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Review Article

SYSTEMATIC REVIEW: EVALUATION OF CYTOKINE STORM TREATMENT FROM COVID 19 PATIENT BASE ON CLINICAL TRIAL

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ABSTRACT

These cytokine storms are extremely dangerous. Cytokine storm is considered the reason for the high mortality rate of COVID 19 patients. An undetected reason causes a Cytokine storm in a patient, but this is associated with the characteristics of a person's immune system. Most COVID-19 patients recover with mild and moderate symptoms within one week; some develop severe pneumonia in the second week, followed by cytokine storm, ARDS, multiorgan failure, and disseminated intravascular coagulation (DIC) within the 3rd week. The high mortality rate in COVID-19 patients is most likely due to a cytokine storm in the patient's body. Cytokines are also immune system proteins that regulate interactions between cells and trigger immune reactivity, both in innate and adaptive immunity. To evaluate all treatments that can be used during the treatment of cytokine storm in COVID-19 patients based on clinical trials. Systematic Literature Review (SLR) about studies researching the treatment of cytokine strom in COVID-19 patients. Accumulated treatment was calculated using the confidence ratio for the random effects meta-analysis method of medium and high-quality data.

Based on the literature on clinical trials, we can use Tocilizumab, Ruxolitinib. Baricitinib, Itolizumab, Zilucoplan, Stem Cells (MSC transplantation, Umbilical cord mesenchymal stromal cells, and Placenta-derived decidua stromal cells), Anakinra, Beta-glucans (AFO-202 and N-163 of a black yeast *Aureobasidium pullulans*), LDRT (Low-dose radiation therapy), ALS (Artificial-liver blood-purification system), and CP (Convalescent plasma) medication for treating COVID-19 patient with cytokine storm syndrome. The use of each treatment has its advantages and disadvantages. However. All of the above therapies have shown effectiveness in treating cytokine storms in clinical trials.

Keywords: COVID-19, Cytokine storm, Treatment, Clinical outcome

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a global health problem, on March 10, 2020 WHO declared that the world was experiencing a pandemic. Today, 15 October 2021, there have been 239,437,517 confirmed cases of COVID-19, including 4,879,235 deaths, reported to WHO [1]. The coronavirus disease caused by the SARS-CoV2 virus causes infecting the lower respiratory tract and causes pneumonia in humans, with symptoms that appear milder than SARS or MERS infection but eventually become a lethal hyperinflammatory disease and respiratory dysfunction [2]. COVID-19, which is caused by the SARS-CoV2 virus, is potentially fatal. Diseases that are a major global public health concern. The SARS CoV2 virus infects the lower respiratory tract and causes pneumonia in humans [3]. SARS-CoV2 infection and disease can be divided into three phases: I. asymptomatic, phase with or without detectable virus; II. less severe symptoms, phase with upper airway involvement; and III. severe, potentially lethal disease with hypoxia, 'ground glass' infiltrates in the lungs, and progression to acute respiratory distress syndrome (ARDS) [4]. These cytokine storms are extremely dangerous. Cytokine storm is considered the reason for the high mortality rate of COVID 19 patients. There is an undetected reason causes a Cytokine storm in a patient, but this is associated with the characteristics of a person's immune system [5]. Most COVID-19 patients recover with mild and moderate symptoms within one week; some develop severe pneumonia in the second week followed by cytokine storm, ARDS, multiorgan failure, and disseminated intravascular coagulation (DIC) within 3 w of illness [6] There was a very significant relationship between comorbidities with treatment and duration of treatment of Pneumonia in COVID-19 patients [7, 40] Patients with pneumonia-degenerative diseases comorbidities had the largest number of patients, and 63.6% had a treatment duration of fewer than 14 d. [8, 41] The high mortality rate in COVID-19 patients is most likely due to the occurrence of a cytokine storm in the patient's body. Cytokines are immune-inflammatory proteins that function to ward off infection and tame cancer cells in the body. Cytokines are also immune system proteins that regulate interactions between cells and trigger immune reactivity, both in innate and adaptive immunity [9]. Cytokine Storm, which is also known as Cytokine Release Syndrome (CRS) or Cytokine Storm Syndrome (CSS) is the occurrence of Systemic Inflammatory Response Syndrome (SIRS), which can be triggered by various factors; and one of them is infection by a virus [10]. If the incoming virus is new (there is no memory in the immune system) and the pathogenic strength is high; Thus, the release of cytokines tends to be uncontrolled. This occurs when a large number of white blood cells are activated and release inflammatory cytokines. Cytokine production becomes irregular rapidly, damaging healthy cells, usually first in the lungs but potentially spreading to other organs, including the kidneys heart [11].

MATERIALS AND METHODS

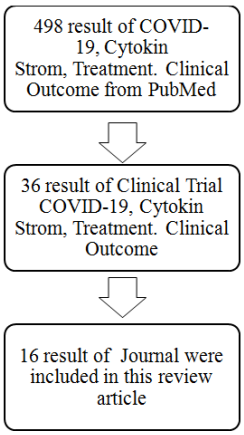

Fig. 1: Framework

Relevant studies were associated with cytokine storm on COVID-19 patients (gender, age, comorbidities, complications, duration of treatment, stage, treatment (Antiviral/Antibiotic), vital signs, clinical complaints, and clinical outcomes of COVID-19 patients) identified from PubMed base on clinical trial. Inclusion criteria were all of the related studies and exclusion criteria were pediatric journals, Cancer journals, pregnant women journal, SIE, SLE, and SLU journal and non-English Journals. Studies were included in the meta-analysis if they match all criteria have been defined.

Tocilizumab

L-6 plays an important role in cytokine storm through various signal transduction pathways. IL-6 binds to the IL-6 receptor (IL-6R) and this complex binds to the transmembrane glycoprotein 130 (gp130), which initiates intracellular signal transduction. This pathway ultimately leads to the promotion of complex biological functions such as proliferation, differentiation, oxidative stress, and immune regulation [12] Tocilizumab is an IL-6 blocking antibody that targets IL-6R thereby inhibiting IL-6R-mediated signal transduction [13] Tocilizumab effectively treat COVID-19 patients in stage 2 (peneunomia/respiratory symptom), possibly due to inhibition of the IL-6-mediated inflammatory storm response [14]. For patients with bilateral lung lesions and elevated IL-6 levels, tocilizumab may be recommended to improve outcomes. The cure rate in the tocilizumab group was higher than in the control group, but the difference was not statistically significant (94.12% vs 87.10%, difference rate 95% CI-7.19%-21.23%, P = 0.4133). The increase in hypoxia for the tocilizumab group was higher from day 4 onwards and statistically significant from day 12 (P = 0.0359). In moderate disease patients with bilateral pulmonary lesions, hypoxia improved earlier after tocilizumab treatment, and fewer patients (1/12, 8.33%) required an increase in inhaled oxygen concentration compared to controls (4/6, 66.67%; difference rate 95% CI–99.17% to–17.50%, P = 0.0217) [15]. Baseline IL-6 greater than 30 pg/ml predicts IMV requirement in patients with COVID-19 and contributes to establish an adequate indication for TCZ administration [16]. Early administration of TCZ was associated with improvement in oxygenation (arterial oxygen tension/fraction of inspired oxygen ratio) in patients with high IL-6 (P =.048). Patients with high IL-6 not treated with TCZ showed high mortality (hazard ratio, 4.6; P =.003), as well as those with low IL-6 treated with TCZ (hazard ratio, 3.6; P =.016) [16]. However, routine use of tocilizumab in patients admitted to hospital with moderate to severe COVID-19 is not supported. Base on the data post-hoc evidence from this study suggests tocilizumab might still be effective in patients with severe COVID-19 [17]. Base on the study, in 180 patients (randomly assigned to the tocilizumab group (n=90) or the standard care group (n=90)) 71 (95% CI −18·23 to 11·19); p=0·42). 33 (36%) of 91 patients in the tocilizumab group and 22 (25%) of 89 patients in the standard care group had adverse events, The most common adverse event was acute respiratory distress syndrome, Serious adverse events were reported in 18 (20%) patients in the tocilizumab group and 15 (17%) in the standard care group; 13 (14%) and 15 (17%) patients died during the study [17] A strategy involving a course of high-dose methylprednisolone (glucocortircoid), followed by tocilizumab if needed, may accelerate respiratory recovery, lower hospital mortality and reduce the likelihood of invasive mechanical ventilation in COVID-19-associated CSS [18] all patients with COVID-19 in the treatment group (n=86) and control group (n=86) had symptoms of CSS and faced acute respiratory failure. Treated patients had 79% higher likelihood on reaching the primary outcome (HR: 1.8; 95% CI 1.2 to 2.7) (7 d earlier), 65% less mortality (HR: 0.35; 95% CI 0.19 to 0.65) and 71% less invasive mechanical ventilation (HR: 0.29; 95% CI 0.14 to 0.65) [18].

Ruxolitinib

Ruxolitinib is a Janus-associated kinase (JAK)1/2 inhibitor approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of polycythemia vera and myelofibrosis [19]. The potential negative impact of ruxolitinib on virus clearance and SARS-CoV-2 antibody production needs to be elucidated. Although no statistical difference was observed, ruxolitinib recipients had a numerically faster clinical improvement. Significant chest computed tomography improvement, faster recovery from lymphopenia, and favorable side-effect profile in the ruxolitinib group were encouraging and informative to future trials to test the efficacy of ruxolitinib in a larger population [20] Forty-three patients were randomly assigned (1:1) to receive ruxolitinib plus standard-of-care treatment (22 patients) or placebo based on standard-of-care treatment (21 patients) ruxolitinib recipients had a numerically faster clinical improvement. Eighteen (90%) patients from the ruxolitinib group showed computed tomography improvement at day 14 compared with 13 (61.9%) patients from the control group (P =.0495). Three patients in the control group died of respiratory failure, with 14.3% overall mortality at day 28; no patients died in the ruxolitinib group. Ruxolitinib was well tolerated with low toxicities and no new safety signals. Levels of 7 cytokines were significantly decreased in the ruxolitinib group in comparison to the control group [20].

Baricitinib

Baricitinib prevented the progression to a severe, extreme form of the viral disease by modulating the patients' immune landscape and these changes were associated with a safer, more favorable clinical outcome for patients with COVID-19 pneumonia [21]. Baricitinib is an oral, selective, and reversible inhibitor of the Janus kinases JAK1 and JAK2 that was previously shown to dampen inflammatory immune responses and approved for indications such as rheumatoid arthritis (RA) [22] Treated a group of patients (n = 20) with baricitinib according to an off-label use of the drug give result that patients were treated with 4 mg baricitinib twice daily for 2 d, followed by 4 mg per day for the remaining 7 d have changes in the immune phenotype and expression of phosphorylated STAT3 (p-STAT3) in blood cells were evaluated and correlated with serum-derived cytokine levels and antibodies against severe acute respiratory syndrome–coronavirus 2 (anti–SARS-CoV-2), patients treated with baricitinib had a marked reduction in serum levels of IL-6, IL-1β, and TNF-α, a rapid recovery of circulating T and B cell frequencies, and increased antibody production against the SARS-CoV-2 spike protein, all of which were clinically associated with a reduction in the need for oxygen therapy and a progressive increase in the P/F (PaO2, oxygen partial pressure/FiO2, fraction of inspired oxygen) ratio [21]. The daily high dose of baricitinib in severe COVID-19 results in early stabilization of the respiratory functions declined requirements of critical care supports, reduced rehospitalization with mortality rate compared to its usual daily dose [23]. Eight milligram and 4 mg of baricitinib was given orally to 122 patients in the high dose (HD) group and 116 patients the usual dose (UD) group, respectively daily for 14 d give result blood oxygen saturation level was stabilized (≥94% on room air) earlie r in the HD group compared to the UD group (5 (IQR: 4-5)/8 (IQR: 6-9), P<0.05). Patients in the HD group required intensive care unit (ICU) and intubation supports more in the UD group than that in patients of the HD group (17.2%/9%, P<0.05; 11.2%/4.1%, P>0.05; N = 116/122, respectively). The 30-day mortality and 60-day rehospitalization rate were higher in the UD group than the HD group (6%/3.3%, P<0.01; 11.9%/7.6%, P>0.05; N = 116/122, respectively) [23].

Itolizumab

Itolizumab is a promising, safe and effective immunomodulatory therapy for the treatment of ARDS due to cytokine release in COVID-19 patients, with survival and recovery-benefit [24] Itolizumab is a humanized IgG1 kappa anti-CD6 monoclonal antibody that binds to domain 1 of human CD6. It selectively targets the CD6-ALCAM pathway resulting in decreased levels of IFN-γ, IL-6, and TNF-α through Th-1 pathway and IL-17, IL-6, TNFα through Th-17 pathway [25, 26]. Thirty-six patients were screened and were randomized (2:1) to Arm-A (best supportive care (BSC)+Itolizumab) and Arm-B (BSC) At end of 1-month, there were three deaths in Arm-B, and none in Arm-A (p = 0.0296; 95% CI =–0.3 (−0.61, −0.08)). At end of study, more patients in Arm-A had improved SpO2 without increasing FiO2 (p = 0.0296), improved PaO2 (p = 0.0296), and reduction in IL-6 (43 vs 212 pg/ml; p = 0.0296) and tumor necrotic factor-α (9 vs 39 pg/ml; p = 0.0253) levels. Transient lymphopenia

(Arm-A: 11 patients) and infusion reactions (7 patients) were commonly reported treatment-related safety events [24].

Zilucoplan

Zilucoplan (complement C5 inhibitor) has profound effects on inhibiting acute lung injury post COVID-19, and can promote lung repair mechanisms that lead to improvement in lung oxygenation parameters [27]. For patients in the experimental arm had received daily 32,4 mg Zilucoplan subcutaneously and a daily IV infusion of 2g of the antibiotic ceftriaxone for 14 d (or until hospital discharge, whichever comes first) in addition to standard of care. And the control group had received standard of care and a daily IV infusion of 2g of ceftriaxone for 1 w (or until hospital discharge, whichever comes first), to control for the effects of antibiotics on the clinical course of COVID-19, for the outcome are primary endpoint is the improvement of oxygenation as measured by mean and/or median change from pre-treatment (day 1) to post-treatment (day 6 and 15 or at discharge, whichever comes first) in PaO2/FiO2 ratio, P(A-a)O2 gradient and a/A PO2 ratio. (PAO2= Partial alveolar pressure of oxygen, PaO2=partial arterial pressure of oxygen, FiO2=Fraction of inspired oxygen) [27].

Stem cell

Conventional treatment with add-on MSC transplantation seems to bring the cytokine storm under control and attenuate disease progression [28]. The immunomodulatory characteristics of MSCs indicate that MSCs can be used as a supportive treatment option for better recovery of critically ill COVID-19 patients. In severe cases, immune system dysfunction is the major cause of death in patients as infection stimulates inflammatory cytokines. MSCs are thought to balance the immune system and stop its overactivation [29]. This ensures that the systemic and local effects of the MSCs given could work faster and more efficiently on COVID-19 infection [28]. MSC transplanation also reduced mortality, decreased ICU stay, and a promising safety profile, MSCs play a specific therapeutic role in the treatment of critically ill COVID-19 patients [28]. The application of infusion UC-MSCs (Umbilical cord mesenchymal stromal cells) significantly decreased IL-6 in the recovered patients (P = .023), application of intravenous infusion MSCs as an adjuvant treatment for critically ill patients with COVID-19 increases the survival rate by modulating the immune system toward an anti-inflammatory state [30] 40 subjects, males (75%) were significantly affected compared with females (P =.049). The mortality rate was 65% (n = 26) and the survival rate was 35% (n = 14), in which 71.4% (n = 10) of the recovered group were from the MSCs group and 28.6% (n = 4) were from the control group, There were 19 subjects (47.5%) who had>2 comorbidities. These subjects had a higher mortality rate than those with<2 comorbidities (79.17% died) [30]. Among the COVID-19 ALI/ARDS patients, DSC (Placenta-derived decidua stromal cells) gave no toxicity or infusion-related adverse effects. DSC therapy decreased the levels of cytokines IL-6, G-CSF, CRP and CCL 2. There was an increase in oxygenation and reversal of pulmonary disease. Four patients could be discharged after a few days. Two patients with COVID-19-induced ARDS and additional serious medical problems died of cardiac arrest and MOF, respectively. DSC therapy could reverse the cytokine storm and should preferably be given to patients with COVID-19 disease with ARDS . DSC infusions had a rapid effect on blood oxygen levels [31].

Anakinra

Recombinant IL-1 receptor antagonist (anakinra) was used during the first wave of pandemic in small series, in different regimens and different disease phases [32] On a larger series of patients with COVID-19 pneumonia, the potential efficacy and safety of the early use of high doses of intravenous anakinra with or without glucocorticoids [33] A total of 128 patients were analyzed; 63 patients received early AIT (30 received anakinra alone and 33 received anakinra plus a glucocorticoid) at admission, and 65 patients did not receive early AIT and were used as controls; of the latter 65 patients, 44 received the SOC treatment alone and 21 received the SOC treatment plus late rescue AIT. After adjustment for all the unbalanced baseline covariates, early AIT reduced the hazard of mortality by 74% (adjusted hazard ratio (HR) = 0.26; P<.001). The effect was similar in patients receiving anakinra alone (adjusted HR = 0.28; P =.04) and anakinra plus a glucocorticoid (adjusted HR = 0.33; P =.07). Late rescue treatment did not show a significant advantage over SOC treatment alone (adjusted HR = 0.82; P =.70)) [33].

Beta-glucans (AFO-202 and N-163 of a black yeast *Aureobasidium pullulans*)

From 24 RT-PCR positive COVID-19 patients were recruited and randomly divided into three groups (Gr): Gr. 1 control (n = 8)-Standard treatment; Gr. 2: Standard treatment+AFO-202 beta-glucan (n = 8); and Gr. 3, Standard treatment+combination of AFO-202 and N-163 beta-glucans (n = 8) for 30 d give result no mortality or requirement of ventilation of the subjects in any of the groups. There was a decrease in D-Dimer values (751 ng/ml to 143.89 ng/ml) and IL-6 values (7.395-3.16 pg/ml) in Gr. 1 in 15 d but the levels increased to abnormal levels on day 30 (D-Dimer: 202.5 ng/ml; IL-6 55.37 pg/ml); which steadily decreased up to day 30 in groups 2 (D-dimer: 560.99 ng/dl to 79.615; IL-6: 26.18-3.41 pg/ml) and 3 (D-dimer: 1614 ng/dl to 164.25 ng/dl; IL-6: 6.25-0.5 pg/ml). The same trend was observed with ESR. LCR and LeCR increased while NLR decreased significantly in Gr. 3. CD4+and CD8+T cell count showed a relatively higher increase in Gr.3 [34].

LDRT (Low-dose radiation therapy)

LDRT appears to be a promising modality of treatment with rapid relief of respiratory distress in selected patients with moderate to severe COVID-19 pneumonia [35] 25 patients with RT-PCR proven COVID-19 pneumonia were treated according to standard COVID-19 management guidelines along with single fraction LDRT of 0.5 Gy to bilateral whole lungs within 10 d of symptom onset and 5 d of hospital admission give result LDRT was well tolerated by all patients. There was a statistically significant improvement in oxygenation as given by the SF ratio between pre-RT and day 2 (p<0.05), day 3 (p<0.001) and day 7 (p<0.001) post-RT. Demand for supplemental oxygen showed a statistically significant reduction between pre-RT and day 2 (p<0.05), day 3 (p<0.001), day 7 (p<0.001) post RT. 88 % patients attained clinical recovery within 10 d post LDRT and median time to hospital discharge from day of LDRT was 6 d. Three patients deteriorated and died [35].

ALS (Artificial-liver blood-purification system)

The artificial-liver blood-purification system (ALS) consists of modules for plasma replacement, plasma adsorption, and blood/plasma filtration and can effectively remove cytokines from the blood. This mainly has been used for the treatment of liver failure and has significantly reduced the mortality of these patients [36] ALS treatment can indeed improve the condition for COVID-19 patients; results showed that treatment with ALS mainly improved both lung and kidney function, a total of 32 cytokines were found to be significantly decreased. The levels of TNF-α and IL-6 significantly decreased after three courses of ALS. The IL-1β level was also decreased after the first course of ALS (37). Although the present study showed that therapeutic strategies with ALS can significantly reduce a patient's cytokine levels, the present study is a nonrandomized clinical trial. Hence, it is difficult to provide clear evidence to determine whether ALS could reduce the mortality rate, so recommend early assessment of COVID-19 patients and timely intervention with ALS to improve the prognosis [37].

CP (Convalescent plasma)

The convalescent plasma comprises a wide variety of blood-derived components, including neutralizing antibodies (NAbs), organic and inorganic compounds, water, and a great number of various proteins (coagulation factors, albumin, etc.) [38] 62 eligible COVID-19 patients were assigned to this clinical trial. All patients were in the secondary infection phase, i.e., pulmonary and hyperinflammatory stage presenting with the symptoms of persistent cough, shortness of breath, and low oxygen levels. In the present clinical trial, the immunomodulatory effect of CP therapy on cytokine storm indices was evaluated, and the results were noteworthy. The CP therapy (plus standard drugs), compared to merely standard treatments, significantly increased the mean level of absolute lymphocytes and

decreased the mean levels of IL-6, TNF-α, and IFN-γ. In addition, the mean level of IL-10 was significantly increased after CP therapy on the day of discharge compared with its base level [37] however, convalescent plasma could not strongly affect the mortality rate in spite of its significant ameliorative effect on cytokine storm [39].

CONCLUSION

Base on the literature on clinical trial we found that we can use Tocilizumab, Ruxolitinib. Baricitinib, Itolizumab, Zilucoplan, Stem Cells (MSC transplantation, Umbilical cord mesenchymal stromal cells, and Placenta-derived decidua stromal cells), Anakinra, Beta-glucans (AFO-202 and N-163 of a black yeast *Aureobasidium pullulans*), LDRT (Low-dose radiation therapy), ALS (Artificial-liver blood-purification system), and CP (Convalescent plasma) medication for treating COVID-19 patient with cytokine storm syndrome. The use of each treatment has its own advantages and disadvantages. Futhermore, all of the above treatments have shown effectiveness in the treatment of cytokine storm in clinical trials.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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