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Global Journal of Medical, Pharmaceutical, and Biomedical Update

Review Article

Pharmacotherapy of Cytokine Release Syndrome in Severe COVID-19 Patients: A Systematic Review

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Received : 31 August 2021
Accepted : 16 September 2021
Published : 07 October 2021

DOI
10.25259/GJMPBU_9_2021

Quick Response Code:

ABSTRACT

The coronavirus pandemic which spread from Wuhan China toward the latter part of 2019 has resulted in 216,303,376 confirmed cases and 4,498,451deaths deaths to date. The novelty and lack of a definitive treatment protocol for the virus and the acute respiratory distress syndrome it produces has resulted in patients being placed on artificial ventilation and most often never recovering therefrom. Very little is known about the pathophysiology of the virus and the biological mechanisms in which it disrupts to bring about the now identified wide array of clinical features which are not solely isolated to the respiratory tract. It is now an established fact however, that one of the major pathways implicated and on which often results in the death and or severe complications in COVID-19 patients is the cytokine storm. The use of new drugs to combat such a cytokine storm is thus important considering the current global COVID-19 situation so as to stop the further progression of the disease in patients and decrease both morbidity and mortality by crippling a major mechanism which hastens death in the hosts. It is, therefore, vital that a systematic analysis and review of the various therapeutic agents are undertaken to select the best drug for the treatment of patients with cytokine storm. This research aims to relate the best therapeutic regimens currently available precisely and concisely to physicians so as to ensure the best possible treatment modality is selected for each patient. An extensive review of the literature was done on the following databases: Google scholar, Trip database, EMBASE, PubMed, and PubMed Central. The keywords and the Boolean operators used for searches were "COVID-19" OR "SARS-CoV-2" AND "Therapeutics" OR "drug therapy" AND "Cytokine Release Syndrome." The discovery and the use of such drugs, namely, Tocilizumab and potent corticosteroids such as dexamethasone and methylprednisolone in the maximum daily doses of 6 mg and 250 mg, respectively, have shown positive outcome to combat cytokine storm in severe COVID-19 patients. The rationale behind the use of these drugs being to suppress the immune system and thus decrease the detrimental cytokine cascade induced in severely ill COVID-19 patients will be instrumental in the treatment and prevention of severe complication. It is vital for the various drugs under trial and implemented in emergency use to be compared and studied so as to best select the drug which can be incorporated into a treatment regimen which is both effective and has diminished adverse effects.

Keywords: Coronavirus, Cytokine release syndrome, Drug therapy, SARS-CoV-2, Systemic inflammatory response syndrome

INTRODUCTION

The coronavirus pandemic which spread from Wuhan China toward the latter part of 2019 has resulted in 216,303,376 confirmed cases and 4,498,451deaths to date.[1-4] The SARS-CoV-2 virus is chiefly implicated as a disease and infection of the respiratory tract,[5] although other systemic manifestations and presentations have been reported.[6,7] The infection with the coronavirus pathogen generally occurs post exposure to droplets generated from the respiratory tract of an infected patient or fomites harboring those droplets.[8] The majority of patients whom suffer from the coronavirus

infection present with an atypical pneumonia and have a ground glass appearance of the lungs on chest radiology.[9,10] A cohort of 15% of the infections progress to a more severe condition and develop acute respiratory distress syndrome (ARDS). The deadly nature and high mortality in patients who develop the manifestations towards the more severe spectrum are attributed to the severe cytokine storm induced in patients by the virus.[11-13]

The novelty and lack of a definitive treatment protocol for the virus and the ARDS it produces has resulted in patients being placed on artificial ventilation and most often never recovering therefrom. A major challenge faced by physicians world-wide due to the novelty of the virus is the fact that little to no prior knowledge is available to understand the unique and complex pathophysiology behind the mechanism of the virus and the manner in which it induces such a severe ARDS.[10] Furthermore, creating great difficulty in the initial phases of the outbreak of the pandemic was that no protocol for the treatment of COVID-19 cases existed. The pathophysiology by which the virus acts and the biological mechanisms which it disrupts to bring about the now identified wide array of clinical features which are not solely isolated to the respiratory tract, may hold the key to aid in the treatment of patients.[14] It is, therefore, vital that a systematic analysis and review of the various therapeutic agents are undertaken so as to select the best drug for the treatment of patients. This research aims to relate the best therapeutic regimens currently available precisely and concisely to physicians so as to ensure the best possible treatment modality is selected for each patient.

IMMUNOPATHOPHYSIOLOGY OF CYTOKINE RELEASE SYNDROME/STORM

It is now an established fact, however, that one of the major pathways implicated and on which often results in the death and or severe complications in COVID-19 patients is the cytokine storm.[15] The most severe form of the coronavirus disease (SARS-CoV-19) manifests itself and may be characterized through ARDS, disseminated intravascular coagulopathies, and multiple organ failure all of which have been attributed to systemic hyperinflation now known as the cytokine storm. The cytokine storm or cytokine release syndrome refers to a conglomerate of clinical conditions precipitated by excessive and uncontrolled immune activation and reactions; this severe immunological cascade has now been established to be a leading factor in the development of the most severe forms of the COVID-19 infection and its life-threatening manifestations.[16]

A meta-analysis conducted by Mulchandi *et al*. describes the underlying mechanism and onset of hypercytokinemia in infected patients. The SARS-CoV-2 virus enters the body through the endothelial lining of the lungs after binding to the ACE-2 receptors (angiotensin converting enzyme receptors) which are found in high concentrations within the pulmonary tract. The use of ACE inhibitors can lead to upregulation of ACE-2 receptors and can increase the port of entry for SARS-Cov-2. This process activates the innate immune system and the primary immune response is initiated which is characterized by a marked rise in inflammatory cytokines. The type 1 interferon (IFN-1) which is delayed in response in COVID-19 patients is synonymous with the most severe manifestations and forms of the disease. An increased viral multiplication and an anomalous exaggeration induced by the IFN-1 are noted and marks the start of the vicious inflammatory cycle and cascade. The increased and ramped up induction of the type I IFN signaling pathways causes massive chemotaxis and immune cellular activation to take place. In light of this immune-dysregulation the pulmonary tract receives a barrage and influx of acute inflammatory cells such as neutrophils, macrophages, natural killer cells, and dendritic cells. The infiltration of these acute phase cells into the lung tissue provides the perfect setting for the dreaded cytokine storm, as the immune cells now present in the lungs act as the source of inflammatory cytokines and induces the second barrage of cytokines, producing the feared cytokine storm.[17-19]

Various cytokines are involved in the most severe forms of the coronavirus infections, namely, tumor necrosis factor-alpha (TNFα), interferon-gamma (IFNγ), and interleukins IL-1B, IL-3, IL-6, IL-8, and IL-10.[20] The use of new drugs to combat such a cytokine storm is thus important in light of the current global COVID-19 situation so as to stop the further progression of the disease in patients and decrease both morbidity and mortality by crippling a major mechanism which hastens death in the hosts.

METHODOLOGY

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this systematic review.

LITERATURE SEARCHES

An extensive review of literature was completed on the following databases: Google scholar, Trip database, EMBASE, PubMed, and PubMed Central. A combination of keywords and Boolean operators were used for the searches, namely: "COVID-19" OR "SARS-CoV-2" AND "Therapeutics" OR "drug therapy" AND "Cytokine Release Syndrome." All of the published manuscripts emphasizing the pharmacotherapy of the cytokine release syndrome in severe COVID-19 patients were screened and included in this systematic review.

Inclusion criteria

All the published full text randomized and non-randomized clinical trials in the English literature were included in the study. All the randomized and non-randomized clinical trials

completed and published between January 01, 2021, and July 19, 2021, which focused on the therapy of the cytokine release syndrome in severe COVID-19 patients were screened thoroughly by three researchers and were included in this systematic review.

Exclusion criteria

The choice to exclude a study was dependent on the availability of data concerning the therapy of cytokine release syndrome in severe COVID-19 patients. Abstracts, Cross-sectional studies, Cohort studies, Case series, Case study, Reports, Editorial, Viewpoint, and letter to the editor type of manuscripts were excluded from this study.

DATA EXTRACTION

Appropriate titles of the studies were initially searched for on the various databases. The selected titles were then screened; for the abstracts and full texts of randomized controlled trials and non-randomized control trials and those which met the eligibility requirements were considered for ultimate selection. All of the literature evaluation was independently conducted by three researchers (JR, IB and AL). The extracted data include study authors, year, gender, design, sample size, study population, control, design severe pneumonia/multi-organ failure/coagulopathies/cytokine release syndrome, baseline inflammatory profile, combination of drug/s, therapeutic protocol, findings, limitations of the study, and study outcome.

METHODOLOGY QUALITY ASSESSMENT

The CONSORT, 25 item checklist was used to assess the methodological quality of the studies that met the inclusion criteria of the randomized controlled trails. The CONSORT criteria checklist is most appropriate for the methodological quality assessment of randomized controlled trials in epidemiology. While, non-randomized studies were evaluated through the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool.

RESULTS AND DISCUSSION

The literature search conducted resulted in a total of 5116 articles, of which 4,619 were identified as irrelevant and duplicates that were excluded in the primary screening. An in-depth evaluation and analysis of the relevant titles and abstracts based on inclusion and exclusion criteria led to the further exclusion of 5 articles from the analysis quality assessment. Ultimately, nine studies have assessed the treatment/management of the cytokine release syndrome in severe COVID-19 patients and were included in the current systematic review [Figure 1].[21-29]

The systematic review revealed two therapeutic contenders that should be utilized in patients suffering from the cytokine release syndrome. A tocilizumab/corticosteroid combination and the second being a therapeutic plasma exchange (TPE).[30-33] These drug regimens having different mechanisms but ultimately being implemented to suppress the immune system and/or decrease the level of circulating to cytokines to thus decrease the detrimental cytokine cascade induced in severely ill COVID-19 patients. The use of these drugs will be instrumental in the treatment and prevention of severe complications.[34,35]

[Tables 1 and 2] depict the number of intervention patients, the number of control group patients, the baseline inflammatory profile, the combination of drugs prescribed, and the outcomes of the therapy in patients suffering from COVID-19. Ramiro *et al*. conducted a randomized control trial with 86 intervention patients and 86 control group patients. The inclusion criteria for the patients being, namely, those suffering from Cytokine release syndrome: High CRP (>100 mg/L), high serum ferritin (>900 μg/L at one occasion, or a two-fold increase of the level at admission within 48 h), and high D-dimer level (>1500 μg/L). A combination therapy was administered to the intervention group of Tocilizumab and methylprednisolone. The combination therapy was administered in conjunction with the following protocol: Tocilizumab on day 2 and day 5 (single-dose TCZ, 8 mg/kg body weight intravenous) and methylprednisolone: 250 mg intravenously on day 1, followed by MP 80 mg intravenously on days 2–5. The outcomes of patients being excellent with the treatment resulting in a hospital mortality equating to 65% lower in the treatment as opposed to the control group.[21]

A similar randomized controlled trial (phase 3) conducted by Soin *et al*. 2021 on Tocilizumab monotherapy on 99 intervention patients and 88 control group patients. The inclusion criteria of the study being patients suffering from moderate to severe disease defined according to the Indian MoHFW clinical management protocol for COVID-19 (moderate defined as respiratory rate 15–30 per min [revised to 24 per min on June 13, 2020] and blood oxygen saturation [SpO_2] 90–94%; and severe defined as respiratory rate ≥30 per min or SpO_2 <90% in ambient air, or ARDS or septic shock). The therapeutic protocol for the study being and initiation dose of a single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg. Additional dose of 6 mg/kg (max 480 mg/kg) administered if clinical symptoms worsened or did not show improvement within 12 h to 7 days.[26] The study outcome revealed polar outcomes as when compared to the study conducted by Ramiro *et al*. as no significant difference was observed between the tocilizumab group and the standard care group in the secondary endpoints; however,

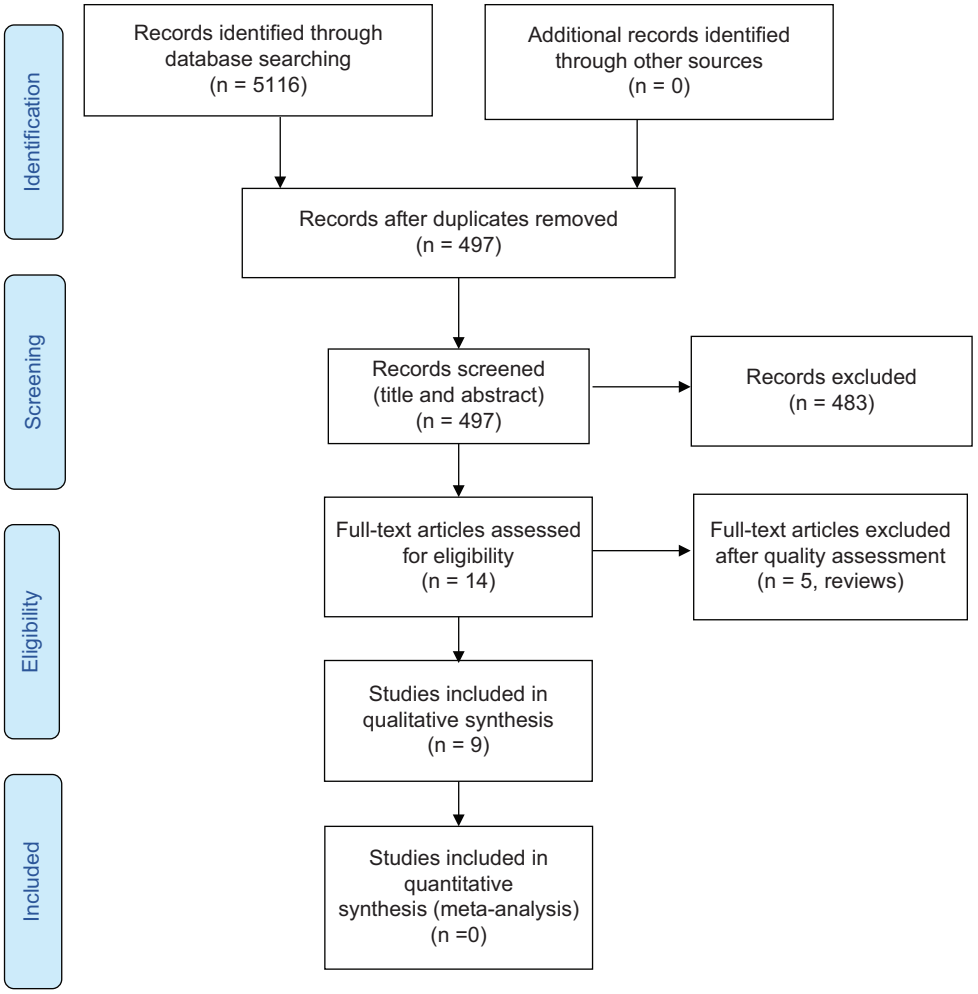

Figure 1: Inclusion of articles by preferred reported items for systematic reviews.

post hoc analyses revealed a subset of patients with severe disease in whom tocilizumab might reduce mortality. This therefore favoring the combination therapy of tocilizumab and methylprednisolone which had far greater patient outcomes when used together as opposed to tocilizumab monotherapy.[36,37]

A randomized controlled trial (phase 3) conducted by Lescure *et al*. 2021 which compared high dose versus low doses versus control group studies of the drug Sarilumab which included 173 patients on high dose therapy, 159 patients on low dose therapy, and 84 patients receiving a placebo therapy. The relative inclusion criteria for the study were patients suffering from pneumonia whom required oxygen supplementation or intensive care treatment. The therapeutic protocol for the study was conducted as follows Sarilumab 400 mg for the high dose group, sarilumab 200 mg for the low dose group, and 0.9% NaCl for the placebo group. The patient outcome between the high and low dose therapy was negligible. The decline in the patients mean CRP was steeper in the sarilumab groups than in the placebo group, with a rebound at day 7 in the 200 mg group and day 15 in the 400 mg group.[23]

An open label randomized controlled trial conducted by Faqihi *et al*. 2021, treated 43 patients with TPE therapy and 44 control or non-intervention patients with the empirical therapies which include doses of antivirals (ribavirin 400 mg every 12 h for 14 days), dexamethasone (6 mg/day for 7 days), anticoagulants, and ICU management. The TPE was administered without protective antibodies at a dose of 1.5 plasma volumes used for initiation treatment, then one plasma volume daily (sessions lasted for 4 h) to a maximum of five doses. TPE resulted in a significant decrease of SOFA scores in the intervention group compared with the controls' added to standard therapy compared with standard therapy alone resulted in clinical recovery but did not significantly affect 35-day mortality.[24] It is stipulated that TPE is advantageous in preventing and or reducing the cytokine storm as it has the innate ability to remove proportions of inflammatory

Table 1: Summary of the studies, sample size used, and inclusion criteria.

Author, year	Gender	Design	No. of intervention patients	Control group of patients	Inclusion criteria: severe pneumonia/ multi-organ failure/coagulopathies/ cytokine release syndrome
Ramiro *et al*., 2020[21]	68M 18F	Randomized controlled trial	86	86	Cytokine release syndrome: high CRP (>100mg/L), high serum ferritin (>900µg/L at one occasion, or a two-fold increase of the level at admission within 48h) and high D-dimer level (>1500µg/L)
Declercq *et al*., 2020[22]	Not reported	Randomized controlled trial (Phase 2)	54	27	Signs of cytokine release syndrome characterized by either high serum ferritin, or high D-dimers, or high LDH or deep lymphopenia or a combination of those
Lescure *et al*., 2021[23]	261M 155F	Randomized controlled trial (Phase 3)	High dose: 173 Low dose: 159	Placebo: 84	Pneumonia with required oxygen supplementation or intensive care
Faqihi *et al*., 2021[24]	72M 15F	Randomized controlled trial (open label)	43	44	Requirement for intubation, ICU admission; ARDS
Kumar *et al*., 2021[25]	26M 4F	Randomized controlled trial (Phase 2)	20	10	Moderate to severe ARDS and/or high levels of pro-inflammatory markers. Oxygen saturation≤94% Baseline serum ferritin level≥400 ng/mL or IL-6 levels greater than 4 times of upper limits of normal value
Soin *et al*., 2021[26]	153M 27F	Randomized controlled trial (phase 3)	91	88	Moderate to severe disease defined according to the Indian MoHFW clinical management protocol for COVID-19 (moderate defined as respiratory rate 15–30 per min [revised to 24 per min on June 13, 2020] and blood oxygen saturation [SpO_2] 90–94%; and severe defined as respiratory rate≥30 per min or SpO_2<90% in ambient air, or ARDS or septic shock
Díaz *et al*., 2020[27]	30M 42F	Non-randomized Clinical trial	19	53	Subjects older than 64 years with at least one comorbidity considered to pose a serious risk for the disease (hypertension, ischemic heart disease, diabetes mellitus, cancer, chronic kidney disease, obesity, malnutrition, or chronic obstructive pulmonary disease
Gluck *et al*., 2020[28]	3M 7F	Non-randomized Clinical trial	10	n/a	Eligible patients were COVID-19 positive by polymerase chain reaction, met criteria for Penn class 3 or 4 CRS, were aged 12–80 and required supplemental oxygen or mechanical ventilation
Hernandez-Cedeño *et al*., 2021[29]	11M 13F	Non-randomized Clinical trial	24	n/a	Severe or critical condition according to the Cuban national protocol approved by the Ministry of Public Health for COVID-19

NA: Not applicable, M: Male, F: Female

cytokines, for example: TNFα, IFNγ, and interleukins IL-1B, IL-3, IL-6, IL-8, and IL-10. This thereby decreasing the inflammatory reactants within the patients system.[38]

A further clinical trial conducted on TPE by Gluck *et al*., 2020 on ten patients depicted the positive results produced by TPE. The ten patients were administered five single volume plasma

Table 2: Summary of Baseline inflammatory profile, combination of drugs, therapeutic protocol, main findings, limitations and outcome.

Author, year	Baseline inflammatory profile: Ferritin (µg/L) CRP (mg/L) D-dimers (mg/L)	Combination of drug/s	Therapeutic protocol	Main findings	Potential limitations	Outcome of therapy ±
Ramiro *et al*., 2020[21]	**Control:** CRP: 167 Ferritin: 1849 D-dimers: 5633 **Treated:** CRP: 160 Ferritin: 1493 D-dimers: 3935	Tocilizumab and/or methylprednisolone	Tocilizumab: day 2 and day 5 (single-dose TCZ, 8mg/kg body weight intravenous) methylprednisolone: 250mg intravenously on day 1, followed by MP 80mg intravenously on days 2–5	Hospital mortality was 65% lower in the treatment group than in the control group (HR: 0.35; 95% CI 0.19 to 0.65)	No known limitations	+
Declercq *et al*., 2020[22]	Not yet reported	Zilucoplan and ceftriaxone	Zilucoplan: subcutaneously and a daily IV infusion of 2 g of the antibiotic ceftriaxone for 14 days Ceftriaxone: daily IV infusion of 2 g	Not yet reported	Not yet reported	±
Lescure *et al*., 2021[23]	**Placebo:** CRP: 95·5. Ferritin: 979.6 D-dimers: 500 **200 mg:** CRP: 94·1 Ferritin: 694.6 D-dimers: 480 **400 mg:** CRP: 96.1 Ferritin: 737 D-dimers: 540	Sarilumab	Sarilumab 400 mg sarilumab 200 mg 0.9% NaCl for placebo	No significant difference in survival between sarilumab 400 mg (n=60 [88%]) and placebo (*n*=23 [79%]; difference+8·9% [95% CI−7·7 to 25·5]; *P*=0·25) The decline in mean CRP was steeper in the sarilumab groups than in the placebo group, with a rebound at day 7 in the 200 mg group and day 15 in the 400 mg group	Efficacy endpoints insufficiently sensitive for the wide range of disease severity studied in this trial.	-
Faqihi *et al*., 2021[24]	**Control:** CRP: 234 Ferritin: 1573 D-dimers: 2.5 **Treated:** CRP: 246 Ferritin: 1665 D-dimers: 4.9	Therapeutic plasma exchange	A dose of 1.5 plasma volumes used for initiation treatment, then one plasma volume daily (sessions lasted for 4 h) to a maximum of five doses	TPE resulted in a significant decrease of SOFA scores in the intervention group compared with controls. TPE added to standard therapy compared with standard therapy alone resulted in clinical recovery but did not significantly affect 35-day mortality	Study was terminated early because of waning SARS-CoV-2 numbers Open-label and single-center study	+

(Contd...)

Table 2: *(Continued)*

Author, year	Baseline inflammatory profile: Ferritin (µg/L) CRP (mg/L) D-dimers (mg/L)	Combination of drug/s	Therapeutic protocol	Main findings	Potential limitations	Outcome of therapy ±
Kumar *et al*., 2021[25]	**Control:** CRP: 103.88 Ferritin: 496.93 D-dimers: 5150 **Treated:** CRP: 73.74 Ferritin: 669.79 D-dimers: 3500	Itolizumab	Initiation dose of 1.6 mg/kg i.v infusion of Itolizumab followed by a 0.8 mg/kg dose weekly	Itolizumab improved patients' survival through reduction in the 1-month mortality rate. A statistically significant difference (P=0.029; 95% CI=−0.3 [−0.61, −0.08] 3 deaths recorded in the control group and none in the intervention group	Small study sample of only 30 patients total	+
Soin *et al*., 2021[26]	**Control:** CRP: 52 Ferritin: 52 D-dimers: not performed **Treated:** CRP: 53 Ferritin: 54 D-dimers: not performed	Tocilizumab	Initiation dose of a single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg. Additional dose of 6 mg/kg (max 480 mg/kg) administered if clinical symptoms worsened or did not show improvement within 12 h to 7 days	No significant difference was observed between the tocilizumab group and the standard care group in the secondary endpoints Post-hoc analyses revealed a subset of patients with severe disease in whom tocilizumab might reduce mortality	Unmasked study with no placebo. Most patients received concomitant corticosteroids during the trial, and about half received antiviral therapy with remdesivir. The use of concomitant medications in patients could have muted any beneficial effect that tocilizumab might otherwise have had	±
Díaz *et al*., 2020[27]	D-dimer was increased in 84.6% of the patients	Itolizumab	One dose of the antibody, while 89.5% received two doses	Among every 3 moderately ill patients treated with itolizumab, 1 admission to the ICU was prevented (P=0.042, χ^2 test; NNT 3.12)	lack of a concurrent control group. The short kinetics of IL-6 levels, limited follow-up of the patients	+

(Contd...)

Table 2: *(Continued)*

Author, year	Baseline inflammatory profile: Ferritin (µg/L) CRP (mg/L) D-dimers (mg/L)	Combination of drug/s	Therapeutic protocol	Main findings	Potential limitations	Outcome of therapy ±
Gluck *et al*., 2020[28]	**Control:** (before TPE) CRP: 149.9 Ferritin: not mentioned D-dimers: not mentioned **Post intervention:** CRP: 24.8 Ferritin: not mentioned D-dimers: not mentioned	Therapeutic plasma exchange	Five single volume plasma exchanges over 8 days within a 14-day period	Six of the ten patients, including all four Penn class 3 and two of the six Penn class 4 patients, experienced a clinical benefit All four non-ventilated patients were liberated from supplemental oxygen after TPE. The response was rapid with an 87% average reduction of oxygenation requirements following the second TPE (day 3) and average time to return to room air of 5.25 days	Small study sample of only 10 patients	+
Hernandez-Cedeño *et al*., 2021[29]	**Seriously ill patients:** CRP: 93 Ferritin: 663 D-dimers: not mentioned **Critically ill patients:** CRP: 182 Ferritin: 1070 D-dimers: not mentioned	CIGB-258	CIGB-258 dose of 2 mg or 1 mg every 12 h, for critically or seriously ill patients, respectively.	Seriously ill patients had a marked improvement in their clinical condition after 48 h All patients included in this study were discharged from the hospital Granzyme B and perforin levels decrease significantly in the serum of patients 96 h post-initiation of the treatment	No placebo-controlled trials performed	+

–: Indicates little sign of improvement in patient outcome after intervention, +: Indicates greater sign of improvement in patient outcome after intervention

exchanges over 8 days within a 14-day period. The plasma analysis of the patients showed a radical decrease in the CRP level as follows, control: (before TPE) CRP: 149.9 mg/l post-intervention: CRP: 24.8 mg/l. The patient outcome was also very positive as six of the ten patients, including all four Penn Class 3 and two of the six Penn Class 4 patients, experienced a clinical benefit. All four non-ventilated patients were liberated from supplemental oxygen after TPE. The response was rapid with an 87% average reduction of oxygenation requirements following the second TPE (day 3) and average time to return to room air of 5.25 days.[28] Although the small number of patients enrolled in the study are its greatest pitfall, when correlating such results with that of Faqihi *et al*. 2021 whom also had such positive results with TPE, it is

evident that TPE is a truly viable and useful drug and therapy to combat the cytokine storm in COVID-19 patients.[24,28]

A clinical trial conducted by Hernandez-Cedeño *et al*., 2021, on patients using CIGB-258, a peptide derived from human heat-shock protein 60, has shown positive results. The study was conducted on 24 patients whom met the following clinical criteria: Patients whom were in a severe or a critical condition according to the Cuban national protocol approved by the Ministry of Public Health for COVID-19. CIGB-258 was administered in a dose of 2 mg or 1 mg every 12 h, for critically or seriously ill patients, respectively. The drug had positive results as the seriously ill patients had a marked improvement in their clinical condition after 48 h. All patients included in this study were discharged from the hospital. Granzyme B and perforin levels decrease significantly in the serum of patients 96 h post-initiation of the treatment.[29] The results from this study and the likelihood of CIGB-258 being an alternative treatment to counter the cytokine storm are promising however the limitations of this study call for a larger intervention group as well as the need for a placebo group is severely in need. Once the above limitations are rectified and further study is conducted that the actual use of CIGB-258 can be thoroughly and accurately assessed.[29]

It is evident that two sets of therapies in the study yielded the best patient outcome. Tocilizumab in combination with methylprednisolone and the therapeutic plasma exchange therapy (TPE) was proven to be the most efficacious in the treatment of cytokine release syndrome in severe COVID-19 patients.[26,28] Tocilizumab is a biologic drug, which is immunosuppressive in nature. It is evident, however, that the use of tocilizumab is enhanced when administered in combination therapy with methylprednisolone, thus producing a far greater patient outcome.[39] Methylprednisolone is a corticosteroid drug which is also immunosuppressive in nature and thus the two immunosuppressive drugs used in combination far outweighs their use and efficacy as when used in a monotherapy. This is evident as when tocilizumab is used in a monotherapy the results are far less efficacious and desirable as when used in combination. These two drugs work in unison to prevent the severe hyperimmune state seen in the cytokine storm through their immunosuppressive actions. TPE therapy was proven to be an effective therapy in the prevention and or treatment of the cytokine storm.[24] The TPE therapy acts differently to the immunosuppressive drugs (Tocilizumab/methylprednisolone). The principal of dilution of circulating cytokines is at play in TPE therapy and may be more beneficial than a complete immunosuppression therapy as to diminish the side effects such as Mucormycosis, secondary infections, and avascular necrosis which have been noted.[40] It is advised that further investigation should be undertaken to test whether if a combination and or staggered dosing of TPE and immunosuppression agents such as tocilizumab and methylprednisolone use together will produce an enhanced effect on patients as they act through different mechanisms and thus may further circumvent and or diminish the severity of the cytokine release syndrome; subsequently decreasing morbidity and mortality in severe COVID-19 patients.[41]

CONCLUSION

The biologic drug tocilizumab and potent corticosteroids such as methylprednisolone used in combination at the dosages of 8 mg/kg body weight and 250 mg on day 1, followed by 80 mg days 2–5, respectively, have been proven to suppress the immune system and thus decrease the detrimental cytokine cascade induced in severely ill COVID-19 patients. Similarly TPE at the dosages of 5 single volume plasma exchanges over 8 days within a 14-day period have also been shown to produce positive patient outcomes and will be instrumental in the treatment and prevention of severe complications attributed to the cytokine storm. It is advised that physicians select one of the above treatment regimens which are best suited to their patient's specific overall profile.

Recommendation

None.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Robinson J, Banerjee I, Leclézio A. Pharmacotherapy of Cytokine Release Syndrome in Severe COVID-19 Patients: A Systematic Review. Glob J Med Pharm Biomed Update 2021;16:8.