added to a standard-of-care regimen which included hydroxychloroquine or dexamethasone, lopinavir/ritonavir, and contrasted with just standard-of-care (N=262; 122 colchicine, 140 control). Survival analysis demonstrated that colchicine administration was linked to a decreased risk of death for inpatients compared to standard of care at the end of follow-up (40). The effectiveness of colchicine for treating individuals suffering from moderate to severe COVID-19 infection who were admitted to the BronxCare Hospital center in New York City from 21 March 2020 to 02 May 2020 was investigated in a case-control study conducted by Sandhu et al. Individuals who received colchicine in addition to standard of care positioned in the colchicine arm (n=34), while individuals in the control arm received only standard of care therapy (n=78). Both initial and final statistical data analysis revealed that colchicine caused an increase in the rate of discharge (50.9% vs 27.1%) and a reduction in the rate of intubations (52.8% vs 73.6%), and mortality (49.1% vs 72.9%). Moreover, final statistical data analysis showed that patients in the colchicine arm had similar co-occurring disorders, except for renal disease, which was higher in patients who received only standard care therapy (65.3% vs 35.2%). Additionally, inflammatory markers (e.g. D-dimer, CRP) were significantly reduced in patients who received colchicine (17). In accordance with data analysis of the abovementioned studies, the administration of colchicine in COVID-19 individuals with early pulmonary envelopment may further improve clinical outcomes. Besides, the application of other permitted treatments in combination with colchicine could have biased the influence of colchicine in these studies. Hence, more trials including a larger number of outpatients/inpatients and also longer-term interventions are required to appraise the benefits of colchicine in COVID-19 patients. There are a number of ongoing trials registered on ClinicalTrials.gov that are assessing the role of colchicine in individuals with COVID-19.

Interferon β (INF-β)

Interferons (IFN) are essential components of the innate antiviral response and play a critical role in the antiviral immune response due to their potent antiviral and immunomodulatory activities. It is believed that innate immune responses work effectively to limit disease severity once infection occurs (41). Interferons (INFs) may exert their antiviral effects via suppressing viral protein synthesis and replication or virus maturation and release from infected cells (42). Immunomodulatory effects of INFs may be correlated to enhancing the cytotoxic action of T cells, natural killer (NK) cells, and macrophages (43). Interferons can be divided into three families including types I (α & β), II (γ), and III (λ) (44). All viral infections, especially SARS-CoV-2, suppress the release of interferon-β (IFN-β) from host cells via proficient ways (45). Based on its antiviral and anti-inflammatory activities, IFN-β is known as one of the

promising agents against COVID-19 among other date options. Hence, some clinical studies have been rolled out to assess the potential influence of IFN-β in modulating COVID-19. Their clinical analysis showed that an early administration of IFN-β to individuals with COVID-19 even cases suffering from severe COVID-19 could be a promising approach in controlling COVID-19 infection (46).

Interferon β (INF-β) in COVID-19 clinical trials

Payandemehr et al. designed and carried out a single-arm, open-label clinical study to examine the possible efficiency and safety of IFNβ-1a as an effective candidate in the management of COVID-19. In this study, twenty cases with moderate to severe symptoms were treated with hydroxychloroquine plus lopinavir/ritonavir plus oseltamivir plus ribavirin along with subcutaneous IFNβ-1a during the hospitalization. The results demonstrated that patients' outcomes significantly improved after interferon beta-1a administration. It appears that the use of interferon beta-1a in combination with mentioned treatment can benefit patients with COVID-19. Given the limited patient population and the absence of a control group to compare the results with, it is somewhat difficult to confirm the therapeutic influence of interferon beta-1a on COVID-19. Hence, larger studies with a control arm are required to confirm the therapeutic effects of IFNβ-1a on hospitalized COVID-19 patients (28).

One other non-controlled prospective trial reported that administration of IFNβ-1a in conjunction with lopinavir/ritonavir and hydroxychloroquine was in favor of patients with COVID-19 (n=20). In this regard, a significant reduction in viral clearance was observed in ten days. Besides, radiological research displayed noteworthy improvement after the 2-week period in all patients. Most important of all, no deaths or significant drug-related side effects were noted in the 2-week period (47). The findings of a phase 2 pilot study that was double-blind, randomized, and placebo-controlled were released by Monk and colleagues. The authors assessed the safety and efficiency of nebulized IFNβ-1a among 101 hospitalized adult patients with COVID-19 in The Lancet Respiratory Medicine-Journal. In total, 101 patients were enrolled in this study between March 30 and May 30, 2020, 48 of whom were given inhaled INFβ and the remaining 50 patients were assigned to receive a placebo. Based on the WHO Ordinal Scale for Clinical Improvement Scale (OSCI), the authors found that inhaled INFβ increased the odds of clinical improvement more than a placebo did. Furthermore, three patients who received a placebo and none who received inhaled INFβ experienced death. Nonetheless, there was no discernible variation in hospital discharge rates between the two cohorts. Although the results of this trial showed the safety and efficacy of inhaled INFβ, no influence of inhaled INFβ-1a therapy on time to discharge or mortality was observed. Therefore, larger and longer-term trials are required to authorize the effectiveness of INFβ in this setting (48). Rahmani et al., performed an open-label, randomized clinical study to consider the efficiency and safety of IFNβ-1b therapy in individuals with severe COVID-19. In this study, patients were randomized (1:1) into the control group (N=33) and the IFN group (N=3). Members of the control group received the national therapeutic regimen including hydroxychloroquine + atazanavir/ritonavir or lopinavir/ritonavir while members of the IFN group, obtained IFNβ-1b plus the national therapeutic regimen. They reported that the length of time to clinical improvement decreased following administration of IFN β-1b. Furthermore, IFNβ-1b helped to reduce both the number of severe COVID-19 individuals admitted to ICU and the requirement for invasive ventilation. Conversely, the control group experienced higher rates of several adverse events than the IFN group did (49). Davoudi-Monfared et al. also conducted a randomized clinical study to evaluate the efficiency and safety of IFNβ-1a therapy in severe COVID-19 cases. They compared the effectiveness of IFN-α plus national therapeutic regimen (hydroxychloroquine + atazanavir-ritonavir or lopinavir/ritonavir) with the national therapeutic regimen in individuals with severe COVID-19 (control: n=39 and IFNβ: n=42). Data analysis revealed that there was no discernible difference in clinical response between the two groups. However, early beginning of hydroxychloroquine + atazanavir-ritonavir or lopinavir/ritonavir plus IFNα combination therapy significantly was linked to a decrease in 28-day overall mortality. The addition of IFNα to recommended medications also could increase discharge rate on day 14 (50).

Li et al. conducted a multicenter randomized (1:1) trial on hospitalized individuals with moderate-to-severe COVID-19. They evaluate the influences of genetically modified IFNα (rSIFN-α) and traditional IFN-α (TINF-α) on the time to improvement in clinical and radiological features, the total clinical improvement rate as of day 28, and negative conversion of SARS-CoV-2 RNA (TINF-α arm: n=46 and rSIFN-α arm: n=48). They revealed that rSIFN-α plus antiviral agents showed more impact than TINF-α plus antiviral agents. Therefore, rSIFN-α alone or combination therapy might be worth further investigation in COVID-19 (51). Ngai Hung et al. carried out a phase 2 study that was multicenter, open-label, prospective,

randomized, and involved 127 patients who were recruited into two groups: combination (lopinavir/ritonavir, ribavirin, and IFNβ-1b) and control (lopinavir/ritonavir), at six hospitals in Hong Kong, between February 10 and March 20, 2020; 86 patients were randomly assigned to the combination group, and 41 patients were assigned to the control group. The finding revealed that using triple antiviral medications for early treatment was safe and more effective at alleviating symptoms and reducing viral shedding duration and hospitalization than lopinavir/ritonavir alone in mild-to-moderate COVID-19 individuals (52). Additionally, favipiravir plus inhaled INFβ-1b was studied in a controlled open-label randomized study to see how it affected hospitalized COVID-19 patients. In this study, 44 patients were assigned to favipiravir plus inhaled INFβ-1b and 45 patients were randomized to receive national medication that had hydroxychloroquine (HCQ). The findings revealed that there were no statistically significant variations in the inflammatory biomarkers (interleukin 6, ferritin, lactate dehydrogenase, and C-reactive protein) transfers to the ICU, hospital discharges and overall mortality between the two groups (53). Darazam et al. report the results of a three‐armed, individually randomized, open-label, controlled study in which severe COVID-19 cases were given IFNβ1a and IFNβ1b. Comparing the efficacy of IFNβ1a and IFNβ1b against one another and a control group was the goal of this study. A total of 60 individuals with severe COVID-19 were randomly allocated in a 1:1:1 ratio to IFNβ1a, IFNβ1b, or the control group. All three arms orally received a single dose of hydroxychloroquine and lopinavir/ritonavir for ten days. Comparing IFNβ1a to the control group, the authors found that there was a significant difference in the amount of time it took for clinical improvement. Conversely, no statistically significant distinction was observed between the IFNβ1b and control groups. Regarding the negative effects, there were also no statistically significant differences between the groups. Additionally, compared to the control group, the two intervention groups' mortality rates were lower (54). Although the authors point toward the superior effectiveness of IFNβ1a especially in terms of the primary outcome compared to IFNβ1b against severe COVID-19 in this study, larger studies are required to confirm this finding.

Intravenous immunoglobulin gamma (IVIG)

Intravenous immunoglobulin is a blood preparation that is extracted and concentrated from healthy donors and comprises polyclonal immunoglobulin G. Since its first application for the treatment of patients with refractory idiopathic thrombocytopenia in 1981 (55), it has been administered as an immunomodulatory agent in the management of autoimmune and inflammatory conditions such as Kawasaki syndrome, immune thrombocytopenic purpura (ITP), multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy (56). Patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have benefited greatly from the administration of IVIG (57, 58). Given the presence of a devastating immune response among numerous patients with COVID-19 (5, 59), as well as similarities in underlying immunological pathogenesis between SARS and SARS-COV-2, it seems that treatment with IVIG to be particularly beneficial in the improvement of passive immunity and the management of the inflammatory immune response in COVID-19 patients (60). The mechanisms by which IVIG operates in many diseases are not yet fully understood. However, some of the proposed mechanisms of action involved in modulation of the immune response include an increase in autoantibody degradation by newborn Fc receptor, suppression of complement-mediated tissue damage, neutralization of autoantibodies, suppression of activating several innate immune cells such as monocytes/macrophages, dendritic cells, neutrophils and secreting inflammatory factors, downregulation of inflammatory mediators, blockage of B-cell activation, suppressing effector T helper cells (Th1 and Th17), and elevating regulatory T cells (Tregs) reciprocally (56, 61).

Intravenous immunoglobulin gamma in COVID-19 clinical trials

Despite its broad application as an anti-inflammatory agent at high doses, there is limited validation for the IVIG prescription in COVID-19 patients. Thrombosis as an important adverse effect of IVIG could be one of the reasons for concern in individuals with severe COVID-19 who might have higher D-dimer levels (62). Due to the controversial effects of IVIG on patients with COVID-19 respiratory disease, its application remains an impediment to suggest this agent as an efficient course of therapy against COVID-19. Nonetheless, the following trials have documented IVIG use in COVID-19 patients: the findings of a placebo-controlled, randomized, double-blind clinical study involving patients with severe COVID-19 infection who did not improve with the national therapeutic regimen that was first administered were published by Gharebaghi et al. In this study, IVIG was administered to 30 patients while a placebo was given to 29 patients. IVIG administration was linked to a significantly lower death rate, according to a multivariate regression analysis (63). Those who were in the placebo group had impaired renal function and elevated

white blood cell count indicating that these patients may have had a worse prognosis that has enhanced their risk of mortality compared to the intervention group.

Tabarsi et al. evaluated the effects of IVIG on the care of COVID-19 patients who are extremely sick. Eighty-four patients participated in this randomized open-label controlled trial, with thirty-two in the control group and fifty-two in the intervention arm. Hydrocortisone, an antihistamine, and paracetamol were administered for patients in the intervention arm prior to receiving IVIG. Patients in both arms received supportive care, hydroxychloroquine, and lopinavir/ritonavir. The authors found no statistically significant differences in total loss and the necessity for mechanical ventilation between the two groups. The findings from the study did not show the additional clinical benefit of adding IVIG to the standard of care. Nonetheless, among the survivors, there was a notable variation in the average duration of hospital recovery and ICU stay, as well as the time from admission to the onset of IVIG administration (64).

Sakoulas et al. conducted a small-scale open-label prospective randomized study in 33 patients who had hypoxic COVID-19 (moderate to severe). Inclusion criteria for the trial were PO2 ≤ 96% on ≥ 4 L O2 via nasal cannula in patients ≥18 years old who were not on mechanical ventilation. Patients were randomized into 16 interventional arms and 17 control arms. Standard of care including glucocorticoids (dexamethasone or methylprednisolone) remdesivir and convalescent plasma plus IVIG plus were administered for the intervention group, while the control group only received the recommended level of care. A total of 7/16 patients in the IVIG arm and 10/17 patients in the control arm were on steroids at baseline. The remaining nine IVIG patients were given methylprednisolone 30 minutes prior to the administration of IVIG to prevent IVIG-associated headaches. Among patients with an A-a gradient of > 200mm Hg at enrolment, the IVIG group was associated with a lower rate of development to the need for mechanical ventilation, a shorter median length of stay in the ICU, and greater development after seven days in PaO2/FiO2 than the standard of care. There are some issues in this small study that must be considered with caution. The addition of remdesivir into the standard of care, the prophylactic administration of methylprednisolone to the patients in the intervention arm and the shift away from primary mechanical ventilation and intubation to more forceful self-pronging techniques are some of the debatable issues in the current research (65). In a retrospective analysis directed by Xie et al., the effects of IVIG on 58 patients diagnosed with severe and crucial pulmonary COVID-19 were investigated. In this study, grouping was performed based on the administration of IVIG ≤48 h after ICU admission, and those initiated >48 h after ICU admission. The data analysis showed statistically significant variations in 28-day mortality between the two groups, the length of stay in the ICU, length of hospital stay, and the proportion of patients requiring mechanical ventilation. In comparison to the > 48 h group, the percentage of patients in the ≤48 h group who needed mechanical ventilation was statistically lower. Moreover, the ≤48 h group's length of stay in the hospital and intensive care unit was considerably lower than that of the >48 h group. Findings from this study must be interpreted with caution. Their initial analysis, which was assigned based on IVIG prescription within 24 hours of admission, did not reveal any statistically significant alterations in the 14-day or 28-day mortality rates. The other assigned intervention that was based on the administration of IVIG ≤48 hours or >48 hours of admission demonstrated a statistically significant decline in the mortality rate after 28 days. Additionally, it seems that the paper did not provide adjusted mortality statistics between patients, and these notable variations between the two groups may be related to differences between patients. Hence, the comparison made between the groups will be biased (66). A multicenter retrospective cohort research was performed by Shao et al. to evaluate of 28 and 60-day mortality rate in 174 patients of 325 with severe/serious COVID-19 illness that received IVIG. The 28-day or 60-day mortality rate and survival time did not differ between the IVIG-free control group and the intervention group. The regression analysis showed that primary prescription of IVIG following admission in association with higher daily doses exerted a more profound therapeutic effect. However, this study was also associated with some limitations that should be considered. There are some limitations in the present study. First, the patients from four clinical centers may lack adequate representation. Second, the dose and timing of IVIG therapy in each center may not be precisely consistent (67).

Esen et al. reported the result of an open-label, non-randomized, retrospective cohort study that was accomplished in ICU patients who were critically ill. In this study, out of 93 patients, 51 patients received IVIG treatment according to a locally developed algorithm. The authors involved two cohorts of patients receiving standard care who had severe COVID-19. Including azithromycin, favipiravir, hydroxychloroquine, and oseltamivir. In addition, methylprednisolone, anakinra or tocilizumab, vitamin C, and high dose vasopressors were prescribed in those with elevated inflammatory markers. The result

indicated an overall survival rate of 61% in the IVIG arm and 38% in the control arm, while this difference was not statistically significant when adjusted for imbalances regarding baseline APACHE score. Furthermore, biomarker analysis disclosed a noteworthy reduction in C-reactive protein level in the intervention group. More randomized clinical studies are necessary to approve clinically relevant benefits of IVIG therapy in COVID-19 (68). The purpose of a retrospective cohort study was to investigate the effectiveness of IVIG in COVID-19 patients who were not severe. Based on propensity score matching (PSM), 45 patients out of 639 non-severe patients in this study received IVIG treatment, and 594 patients did not receive IVIG treatment. Following PSM (1:2 ration), there were no statistically significant alterations in viral clearance time, the duration of fever, antibiotic use, and the hospitalization period between the intervention and control groups. In addition, compared to the IVIG arm, fewer patients in the control arm experienced severe illness or passed away. Meanwhile, the authors confirmed that, in comparison to standard care, the prescription of IVIG did not produce any additional benefits in patients with non-severe COVID-19 (69)

In a multi-center retrospective research study conducted within 14 days of the disease onset, Cao et al. assessed the effectiveness of high-dose IVIG therapy in cases of severe COVID-19. In total, 89 patients received standard care alone, while 26 patients received high-dose IVIG in addition to it. The semiparametric Cox comparative hazards regression model and the Kaplan-Meier curve were adjusted by the inverse possibility of treatment weighting (IPTW) and IPTW after multiple imputation (IPTW-MI) analysis were utilized in this study to evaluate the effectiveness of high-dose IVIG. According to data analysis, the IVIG group needed less time than the control group to attain normalization of inflammatory biomarkers like ferritin, IL-6, and IL-10. Additionally, compared to the control group, the IVIG intervention was linked to a lower 28-day mortality rate. Meanwhile, IVIG administration in patients treated during the early phases of disease progression or having few comorbidities exerted higher and more prominent effects (31). To evaluate the safety and effectiveness of routine IVIG in the treatment of COVID-19 cases with moderate pneumonia, an open-label, randomized phase II, multicenter study was conducted in India. One hundred participants were randomized 1:1 to either the standard of care control arm or the intervention arm (IVIG + standard of care). The result revealed that the duration of hospital stay, the median time for body temperature to return to normal, mechanical ventilation, and oxygen saturation were meaningfully shorter in the IVIG group in comparison with the control group. No significant alteration was observed between the two groups with respect to percentages of patients on mechanical ventilation. Median time to negative reverse-transcription polymerase chain reaction (RT-PCR) result was meaningfully shorter with IVIG than the standard care therapy. No serious adverse effects were described in patients on IVIG, in contrast, one patient died in the standard of care control arm. However, the present study was an open-label design and had a small sample size (70). Zantah et al. reported the finding of a retrospective study from Philadelphia, US. The rationale for the study was to compare the effect of anakinra (monoclonal antibody against IL-1β) plus IVIG versus tocilizumab (monoclonal antibody against IL-6) in the management of COVID-19 pneumonia patients' hypercytokinemia. Fifty-one patients were enrolled to receive anakinra/IVIG treatment and thirty-three patients were enrolled to treat with tocilizumab. Data analysis indicated that baseline inflammatory biomarkers such as ferritin, Creative protein (CRP), D dimer, and lactate dehydrogenase (LDH) were similar in both groups. Furthermore, no discernible differences were found in terms of mortality, ICU need or length of ICU stay, and intubation between the anakinra + IVIG and tocilizumab groups. Inflammatory markers, the rate of respiratory improvement measured by ROX (Respiratory rate – Oxygenation) index, and National Early Warning (NEWS) Score were also similar between the two groups. However, the combination of anakinra with IVIG and no randomization to treatment may put the obtained results from this study at risk. Thus, the direct benefits of IVIG are difficult to estimate (71).

Tocilizumab (TCZ)

Tocilizumab as a recombinant humanized monoclonal antibody can be directed against the IL-6 receptor. Its therapeutic application is moderate to severe rheumatoid arthritis worldwide (72) . Tocilizumab can block pro-inflammatory activity of IL-6, and is involved in pathogenesis of pneumonia which is the most common cause of death in COVID-19 patients (73). As like many viral infections, patients with COVID-19 infection show mild self-limiting symptoms. However, the SARS-CoV2 virus can trigger a severe hyperinflammatory syndrome named as cytokine storm for some patients. In hospitalized patients a systemic dysregulation of pro-inflammatory cytokines occur (9). Such hyper-inflammatory response is related to wide lung and endothelial cell impairment, microangiopathy, and microvascular dysfunction (74). Hyperinflammatory state is characterized by augmentation of abnormal inflammatory markers, such as elevated serum

IL-6, C-reactive protein, and ferritin levels (9, 75). It was shown that higher concentration of IL-6 in serum is correlated with higher level of viremia (76). Therefore, anti-IL6 therapy might be a solution in limiting the hyperinflammatory syndrome and consequent respiratory and multiorgan failure which occurred about the second week of infection (77). In COVID-19 patients with IL-6-increased level, tocilizumab might inhibit proinflammatory activity of IL-6 improving clinical outcomes of patients with severe or critical COVID-19, and also the blockade of the receptor with TCZ could reduce mortality or morbidity in severe COVID-19 (78, 79) . Tocilizumab as IL-6 antibody has shown promising results in patients with COVID-19 pneumonia with a good safety profile (73), however the clinical outcome is not well-defined. The variability in the clinical response of TCZ treatment has probably been related to the contribution of other factors, including race, sex and age-related biological mechanisms, disease severity, genetic makeup, and timing of treatment that we will discuss.

Tocilizumab in COVID-19 clinical trials

A total of 42 critically patients, who required either mechanical ventilation or admission to the ICU, were enrolled in a prospective clinical trial. The individuals were above the age of 18, tested positive for RT-PCR, and had a SpO2 level below 90. A dosage of 400mg of tocilizumab was administered intravenously, and the clinical outcomes were assessed over a period of 28 days. The primary outcomes assessed were alterations in oxygenation support, requirement for invasive mechanical ventilation, and mortality. Additional outcomes were pulmonary radiological alterations, IL-6 concentrations in plasma, levels of C-reactive protein, and any unfavorable medication responses. Out of the total number of patients, only 6 (14%) individuals needed invasive ventilation, while 35(83.33%) patients showed clinical improvement. By the 28th day, a cumulative of 7 individuals died, with 6 in critical condition and 1 in severe condition. Additionally, neurological detrimental effects were identified in 3 patients. Tocilizumab may have the potential as a beneficial treatment in cases of severe or critical stage (80).

A retrospective analysis was conducted on 146 individuals who were admitted to the hospital and diagnosed with COVID-19. Tocilizumab, at a dosage of 8 mg/kg (maximum 800 mg), was administrated and repeated after 12 hours. Approximately 3-9 days after admission clinical information and IL-6 levels were measured and invasive mechanical ventilation, arterial oxygen and mortality were considered as outcome. Most of patients (66%) were males with median age of 63 years and 40% received tocilizumab. Notably, those in the group receiving TCZ experienced more severe cases of COVID-19, characterized by decreased PaO2 levels, elevated serum LDH and CRP levels, and higher baseline IL-6 levels. Administering TCZ early resulted in improved oxygenation after six days in patients with high IL-6 levels. In contrast, patients with high IL-6 levels who did not get TCZ had a significantly higher mortality rate (hazard ratio = 3.6), as did individuals with low IL-6 levels who received TCZ. The results showed that high level of Il-6 is an indicator of effectiveness of TCZ. However, a subset of patients suffering from severe COVID-19 exhibit diminished levels of IL-6 in their bloodstream. It is likely that these patients would have benefited more from the inhibition of IL-1 or TNF-α rather than TCZ. Adverse effect was not observed after use of tocilizumab (78). In those patients that developed hyperinflammation syndrome leading to respiratory failure and do not show improvement with IL-6 antagonist as tocilizumab, biological agents targeting alternative components of the inflammatory cascade might be the solution. In a 53-year-old patient who underwent a hematopoietic stem cell transplant and developed severe COVID-19, the excessive inflammation was successfully treated with ruxolitinib, resulting in a reduction in serum IL-6 levels and C-reactive protein (81).

Non-responsive patients exhibited decreased serum levels of miR-146a-5p following TCZ medication. The miRNA in serum samples of sever hospitalized patients that received single-dose of tocilizumab (TCZ) was compared with gender- and similar healthy control subjects. This miRNA might be the link between hyperinflammation and the progression of COVID-19 in a clinical setting (82). A cohort study was conducted to examine the impact of tocilizumab on mortality rates at 14 and 30 days in hospitalized patients with pneumonia who tested positive for real-time PCR. The individuals had a resting oxygen saturation level of 93% or lower, or they needed assistance with oxygen. There was no age or gender limitation. tocilizumab at a dosage of 8 mg/kg, lowered lethality rates at days 14 and 30 of 920 patients. Multivariable logistic regression analysis in 30 days showed that, older age, and a lower PaO2/FiO2 ratio had negative impact on survival, while the use of concurrent use steroids with tocilizumab had positive impact on survival. However, in patients that needed mechanical respiratory support initially, tocilizumab was not effective (73). In a separate cohort trial, individuals with COVID-19 and moderate or severe pneumonia, who needed a minimum of 3 L/min of oxygen or were admitted to the intensive care unit, were monitored for 28 days. The participants were administered TCZ at a dosage of 8 mg/kg

intravenously in addition to the standard therapy, which included antibacterial agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants. TCZ decreased the likelihood of requiring mechanical breathing or experiencing death by day 14 but did not have an impact on the mortality rate by day 28 (83). A total of 129 patients, with a mean age of 57±14 years and comprising 68% men, who were diagnosed with severe or critical COVID-19 and had aberrant levels of at least two serum biomarkers (C-reactive protein, D dimer, lactate dehydrogenase, or ferritin), were enrolled in a clinical trial conducted in Brazil 2020. Patients received standard care or tocilizumab (8mg/kg IV) plus standard care. Adverse effect and clinical outcome were not different after 15 days between two groups (84).

An evaluation was conducted on the prompt delivery of tocilizumab in adult patients aged 18 years and above who were admitted to the hospital with proven COVID-19 pneumonia, as evidenced by radiologic imaging. These patients also had a Pao2/Fio2 ratio ranging from 200 to 300 mm Hg, along with fever and high levels of C-reactive protein. In this open-label randomized clinical trial, patients in the experimental group were administered intravenous tocilizumab at a dosage of 8 mg/kg up to a maximum of 800 mg/kg. The first dose was given within 8 hours, followed by a second dose after 12 hours. The control group was provided with supportive care in accordance with the protocols of each clinical center. Due to a decline in their clinical condition, individuals are administered tocilizumab as an intervention to mitigate the situation. Among the 123 patients, 28.3% of those in the tocilizumab group and 27% of those in the control group (who got standard therapy) experienced clinical deterioration within a 14-day period. No benefit on disease progression and no difference in mortality was observed following the use of TCZ (85).

Tocilizumab did not demonstrate efficacy in reducing intubation or mortality in hospitalized non-ventilated COVID-19 patients. In a double-blind, placebo-controlled trial patients aged from 19 to 85 years and positive PCR were involved. They exhibited a minimum of two of the following indications: elevated body temperature, infiltration in the lungs, or a requirement for more oxygen. They had also one of these clinical markers; C-reactive protein >50mg/l, ferritin>500ng/ml, D-dimer> 100ng/ml and LDL>250/l. 243 patients (141 men, and 102 women) were randomly assigned to receive standard care plus placebo or a single dose of tocilizumab (8 mg/kg, IV). The hazard ratio for intubation or death in the tocilizumab group, as compared to the placebo group, was 0.83. Additionally, the hazard ratio for illness deterioration was 1.11. After 14 days, the clinical condition deteriorated in 18.0% of patients in the tocilizumab group and 14.9% of patients in the placebo group. Additionally, 24.6% of patients in the tocilizumab group and 21.2% of patients in the placebo group still required supplementary oxygen. The incidence of infection was lower in the group treated with tocilizumab. The findings indicated that tocilizumab did not demonstrate efficacy in avoiding intubation or mortality in moderately sick patients admitted to the hospital (30). But in a similar study published three months later, the evaluation of treatment effectiveness using a time-to-event analysis showed that tocilizumab outperformed the placebo in terms of clinical failure. Primary outcome was reducing of progression to mechanical ventilation. Different results might be due to more patients (249) of different race and ethnic groups that were enrolled. The other reasons are the use of two dose of tocilizumab instead of a single dose (8mg/kg) and 28 days of follow-up. However, there was no disparity in the occurrence of mortality (86).

Patients in a multicenter trial were randomly allocated to one of two groups: the combination group, which received a 14-day therapy of favipiravir combined with tocilizumab, or the favipiravir plus tocilizumab group. It is worth noting that favipiravir is an antiviral medicine licensed for treating influenza by targeting RNA-dependent RNA polymerase. The administration of tocilizumab was done intravenously at a dosage of 8 mg/kg. Favipiravir, on the other hand, was taken orally at a dosage of 1600 mg twice a day on the first day, and 600 mg twice daily from the second to the seventh day. The primary result, which measured the rate of remission of lung lesions, was considerably greater in the combination and tocilizumab group compared to the favipiravir group. No discernible distinction was observed between the tocilizumab group and the combo group. There were no significant negative incidents reported. Tocilizumab, with or without favipiravir, can significantly enhance clinical outcomes by resolving pulmonary inflammation in patients with elevated levels of IL-6. Nevertheless, the clinical trial had an insufficient sample size of only 28 participants (87) and no gender effect was considered (88).

Rituximab

Rituximab (RTX), a monoclonal antibody that targets CD20, is utilized to treat many disorders including rheumatoid arthritis, hematological malignancies, immune-mediated renal diseases, and neurological disabilities. RTX is able to target CD20, an integral membrane protein expressed on the surface of all B-cells, resulting in B-cell killing. Thus, RTX disrupts humoral-mediated immunity via depletion of lymphocytes of the B lineage. RTX is

generally well-tolerated and causes mild side effects including infusion reactions with rash, fever, headache, and chills. However, RTX is an immunosuppressive drug that can lead to neutropenia, hypogammaglobulinemia, and viral reactivation (89). In addition, severe reactions such as acute hypoxemic respiratory failure, pulmonary infiltrates, respiratory distress, myocardial damage, cardiac arrhythmias, or cardiogenic shock may occur with the first dose (90).

Rituximab in COVID-19 clinical trials

There is no agreement on whether immunosuppressive and immunomodulatory medications have a negative impact on the clinical progression and outcome of critically ill patients with COVID-19 infection (89). Some reports have indicated that patients who were already treated with immunosuppressive medicines were more vulnerable to COVID-19 infection and presented worse results (91). Several studies also demonstrated higher rates of hospitalizations due to COVID-19, respiratory difficulty demanding tracheal intubation and mechanical ventilation, and higher mortality among RTX-treated patients (92-95). In a single-center retrospective cohort study performed by Alhowaish et al., rituximab therapy was associated with unfavorable results in patients with COVID-19 infection. They studied 35 adult patients who received RTX for numerous conditions and were found to have COVID-19 symptoms. The result analysis revealed that almost 15 patients required hospitalization and 9 patients admitted to in the intensive care unit, as well. The authors suggested that treatment with RTX should be avoided unless the advantages evidently outweighs the disadvantages (89).

Likewise, a cohort study conducted by Singh et al. to explore the effects of RTX on COVID-19 consequences in patients with rheumatoid arthritis from April 2020 to September 2021. Approximately, 22,956 patients were positively diagnosed with COVID-19 of which 364 patients were treated with RTX. They found that the use of RTX in patients with rheumatoid arthritis is accompanied with poor COVID-19 outcomes such as hospitalizations and intensive care unit admissions in comparison with those receiving conventional disease-modifying antirheumatic medications (96). Similarly, a descriptive study performed by Martos et al. on COVID-19 infections in rheumatoid arthritis patients treated with RTX demonstrated a high rate of severe disease and hospitalization (61.5%), and death (23.1%). The aim of this study was to investigate the characteristics and outcomes of patients with rheumatic and musculoskeletal diseases (RMD) who received RTX. In this descriptive study, they introduced 76 patients of which 13 (17.1%) patients with probable or confirmed COVID-19 infection were enrolled. Of these 13 patients, 5 patients suffered from rheumatoid arthritis, 3 from systemic necrotizing vasculitis, 2 from Sjogren's (SHOW-grins) syndrome, and 2 from systemic lupus erythematosus (SLE). Furthermore, 7 (53.8%) patients had lung involvement due to RMD. COVID-19 in 8 patients (61.5%) caused severe disease resulting in hospitalization of which 7 developed bilateral infiltration and respiratory failure. Among these 8 patients, 3 patients died. The authors suggest that RMD patients exposed to RTX seems to be at a higher risk for unfavorable outcomes due to COVID-19 (92). In a tertiary center, Ekin et al. investigated the influences of COVID-19 infection on the mortality of patients taking the medicine rituximab from March 2020 to November 2021. Out of 336 patients who were treated with at least one dose of RTX, 111 patients with rheumatologic conditions and who were identified with COVID-19 infection were included. In this study, a range of conditions such as age, COVID-19 vaccination coverage, co-occurring conditions, and some clinical laboratory parameters were assessed. The results of the study recommend that treatment with RTX enhanced the risk of mortality in patients with COVID-19 and inflammatory rheumatic diseases. However, they found that vaccination at the full dose and adjusted against COVID-19 played a vital role in this patient group (97).

Corticosteroids

Corticosteroids are powerful medications that modulate the immune system and reduce inflammation through both genomic and nongenomic mechanisms (98). Corticosteroids mitigate inflammation and have previously been employed in respiratory conditions such as asthma, COPD, severe bacterial pneumonia, and acute respiratory distress syndrome (ARDS). Nevertheless, there is ongoing debate regarding the efficacy of corticosteroid therapy for individuals with respiratory infections caused by the coronavirus. A comprehensive analysis comprising 29 studies on the use of corticosteroid medication for SARS infection revealed that 25 trials yielded unclear findings, while 4 studies reported adverse outcomes. Several studies have demonstrated a favorable response to steroids due to their ability to diminish inflammation (99). Approximately 31% to 42% of hospitalized COVID-19 patients develop ARDS because of dysregulation of immune system, emphasized by increases levels of inflammatory cytokines, with subsequent increased risk of death (9, 20). Cytokines had a crucial role in determining the severity and prognosis of COVID-19. The production of cytokine storm by SARS-CoV-2 was verified in COVID-19 patients in the ICU (100). When a cytokine storm occurs, the innate immune system triggers pulmonary fibrosis, causing symptoms such as

shortness of breath, reduced oxygen saturation, and systemic damage. This can lead to ARDS and ultimately end in the death of the patient (5). Glucocorticoids, when used as an immunosuppressive medication, can effectively decrease inflammation in the respiratory system and prevent the onset of cytokine storms and ARDS. However, they do not possess strong antiviral properties in laboratory and live settings (101). The WHO primarily advised the utilization of corticosteroids for treating COVID-19 due to their lack of efficacy in SARS patients and potential damage (102). Subsequently, the utilization of corticosteroids resurfaced after it was linked to a decrease in mortality in China (103). So during pandemic, the use of steroids was recommended by New Coronavirus Pneumonia Diagnosis and Treatment Plan in China (http://www.cac.gov. cn/2020-03/04/c_1584872634644633.htm), which recommended methylprednisolone at low dose of 1–2 mg/kg/d for 3 to 5 days in those patients who experienced a rapid reduction in oxygen ratio and deterioration of pulmonary imaging after being hospitalized. In fact, methylprednisolone reduced rate of mortality and mechanical ventilation in COVID-19 patients with moderate to severe symptoms (104). Corticosteroids suppress immune system and reduce lung-tissue damage, the time on mechanical ventilation, permanence in ICU and possibly also mortality. Nevertheless, corticosteroids induce hyperglycemia and also increase time to viral clearance due to their immunosuppressive action (105). Immunosuppressive property of corticosteroids has possible impact on worsening clinical course in COVID-19 patients.

The utilization of corticosteroids may lead to an elevation in the amount of virus present in individuals with SARS-CoV infection. The administration of corticosteroids at an early stage in mild instances and at a later stage in severe cases (ARDS) could potentially be the cause of the harmful consequences observed in these patients. Therefore, it is advised against prescribing corticosteroids to individuals who are not admitted to the hospital (106). Neither in mild-to-moderate COVID-19 cases. They should be administered timely and in correct dose (107). A multicenter clinical trial showed detriment in ARDS and increased mortality when medication was initiated at a later stage of the disease (108). Empirically, corticosteroids have been administered inconsistently to individuals with COVID-19, and observational research indicates that they can have both advantageous and detrimental effects (29). The administration of corticosteroids in COVID-19 disease remains a subject of debate and disagreement (109). There is research that questions the effectiveness of corticosteroid medication.

Corticosteroids in COVID-19 clinical trials

Research of 5270 patients revealed that corticosteroid medication provides benefits to critically ill patients. However, it is important to note that corticosteroids may also lead to increased mortality rates and longer hospital admissions in patients with ARDS (110). Typically, SARS-CoV-2-associated ARDS is inherently detrimental, as approximately 35% to 40% of patients succumb to it within a brief period of time (111). The effect of Corticosteroids was studied on 774 patients with severe COVID-19 and ARDS. In 28 days of follow-up, 44.3% of those who received corticosteroids died. Hazard rate depends on dose (high dose>200 mg of prednisolone) and time of initiation (within 3 days of hospitalization). Besides a delay in CoV-2 coronavirus clearance, a significant rate of side effect including myocardial and liver injury and shock was also observed in corticosteroid treated group (1). In a retrospective cohort analysis of 309 critically ill patients with Middle East Respiratory Syndrome (MERS), the use of corticosteroid therapy did not have a significant impact on mortality rates or the time it took for the virus to be cleared from the body (112).

The administration of dexamethasone at a dosage of 20 mg per day initially, followed by 10 mg per day for ten days, did not result in any notable clinical improvement in patients with mild to moderate ARDS (113). Among the 7,235 patients involved in five RCTs, 2,508 patients were administered corticosteroid treatments (specifically dexamethasone or methylprednisolone). However, the use of corticosteroids did not result in a decrease in mortality among hospitalized COVID-19 patients within 28 days. Additionally, there was no significant difference in clinical benefit or adverse events compared to standard care. Nevertheless, the utilization of corticosteroids has substantially augmented the rate at which individuals with COVID-19 are released from medical care (113). A separate study found that administering a high dosage of dexamethasone did not have an impact on the requirement for a ventilator in individuals suffering from ARDS caused by COVID-19. In this clinical trial, one group of patients was administered dexamethasone at a dosage of 16mg per day for five days, followed by a reduced dosage of 8mg per day for up to ten days. The other group received a constant dosage of 6mg per day for up to ten days. The study found no significant differences between the treatment groups in terms of mortality, infection rate, muscle weakness, and glycemic control during the 28-day follow-up period (114). A cohort study was conducted on 1444 patients who tested positive for RT-PCR to investigate the relationship between corticosteroid medication and mortality rates in hospitals.

Out of the total number of patients, 39% were administered corticosteroids, while the remaining 61% did not get any corticosteroid treatment. Although no disparity in the death rate was noted, there was a decrease in ICU admissions (115). In parallel, many studies were in favor use of corticosteroids. In a study of conducted in Pakistan; 100 patients with moderate to severe COVID-19 received methylprednisolone 1 mg/kg/day or dexamethasone 8 mg/day given for 5 days. In both groups, oxygen requirement and C-reactive protein(CRP) improved but 15% -17% died (116). Later an observational cohort of COVID-19 showed that methylprednisolone can decrease the risk of death in patients with confirmed COVID-19 pneumonia (103).

The initial findings from the recovery study indicate that the administration of dexamethasone can decrease the mortality rate within 28 days for patients with coronavirus disease 2019 (COVID-19), however, this effect is shown exclusively in patients who undergo invasive mechanical breathing (113). Among the hospitalized patients (n=2014), the administration of dexamethasone at a dosage of 6mg per day for a duration of ten days resulted in a reduction in mortality rates for individuals who were undergoing either invasive mechanical ventilation or receiving oxygen (117). The initial administration of high dosages of dexamethasone proved to be efficacious and demonstrated advantages. In a study conducted in 17 ICUs, the administration of dexamethasone injection at a dosage of 20mg per day from the first to the fifth day, followed by a dosage of 10mg per day up to the tenth day, to patients with established moderate-to-severe ARDS resulted in a decrease in the requirement for mechanical ventilation and death. The incidence of unfavorable incidents related to corticosteroids did not exhibit any significant difference when compared to the control group (108). The efficacy of dexamethasone was validated in a cohort of 350 COVID-19 patients presenting with moderate or severe ARDS. The participants were divided into two groups: the standard treatment group and the standard treatment group supplemented with the same medication regimen of dexamethasone (118). A clinical trial involving 1000 patients with severe hypoxia demonstrated the efficacy of a low dose of hydrocortisone (200 mg/day for 7 days). The experiment was international, randomized, stratified, and blinded (105). Glucocorticoids appear to be safe, even in people who use corticosteroids continuously. Such individuals include those with RMDs or those with a history of using immunosuppressive medications. A study conducted on 2050 persons undergoing treatment for chronic inflammatory arthritis with commonly used corticosteroids or targeted synthetic/biological disease-modifying medications (DMARDs) found that the rate of COVID-19 infection was below 1.5% (119).

A study was conducted to assess the impact of methylprednisolone with tocilizumab on conventional therapy in patients who developed cytokine storm syndrome. This syndrome is characterized by fast respiratory deterioration and elevated levels of at least two out of three biomarkers: CRP (>100 mg/l), ferritin (>900 µg/l), and d-dimer (>1500 µg/l). The trial group was administered a high dosage of intravenous methylprednisolone for a duration of 5 consecutive days. This approach expedited the process of respiratory recovery, diminished death rates, and decreased the necessity for invasive mechanical ventilation in cases of COVID-19-related CSS (107). In summary, based on the clinical trials completed so far, there is compelling evidence indicating a correlation between the use of anti-inflammatory medications at the appropriate time and an improvement in the survival rate. This is evident in the current guidelines issued by prominent public health agencies worldwide, which advocate the utilization of anti-inflammatory medications to alleviate the cytokine storm associated with COVID-19. Additional evidence is necessary to completely clarify the correlation between these medications and the severity of COVID-19.

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