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The Efficacy of Tocilizumab as a Therapeutic Treatment for SARS-CoV-2 Infections: An Integrative Literature Review

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The Efficacy of Tocilizumab as a Therapeutic Treatment for SARS-CoV-2 Infections:

An Integrative Literature Review

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Abstract

The novel coronavirus SARS-CoV-2 and resulting COVID-19 infection has spread from a cluster of unidentified pneumonia cases in Wuhan, China, into an ongoing global health crisis. The strain on the healthcare systems and loss of human life has made finding ways to treat severe COVID-19 infections of the utmost importance. Mortality from COVID-19 has been shown to result from an overwhelming inflammatory response similar to the cytokine release syndrome seen in certain autoimmune reactions (Tleyjeh et al., 2020). It also can be seen after chimeric antigen receptor T-cell (CAR-T) therapy for certain cancers. It is hypothesized that treatments targeting the prevention of the "cytokine storm" would improve patient outcomes. One of the specific intended targets is that of interleukin 6 (IL-6), one of the pro-inflammatory cytokines found in the cytokine release syndrome (CRS). Tocilizumab is a medication that is potentially given post CAR-T therapy to prevent CRS (Campochiaro et al., 2020) This medication works by inhibiting IL-6 and halting the immune response that triggers the inflammatory cascade. This review of the literature examines the efficacy of tocilizumab in the treatment of severe COVID-19 infections.

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Introduction

Introduction to the Inquiry

The novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified at the end of 2019 following an outbreak of unexplained pneumonia cases in Wuhan, China (Alzghari & Acuna, 2020). The resulting infection, officially labeled the coronavirus disease 2019 (COVID-19) on February 11, 2020, has since spread into a global pandemic and a public health crisis (Xu et al., 2020). As of November 24, 2021, COVID-19 has been identified in 259 million cases and 5.17 million deaths worldwide and is still causing turmoil throughout the globe (Centers for Disease Control and Prevention, [CDC], 2021) The United States has had 47.8 million cases and 772,180 deaths thus far, and the numbers continue to climb (CDC, 2021). Treatment for COVID-19 is supportive in nature and aims to shorten disease course and diminish disease severity. Therefore, the research regarding these potential therapies is of paramount importance.

SARS-CoV-2 is a ribonucleic acid (RNA) virus from the genus Betacoronavirus that utilizes a glycoprotein, or spike protein, to bind to the host's angiotensin-converting enzyme 2 (ACE2) receptor (Stasi et al., 2020). Once the spike protein is bound to the ACE2 receptor, the virus gains entry to the host cell via the protease TGRBSS2 (Stasi et al., 2020).

COVID-19 has extremely variable clinical course from person to person. In some cases, it is asymptomatic while others become critically ill and develop acute respiratory distress syndrome (ARDS) (Salveti et al., 2020). Individuals with altered immune function and the elderly are particularly susceptible to severe disease and have higher mortality rates (Xu et al, 2020). Individual susceptibility of the host to potentiating a dysfunctional immune response seems to be associated with increased severity of the disease process (Menzella et al., 2020). Lan

et al. (2020) found that severe cases of COVID-19 have an overall mortality rate of 6.36%, although multiple variants have different outcomes and mortality rates differ greatly across age groups.

Background and Reason for Inquiry

Individuals with a severe clinical course requiring intensive care treatment often present in a hyperinflammatory state. The lab values of these critically ill patients show elevated serum interleukin-6 (IL-6) levels and other pro-inflammatory cytokines, which represent a "cytokine storm" or cytokine release syndrome (CRS) (Lan et al., 2020). Dastan et al. (2020) used an IL-6 level over 10 pg/mL as a marker of hyperinflammation. Elevated tumor necrosis factor and granulocyte colony stimulating factor were also noted (Mady et al., 2020). CRS seems to play a role in severe COVID-19 (Klopfenstein, et al. 2020).

Mady et al. (2020) found that the increase in inflammatory factors can cause a myriad of clinical problems that worsen the disease course. Post-mortem examination of COVID-19 lung tissue found micro thrombosis, proteinaceous exudate, and alveolar edema, which suggests that the hyperinflammation and associated thromboembolic disease enhanced the lung tissue damage and resulting fibrosis (Mady, et al, 2020). Other laboratory values such as an elevated C-reactive protein (CRP), ferritin, and D-Dimer were also noted and further represent a dysregulation of the immune system (Mady et al., 2020). Campochiaro et al. (2020) defined hyperinflammation as having a CRP greater than or equal to 100 mg/L and a ferritin of greater than or equal to 900 ng/mL. Klopfenstein et al. (2020) reported that elevations in CRP, ferritin, and IL-6 to represent a significant increase in mortality for this patient population.

CRS is associated with many of the negative clinical outcomes seen in COVID-19 and may contribute to an elevated morbidity and mortality (Price et al., 2020). In CRS, the release of

pro-inflammatory cytokines occurs in response to the activation of the immune system's inflammatory cascade. The resulting inflammation is associated with cardiovascular events, multi-organ failure, and death (Price et al., 2020). Klopfenstein et al (2020) also attributes the lung injury titled acute respiratory distress syndrome (ARDS) seen in COVID-19 to this cytokine inflammatory response. The post-viral hyperinflammation usually occurs in the second week of the illness and is associated with worsening severity of the disease (Klopfenstein et al, 2020).

When the immune system is acting properly, macrophages are activated via two methods, damage-associated molecular patterns (DAMPS), and pathogen-associated molecular patterns (PAMPS). DAMPS are pieces of cells damaged by the virus. PAMPS are part of the virus themselves, such as viral RNA (Tleyjeh et al., 2020). These molecules activate receptors which then trigger an innate antiviral immune response and adaptive immunity to fight the infection and begin the healing process.

Severe COVID-19 disease seems to be caused by the dysregulation of this innate immune response, most likely activated by a type of cell death called pyroptosis. Pyroptosis activates several proinflammatory cytokines (including IL-6) that promote immune recruitment to the affected tissues. This immune overreaction promotes an increase of cell damage (Tleyjeh et al., 2020).

The elevation of these cytokines and other proinflammatory markers are associated with higher disease severity and worsening overall prognosis in COVID-19 infection (Tleyjeh et al., 2020). Therefore, treatments aiming to reduce this immune reaction and decreasing the levels of proinflammatory markers are now being evaluated.

There are various antiviral and immunomodulatory agents being used to attempt to improve patient outcomes, and research is ongoing. One of the therapeutic options being studied

is the use of tocilizumab to blunt the uncontrolled immune reaction and cytokine storm seen in severe COVID-19 infections.

Tocilizumab (TCZ) is being used to attempt to reduce morbidity and mortality in severe to critically ill patients with COVID-19 (Malekzadeh et al., 2020). TCZ is currently approved for use in the treatment of rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis. It is also one of the approved therapeutics in use to treat CRS, a life-threatening complication noted following chimeric antigen receptor T-cell therapy (CAR T-cell therapy) for certain cancers (Campochiaro et al., 2020).

Individuals who present with severe and critical COVID-19 disease have clinical and laboratory signs that are also seen in CRS. They often have high fevers, severe muscle pain and fatigue. Their labs show elevated inflammatory markers such as C-reactive protein, ferritin levels, and IL-6. Due to these similarities, TCZ was approved in many countries for off-label use in the setting of the global pandemic to attempt to slow or curtail progression of the disease course (Campochiaro et al., 2020).

TCZ is a recombinant humanized monoclonal antibody that works as an IL-6 receptor antagonist (Lan et al., 2020). The goal for the TCZ therapy in the setting of COVID-19 is to block the pro-inflammatory activity that leads to multi-organ failure in this patient population. Pneumonia and the subsequent respiratory failure is the most common cause of death in patients with COVID-19 infections (Perrone et al., 2020). By neutralizing the IL-6 inflammatory factor in the cytokine release syndrome, the aim is to then block the resulting cytokine storm and diminish the severity of disease (Klopfenstein et al., 2020).

Purpose of the Inquiry

Investigating the efficacy of possible COVID-19 therapeutics is of utmost importance, as the COVID-19 pandemic continues to have a profound impact on society and the healthcare system. The purpose of this scholarly inquiry is to examine the literature describing the use of TCZ in the treatment of severe to critical COVID-19 infections. The rationale for the inquiry is to identify best-practice TCZ treatment for this patient population, as the science surrounding this novel infection is evolving.

Clinical Question

Based on the above information, a clinical question was created to guide the literature search and resulting literature review. The clinical question, in the PICO format where (P) is Population, (I) is the Intervention, (C) is the Control, and (O) is the Outcome is as follows: for patients with severe to critical COVID-19 infections, does the administration of TCZ compared with standard treatment have a positive impact on patient outcomes? Outcomes for the sake of this inquiry would be limited to reduced morbidity, mortality, or other clinical improvements such as the level of oxygen support.

Inquiry Method

The method used for this scholarly inquiry paper was an integrative literature review. This method of inquiry provides an extensive review of the of the evidence in the literature with the aim of further understanding the clinical problem and evaluating the possible intervention. The literature is then assessed to provide insight and recommendations regarding the clinical problem described above.

Literature Review

Introduction

A literature review was conducted using several search engines to evaluate the use of TCZ in the treatment of severe COVID-19 infection and to review the current studies available on the emerging topic. The articles that were selected for this review were chosen based on their level of evidence. The level of evidence was rated according to Ackley, Swan, Ladwig, and Tucker (2008). Several themes from the literature were identified. The available evidence was evaluated, and recommendations made for the clinical problem based on these findings.

Search Strategy

Multiple search engines were used to conduct the extensive literature search on the topic (see Table 1). The initial search engines included were: CINAHL, PubMed, and Science Direct. Keywords to help guide the initial investigation included: COVID-19, coronavirus, and monoclonal, and outcomes. To further narrow the search, the keywords of tocilizumab, treatment, and COVID were also searched together.

The initial search was conducted on two dates in December of 2020 and January of 2021. The articles chosen for this inquiry were all current, as COVID-19 is an emerging disease. All studies used in this inquiry were published in 2020. The articles chosen based on abstracts that evaluated the use of TCZ in the treatment of severe coronavirus. Excluded articles included studies using other monoclonal antibody treatments or those that had very low-level evidence such as case studies. The chosen studies for this integrative literature review can be viewed in Table 2. The articles that were selected range in level of evidence from systematic review to retrospective cohort studies.

Levels of Evidence

Each chosen article was evaluated via the evidence framework designed by Ackley, et al. (2008) and are listed for review in Table 3. The assigned levels of evidence are as follows: two

systematic reviews and meta-analyses (Level I evidence), seven controlled trials without randomization (Level III evidence), and six case-control or cohort studies (Level IV evidence). High-level research was difficult to find, as the pandemic is still evolving and lower-level case study articles were generally excluded.

Appraisal and Themes

A review of the chosen articles was conducted, investigating the safety and efficacy of TCZ as a possible treatment of severe COVID-19 infections. Various themes emerged from the literature review and are summarized in Table 4. These included: CRS/cytokine storm, the route of administration, concurrent steroid use, treatment safety, and varying recommendations for use.

CRS/Cytokine Storm

The most consistent theme found within the literature was regarding the hyperinflammatory response found in severe COVID-19 infections, and how targeted prevention or treatment of this response is a possible key to improving patient outcomes. This theme was mentioned in some form in all fifteen chosen articles.

Clinical severity in COVID-19 infection appears to be related to the cytokine storm brought on by the overproduction of inflammatory mediators and seems to be associated with higher mortality (Rossotti, et al., 2020). Patients hospitalized with severe COVID-19 disease have elevated laboratory values of inflammatory cytokines, especially interleukin 6 (IL-6) (Alzghari & Acuna, 2020). Dastan, et al., (2020) attributes the pathophysiology of COVID-19 to this hyperinflammatory response, or CRS.

The inflammatory cascade, activated by the body in response to the pathogen, leads to the severe multi-organ failure and resulting complications that leads to death in this patient population. Due to this cascade effect, early recognition and treatment of CRS is of utmost

importance (Dastan, et al., 2020). Klopfenstein et al. (2020) identified elevated inflammatory markers such as ferritin, CRP, and IL-6 as associated with increased mortality and that neutralizing CRS markers could potentially reduce disease severity.

Lan et al. (2020) stated that while many different markers were part of the CRS inflammatory cascade, IL-6 was deemed the most important, and that blocking IL-6 may inhibit the cascade. Mady et al. echoes the importance of IL-6, calling it a "pivotal inflammatory mediator in the development of COVID-19 associated hyperinflammation" (2020, p. 418). Elevated CRP, D-dimer, ferritin, and lactate dehydrogenase were also noted as markers found in those patients with evolving respiratory collapse (Mady et al., 2020).

The pathogenesis of COVID-19 can vary greatly. In mild or asymptomatic cases, the immune response by the infected individual is controlled and effective at reducing viral load (Malekzadeh et al., 2020). This is lost, however, if the virus can evade and trigger a dysregulated immune response by the host, setting off the cascade and mass release of inflammatory cytokines. The combined response of direct destruction of infected cells and the secondary damage done by the hyperinflammatory immune response together leads to respiratory damage and resulting poor clinical response (Malekzadeh et al., 2020).

Menzella et al. (2020) also discusses the variability of clinical severity seen in COVID-19. Factors such as viral load, patient comorbidities, and individual susceptibility are noted to impact and moderate the body's response, and the cytokine storm is attributed to the evolution of some cases to organ failure and death (Menzella et al., 2020). Menzella et al. (2020) also observed that higher IL-6 levels were found in the more complicated disease states then those with paucisymptomatic cases.

Perrone et al. (2020) associates the excessive immune response by the host as the cause of COVID-19 pneumonia and evolving ARDS. IL-6 is also identified as the instigating factor in CRS as well as other rheumatic diseases, such as rheumatoid arthritis (Perrone et al., 2020). In contrast, Price et al. (2020) marks CRS by elevations in CRP versus IL-6. The article then states that elevated IL-6 seems to have an important contribution to the CRS seen in COVID-19, and that blocking the IL-6 pathway may decrease disease severity (Price et al., 2020).

Salvati et al. (2020) highlights the similarities of the cytokine storm seen in severe COVID-19 infections with those seen in CAR T-cell-induced CRS, an adverse reaction following CAR T-cell infusion for certain cancers. Tocilizumab has been approved for the treatment of CAR T-cell CRS since 2017, explaining why it may have a potential benefit for the hyperinflammatory CRS in COVID-19 (Salvati et al., 2020).

The overactive immune response may be activated by pyroptosis, a type of cell death that initiates a chain reaction utilizing several inflammatory cytokines and chemokines, including IL-6. IL-6, along with other cytokines, recruit cytotoxic T cells and neutrophils to affected tissues and the resulting inflammation causes the multiorgan damage seen in severe COVID-19 (Tleyjeh et al., 2020). This delayed, overactive immune response and cytokine storm is also seen in other respiratory diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The elevated inflammatory markers seen in these syndromes are like those seen in severe COVID-19, implying that CRS plays a role in the pathogenesis of COVID-19 as well (Xu et al., 2020).

TCZ, a humanized monoclonal antibody used to combat CRS secondary to other diseases, may also be an effective treatment for COVID 19, as targeting the IL-6 receptors may interrupt the inflammatory cascade and improve patient outcomes (Tleyjeh et al., 2020). Zhao,

Cui, and Tian (2020) hypothesized that IL-6 binding to the IL-6 receptor may transmit inflammatory signals as well as activate other signal pathways, contributing to ARDS and poor patient outcomes. The article states that blocking the IL-6 pathway may be a way to avoid the organ dysfunction associated with the inflammatory cascade, explaining why TCZ was worth further study (Zhao, et al., 2020). Campochiaro et al., echoes that "timely inhibition of inflammation with tocilizumab could be clinically effective for this population" (2020, p. 44).

The level of evidence to support the reduction of CRS as a therapeutic target is well-documented. Nearly every article found in the literature review discusses the inflammatory process and that curtailing this cascade would have clinical benefit. The systematic review by Tleyjeh et al. (2020) discusses the treatment of inflammatory CRS in other disease processes using an IL-6 receptor blockade with TCZ, and how this treatment may also be beneficial to treat COVID-19. Campochiaro et al. (2020) tracked the inflammatory marker CRP during their retrospective study – finding that patients that improved clinically post-TCZ infusion had significantly lower median CRP levels than those that did not improve (128 versus 186, respectively, $p = 0.038$). This level of evidence is moderate at Level III, but still significant data that curtailing the inflammatory response may be associated with better clinical outcomes. It would be interesting to investigate whether trending CRP levels or other inflammatory markers such as IL-6 would be more specific to COVID-19, and to choose one based on the evidence found as recommendation for practice moving forward.

Route of Administration

Another theme regarding the use of TCZ that emerged within the literature was the route of TCZ administration. Many of the articles mention a weight-based dose, but neglect to state what route of administration was used. Others are more specific in their dosing and route, but the

route for some of the studies varied. The different routes of TCZ administration may or may not have an impact on the outcomes, and more research needs done. For example, do patients need a different dose of TCZ if given SQ versus IV? Or would the timing of dosing need to be more frequent if given SQ? Does the route change the level of absorption and thus change the amount of inflammatory reduction? Are there more adverse events associated with one route or the other? These questions warrant further study.

The irregularity of the dosing and varying routes of administration affected the level of evidence regarding TCZ administration. For example, Klopfenstein et al. (2020) states that the treatment group of patients received one or two doses of TCZ during the study, but do not state exact dose or route of administration. In contrast, the systematic review by Alzghari and Acuna (2020) listed doses between 80 to 600 mg by intravenous (IV) route, but the number of doses varied.

Menzella et al. (2020) had to tailor their drug formulation and route by drug availability. The COVID-19 cases in Italy grew exponentially during their study, forcing them to use SQ TCZ when IV TCZ became unavailable. When no TCZ was available at all, new subjects were made into a control group (Menzella et al., 2020). Malekzadeh et al. (2020) used only the SQ route for TCZ administration and used two to three doses ranging from 324 mg to 486 mg, depending on patient weight. Rossotti et al. (2020) used the IV route exclusively at a dose of 8 mg/kg with a maximal dose of 800 mg, and a second dose given 12 hours later only if the patient remained febrile. Others, such as Xu et al. (2020), gave only one 400 mg IV dose of TCZ to all treatment subjects.

The differences in the route of administration, drug availability, dose strength, and number of doses varies greatly between some studies and is not mentioned in others. Overall, the

variation in route of administration contributes to a low level of evidence for this theme. Even the Level I evidence, such as the systematic review by Alzghari and Acuna (2020), has varying routes and doses of TCZ given within their included studies. This highlights a gap in the research and a need for more consistent study to fully examine both the efficacy of the drug itself and to optimize the details of administration for more reliable, generalizable results.

Concurrent Steroid Use

A third theme that was found within the literature was the concurrent use of glucocorticoids, such as the steroids dexamethasone and prednisolone, along with TCZ therapy. The use of steroids also differs between studies and impacts the strength of the results. Menzella et al. (2020) named glucocorticoids as the only known effective therapy against COVID-19 and stated that their combined use with TCZ may prevent the need for mechanical ventilation and improve mortality rates in severe cases. Perrone et al. (2020) also found that mortality rates were lower for COVID-19 patients that received both TCZ and concomitant corticosteroids. The difference in mortality rates for the combined therapy was found to be statistically significant at 14 days (Perrone, et al., 2020). This differs from CAR-T therapy, which does not use steroids as an adjunct with TCZ administration.

Steroid use was part of standard therapy for some studies, such as Mady et al. (2020). In contrast, Campochiaro et al. (2020) did not allow concurrent steroids to be eligible for TCZ treatment. Lastly, multiple studies did not mention steroids or, like Klopfenstein et al. (2020), mention only that some patients received them. Steroid use was inconsistent across studies, and the types, doses, and routes varied.

The variation in steroid use between studies makes the level of evidence for this theme low. The studies cited using both TCZ and consistent steroid use all represent Level III evidence.

This moderate-level evidence produces more questions, since they did not have consistent dosing, consistent treatment length, and consistent TCZ dosing. Determining the optimal timing for TCZ treatment also warrants further study – would starting TCZ and steroids together provide better results, or should one come before the other? The theme of concomitant steroid use identifies a gap in the research. It would be beneficial to either study the effectiveness of glucocorticoids alone or keep the use consistent to better evaluate the efficacy of TCZ as an addition to the therapy regimen.

Safety

Safety was a common theme found throughout the literature review. Due to the public health emergency, off-label TCZ use as a possible immunomodulatory therapy was suggested for use in severe COVID-19 cases (Salvati, et al., 2020). Due to the off-label use, many studies researching its efficacy also simultaneously reported on the drug's safety profile. Some, such as the review by Alzghari and Acuna (2020), emphasize the importance of screening for latent TB before use. This was supported by Dastan, et al., who stated that "reactivation of tuberculosis is an important challenge" and recommended TB screening every patient eligible for TCZ (2020, p. 5).

Other safety concerns noted were secondary infections post-TCZ treatment. Bacterial superinfections were listed as a risk by Lan et al. (2020) and recommended further research on the subject. Malekzadeh et al. (2020) reported that no adverse events related to TCZ occurred in their treated patients. Campochiaro et al. (2020) reported some bacterial superinfections and noted that they occurred more often in patients that received higher doses of TCZ.

Other complications noted post-TCZ treatment were a rise in certain liver function tests (i.e., transaminitis) and a transient neutropenia (Campochiaro et al., 2020). Perrone et al. (2020)

reported three cases of allergic events and also mentioned transaminitis, noting that the liver enzyme elevation was severe in three percent of the studied cases.

Rossotti et al. (2020) found that TCZ therapy was associated with a longer hospital stay and speculated that it could be from infectious complications. Their article also noted a significant increase in D-dimer levels despite a decrease in the other CRS-related markers. They noted that this finding indicates "that the risk of thrombotic complications after treatment may not be completely reduced" (Rossotti et al., 2020, p. 16). Rossotti et al. (2020) also observed that a transient decline in respiratory function seen soon after drug administration, and that there is a window of risk where patients may decompensate following treatment before they turn for the better.

The level of evidence for the safety of TCZ was moderate. TCZ is not a new drug, which is beneficial when assessing the risk when using it for COVID-19. Some patients may not tolerate TCZ treatment – those with already-elevated liver enzymes should be assessed on a case-by-case basis. Those with known latent TB or with concurrent bacterial infections would not qualify due to the increased risk for worsening infection.

Risk for secondary infection is increased post-TCZ administration, so assessing individual patient risk in this scenario also needs done. Questions that need more research regarding COVID-19 would be to determine the timing of administration, as well as if repeated doses are beneficial, detrimental, or moot. Overall, the safety profile for TCZ was positive, but a clear risk/benefit analysis needs done on a patient-to-patient basis before administration. Higher level research on the safety of TCZ use in severe COVID-19 is warranted, along with the role of prophylactic antibiotics in this patient population.

Literature Recommendations for Use

The last major theme to come out of the literature is whether TCZ was deemed efficacious for the treatment of severe COVID-19 infections. Most of the chosen studies recommended TCZ for use in severe COVID-19 infections. However, two articles did not recommend its use: Campochiaro et al. (2020) did not find TCZ to be beneficial over standard treatment with enough evidence to support its use, and Lan et al. (2020) stated that they did not find that TCZ added any additional value to this patient population. Campochiaro et al. (2020) represents level IV evidence as a single-facility retrospective cohort study. Lan et al. (2020) is level I evidence as a systematic review and meta-analysis of seven studies – however they cited low-quality evidence within the included studies as their main reason for not being able to recommend TCZ for use until further higher-quality evidence is obtained.

Other articles recommended TCZ use for severe COVID-19 infections, but only with stipulations: Rossotti et al., (2020) recommended TCZ be used with caution regarding the transient decline in respiratory status and potential for adverse secondary infections. Menzella et al. (2020) found TCZ use effective in the subgroup of patients with major respiratory impairment but echoed the need for future studies regarding safety and superinfection. Malekzadeh et al. (2020) found that TCZ had significant impact on clinical parameters and may be especially useful if administered early in the respiratory decline.

Price et al. found that TCZ seemed to decrease mortality in patients demonstrating CRS with COVID-19, but that a "more precise identification of predictors of disease progression may help establish the ideal time for tocilizumab treatment" (2020, p. 1407). Timing was also noted as important by Dastan et al. (2020), stating that it should be administered early in the disease course, before the clinical decline. Salvati et al. (2020) found that TCZ promoted earlier vascular pulmonary recovery but that more research needs done to know if this is a transient positive

outcome or if it would have a greater impact on long-term survival. The level of evidence found in the articles recommending TCZ use with stipulations were mainly level III non-controlled trials or level IV retrospective cohort studies. They cited early administration as their primary stipulation and requested further study of long-term outcomes.

Seven of the fifteen selected articles recommended the use of TCZ in severe COVID-19 infections within the setting of a global health emergency. Alzghari and Acuna (2020) state that TCZ should be approved for compassionate use until further research addressing its safety and efficacy is done. Xu et al. (2020) found TCZ to improve the clinical outcomes in COVID-19 patients and recommended it as an effective treatment.

TCZ was found to reduce the risk for mechanical ventilation and showed some association between its use and lower mortality in the study by Tleyjeh et al. (2020). The meta-analysis by Zhao et al. (2020) observed a significant difference in mortality between TCZ and control groups, suggesting that TCZ therapy is potentially effective against severe COVID-19.

TCZ treatment reduced ICU admissions and mortality in the study by Klopfenstein et al. (2020) and was recommended for use. Mady et al. (2020), despite acknowledging the need for more research, also recommended TCZ as an adjunct therapy in evolving coronavirus disease. Lastly, Perrone et al. (2020) found that TCZ use significantly reduced mortality rates at 30 days and recommended it for use while continuing phase three trials on the subject.

The level of evidence supporting the use of TCZ was moderate, and included multiple level I studies, such as the systematic reviews and meta-analyses by both Alzghari and Acuna (2020) and Zhao et al. (2020). However, most of the included studies came from lower-level evidence such as level IV retrospective cohort studies or level III non-controlled trials. Some, like Mady et al. (2020), lacked a control group. However, the setting of global health crisis has to

be taken into account. Many of these trials were less-than-ideal due to the critical nature of the pandemic, and the recommendation to use a drug in a crisis may vary versus recommendations for its use in a less-dire scenario.

Summary of Evidence and Literature Reviewed

These studies were done on an emergent basis, and the findings must be interpreted as such. The quality and design of many of the studies were lacking. Shortages of TCZ impacted the research - some trials were forced to change the route of administration mid-study, as well as adding a control group when they ran out of drug altogether (Menzella et al., 2020). Perrone et al. (2020) added so many patients that they ended up creating a validation cohort after the study had already begun. These changes and variations in studies made generalization more difficult and made their results harder to interpret.

The quality of evidence was moderate, with some studies not having enough patients to be fully powered. Multiple variables were not consistent throughout, such as what qualified as "standard treatment" or what was considered "severe" COVID-19. These discrepancies need taken into consideration when appraising the research and the recommended outcomes.

The need for effective treatment may also skew recommendations. Goals of care, such as reducing the number of intensive care admissions or reduction in the need for mechanical ventilation, become more vital when hospital resources are scarce, thus any small benefit may be of greater impact in an emergency.

Overall, TCZ was found to be recommended for use to treat severe COVID-19 infection. In the setting of a global health crisis, recommendation for TCZ use may be warranted to attempt to improve patient outcomes and relieve some of the strain on the healthcare system. However, one must consider the low-level evidence, inconsistent study variables, and notable gaps in

research when making clinical decisions regarding its use. A conceptual model that uses a feedback loop will be beneficial for this situation so that recommendations can change as more research is completed on this topic.

Conceptual Framework

Johns Hopkins Nursing Evidence-Based Practice Model

The Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) Model (2017) was selected for this inquiry for multiple reasons. The first reason it was chosen was due to its simplicity and similarity to the structure of the literature review itself. The model uses a three-step process that aligns well with the structure of this inquiry – practice question, evidence, and translation. Within the first step of the JHNEBP Model, a clinical practice question is developed, and the problem is defined. Stakeholders, as well as the team to conduct the inquiry, are identified and a schedule is then created.

The next step of the JHNEBP model examines the evidence by conducting a literature search, a review of the current literature, and an appraisal of the quality of evidence. Afterwards, a synthesis of the evidence is performed. The results of the synthesis help guide practice recommendations and are cultivated into a plan for practice change.

Once an action plan is developed based on the evidence recommendations, support and resources are identified and obtained. The plan for clinical practice is then implemented. Over time, the outcome of the practice changes will be evaluated, reported to the stakeholders, and findings disseminated. Once the process change reaches this point in the model, the action plan can be updated and changed as the outcomes are evaluated.

This framework was also selected because it can be continuously updated as new evidence appears. The cyclical nature of this model allows for more changes to be put into place

as the outcomes are evaluated. This is especially important for this topic, as the science regarding COVID-19 and its treatment is new, ongoing, and evolving.

The themes found within the literature review can all be assessed using this model as more research emerges – the route of administration, the use of concurrent steroids, and the overall drug safety profile for this patient population can all be evaluated and reevaluated using this model. As more evidence is collected, the recommendations may change, leading to different practice changes. This model allows for that, with the translation and dissemination step at the end, which can circle you back to the literature review.

Lastly, this framework takes both internal and external factors into account. Internal factors that may play a part in this clinical problem may include medication availability, appropriate clinical identification of eligible patients, and staffing. External factors could include things such as COVID-19 outbreak status in the area and federal regulations regarding medication use, such as FDA approval. Taking in all factors that may influence a clinical problem is an important factor in any EBP model, but especially important in one that involves a global pandemic. Permission to utilize the JHNEBP Model was granted by Johns Hopkins Nursing. The JHNEBP Model and its respective steps are outlined in Appendix A.

Conclusions, Implications, and Recommendations for Nursing

Introduction

The purpose of this literature review was to evaluate the impact of TCZ therapy for severe COVID-19 infections and to assess the benefit of its use for this patient population. This section will conclude the inquiry, present implications, and give recommendations for practice regarding its use.

Conclusions

The pandemic stemming from the novel coronavirus and resulting COVID-19 infections is perhaps the largest event to affect the global population in nearly a century. The effects on humanity and the healthcare system are ongoing, and evaluating effective therapeutic interventions are still vital to the treatment of these patients. A review of the literature highlights the hyperinflammatory response by the immune system as a treatment target. TCZ treatment aims to prevent or reduce the inflammatory cascade seen in clinically worsening patients with COVID-19. Finding a beneficial way to use TCZ is important for patient morbidity and mortality, as well as secondarily conserving hospital resources.

Implications for Nursing

The effect that this pandemic has had on the nursing profession has been monumental. Staffing shortages are widespread, as nurses leave the profession in droves. The physical and emotional toll has left many nurses struggling. A key element of this struggle has been the lack of treatment for this patient population. Having evidence-based recommendations in place will help create a more solid treatment plan.

Nursing will play a key role in TCZ administration, and education will need given to those administering this drug. TCZ administration will be delivered intravenously via infusion over sixty minutes. Before infusion, nurses should confirm that the patient has been screened for infections such as tuberculosis and hepatitis B, and that the ordering clinician does not suspect any concurrent bacterial infection. The patient should not have an absolute neutrophil count (ANC) below 2000/mm^3 or a transaminitis five-fold above normal.

The nurse should inspect the drug for any leaking or visible particulates before administration. TCZ should be given on its own dedicated IV line and not mixed with any other medications. The patient’s temperature, blood pressure, and pulse should be obtained before

infusion, after the start of the infusion, and at the end of the infusion. Lab monitoring should be done daily to watch for worsening liver function or a developing bacteremia. A daily complete metabolic panel (CMP) or equivalent should be ordered.

The nurse should watch for signs of hypersensitivity or allergic reactions, such as hives or angioedema during and post-infusion. Close monitoring of the patient's respiratory status is also warranted – the nurse should notify the ordering physician if the patient is having signs of a reaction or if their respiratory condition worsens post-administration, such as increasing oxygen needs, or increased work of breathing occurs. Nursing should also be aware of the risk for secondary infections, and report any new fever, rigors, or patient status changes to the provider. Lastly, nursing will also need to educate the patient or the family about TCZ administration, why the drug is being given, and what complications can occur.

An algorithm for patient inclusion would be beneficial, both for the providers to know when to order the drug, and for the nurses to explain to the patients and family about when and why their family member qualifies to receive TCZ. Collaboration and communication between the healthcare team members is key to implementing this treatment intervention successfully.

Further literature review and continued evaluation via the JHNEBP Model can create a transition from crisis-based intervention to evidence-based intervention. Having a treatment algorithm in place will help streamline the process for nursing and providers alike. Improving patient outcomes and reducing hospital strain will also have a positive impact on nursing.

Recommendations

Due to the evolving nature of this topic, a final literature search was conducted in October of 2021. This search was conducted specifically to look for updated recommendations on the use of TCZ in this setting. This search was done using the Cochrane Database of

Systematic Reviews and limited to evidence found within 2021. The Cochrane Review by Ghosn et al. (2021) was found during this search.

Ghosn et al. (2021) now found high levels of evidence to support TCZ use and a reduction in all-cause mortality at 28 days. Ghosn et al. ended their review stating, “We are confident that tocilizumab reduced the number of deaths (from any cause) at 28 days.” (2021, p.4). They state that TCZ treatment “probably reduces slightly the number of serious unwanted effects, such as life-threatening conditions or death” (Ghosn et al., 2021, p. 4). The evidence to support clinical improvement or longer-term mortality reduction currently remains low to moderate. This living systematic review represents the most up-to-date evidence available and supports the prior literature regarding TCZ treatment of severe COVID-19 infections (Ghosn et al., 2021).

The recommendations for emergency drug use during a pandemic will always be evolving. The ability to use TCZ effectively will depend first and foremost on drug availability. Conserving doses should be a high priority and makes finding the right target population very important. The first steps in the JHNEBP Model involve creating an interprofessional team to address the clinical problem. A group of providers, nurses, and pharmacists should all be involved in the action plan, with well-defined ways to communicate information and set dates to evaluate and reevaluate the treatment plan.

The second and third parts of the JHNEBP Model involve using the evidence to create an action plan. This inquiry provides a starting point for these steps in the model. According to the evidence, patients should be considered for TCZ treatment if hospitalized with a diagnosis of COVID-19 confirmed via positive nasal pharyngeal reverse transcriptase Polymerase Chain Reaction (RT-PCR) test (Campochiaro et al., 2020). The primary inclusion criteria for TCZ aim

to identify those patients that are showing signs of increased inflammatory activity or worsening disease symptoms. The chosen lab markers for consideration includes elevated CRP and elevated D-dimer (Mady et al., 2020). Elevated serum levels of IL-6 levels as well as elevated ferritin or fibrinogen may also be considered (Salvati et al., 2020).

Other findings for consideration are if the patient is febrile and has a respiratory rate of greater than 30 breaths per minute (Malekzadeh et al., 2020). If they are short of breath, requiring oxygen delivery via nasal cannula, or if their partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) ratio (PaO2:FiO2) is less than or equal to 300 mmHg, they should also be considered for TCZ treatment (Campochiaro, 2020). Worsening findings on chest X-ray or computed tomography (CT) scan could also be considered on a patient-by-patient basis (Campochiaro, 2020).

The inclusion criteria for this action plan needs to be the most fluid, due to the shifting availability of the drug. Many of the studies cited shortages and that is being seen in practice. Therefore, revaluating the target population and narrowing the inclusion criteria may be necessary if there are weeks with limited supplies. Pharmacy must be involved with this action plan and supply levels evaluated at agreed-upon intervals.

There must be a hierarchy of inclusion criteria depending on availability. For example, if supplies are plentiful, then the net of inclusion could include any patient hospitalized with symptomatic COVID-19 infection listed above. However, if supplies are lacking, finding the target population of patients that are showing signs of increasing inflammation but are not yet critical may be of the most benefit. There is less evidence for TCZ treatment if the patient is already critically ill (Mady et al., 2020).

During a time of scarcity, inclusion criteria must be limited. Patients on nasal cannula may be considered for other oral treatments (such as the oral Janus kinase-inhibitor baricitinib), reserving the IV TCZ for those that cannot breathe well enough to consistently take the medication by mouth (Stasi et al, 2020). Menzella et al. (2020) used tighter inclusion criteria, requiring the patient to be on non-invasive ventilation with at least 60% FiO2, and a PaO2:FiO2 ratio greater than 100mmHg but less than 200mmHg. Inclusion criteria and available options for each patient needs to be a continuing conversation between pharmacy and providers.

Exclusion criteria for TCZ administration is more stable within this action plan. The major factor excluding patients from being able to receive TCZ treatment was that of risk of harm. TCZ risk outweighs the benefit in certain scenarios. Anyone with a history of hypersensitivity to TCZ or its components were therefore excluded (Perrone et al., 2020).

One major exclusion criterion involves the risk of secondary infection, therefore excluding patients with signs of a concomitant bacterial infection (Campochiaro, 2020). Latent tuberculosis was also considered a factor for exclusion (Dastan et al., 2020). A history of infections such as hepatitis B, hepatitis C, HIV, or any concern for bone marrow suppression were also excluded from TCZ treatment. There was also transient documentation of bowel perforation post-TCZ administration, so some excluded those with active diverticulitis (Perrone et al., 2020). This same reasoning excluded those with active peptic ulcer disease in certain studies (Malekzadeh et al., 2020).

Another group of patients that have elevated risk of harm versus benefit to TCZ treatment were those with organ impairment. Some studies excluded those with chronic renal impairment – for example, Dastan et al. (2020) excluded those with a glomerular filtration rate (GFR) of less than 30 mL/min. Liver impairment was most often excluded, and the most common exclusion

criteria for the liver was an existing transaminitis of five-fold above the upper normal limit (Campochiaro et al., 2020). The level of impairment and the risk versus benefit should be done on a patient-by-patient basis, depending on the setting, patient history, and their clinical picture.

The TCZ dose amount and whether to give a second dose is also very dependent on drug availability, and again why this action plan needs a cyclical framework. IV was the preferred administration route. Subcutaneous TCZ was also used and in some studies was found to have positive outcomes, so should be considered if the IV formulation is not available (Malekzadeh et al., 2020).

Within the literature, one 400 mg IV dose was often used, and would be the chosen dose if supplies are scarce (Campochiaro, 2020). A second dose was often given. Some considered a second dose only for those with an elevated body mass index (BMI) (Price et al., 2020). Other studies only gave a second dose if the patient had no change or worsening respiratory status, at the discretion of the provider (Perrone et al., 2020). The preferred method for this action plan would be weight-based dosing of 8mg/kg, with a maximum dose of 800 mg with two consecutive infusions, 12 hours apart (Mady et al., 2020).

A limited number of providers with TCZ ordering capability should be designated to keep supplies in check. There will need to be a pharmacy lead on daily that evaluates dosing and inclusion/exclusion criteria. There should be a green/yellow/red light hierarchy of inclusion criteria that is updated weekly, to determine which inclusion criteria is being used that week and should shift with the supply. Green light inclusion would be all symptomatic hospitalized patients without exclusion criteria. Yellow light inclusion would be to shift the inclusion criteria to those with escalating oxygen needs and increasing inflammatory markers. Red light inclusion

would trigger patient-by-patient consideration, dosing considerations, and the use of alternative routes and medications if needed.

Lastly, treatment recommendations for special populations will always need to be individualized. This includes those that are immunocompromised, pregnant, breastfeeding, those that arrive already critically ill, among others. A monthly meeting between the providers and pharmacists should be arranged to discuss special cases and outcomes, as well as updated literature on the subject. Each piece of the action plan should be evaluated within the JHNEBP Model at this meeting, and changes made as warranted.

Summary

In the setting of a global pandemic, all viable treatment options should be explored. The elevated inflammatory response seen in severe COVID-19 infections is linked to higher mortality. TCZ has been used to stave off the cytokine storm seen in other inflammatory processes. Inhibiting the inflammatory cytokine IL-6 to curtail the resulting CRS and improve patient outcomes is the aim of TCZ treatment. Following this scholarly inquiry, TCZ treatment is recommended for use at this time to treat severe COVID-19 infection.

Additional research is needed to establish higher level evidence and more detailed treatment recommendations for TCZ administration. Many other questions also warrant deeper investigation, such as clarifying the use of concurrent steroids, which inflammatory markers are best for trending COVID-19 infection, whether longer courses of TCZ might be beneficial, and the exploration of other emerging monoclonal therapeutic options. This is an evolving situation, and it should be continuously reevaluated.

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Table 1

Database and Keyword Search

Date of Search	**Search Engine**	**Keywords**	**Number of Hits**		
			Listed	**Reviewed**	**Used**
12/12/2020	CINAHL Complete	COVID-19 or coronavirus	48,635		
		Added AND monoclonal	177		
		Added AND outcomes	48	22	5
12/17/2020	PubMed	Tocilizumab AND treatment AND COVID-19	867	36	6
12/18/2020	PubMed	Tocilizumab AND COVID-19	1,015		
		Added AND outcomes	393		
		Filter for "Clinical Trial"	14	9	1
12/18/2020	Science Direct	Tocilizumab AND COVID-19	2,120		
		Filter for "Research articles"	563		
		Filter for "Subscribed journals"	367	41	2
01/03/2021	Science Direct	Monoclonal antibody treatment AND COVID-19	2,181	12	1

Table 2

Literature Table

Citation/ Search Engine	**Purpose/ Objective**	**Population/ Sample/ Setting**	**Study Design/ Variables/ Instruments**	**Results/ Main Findings**	**Implications/ Critiques**	**Comments/ Themes**	**Level of Evidence**
Alzghari, S. & Acuna, V. (2020). Supportive treatment with Tocilizumab for COVID-19L A systematic review. *Journal of Clinical Virology*, *127*, 1-5. https://doi.org/10.1016.j.jcv.2020.104380 CINAHL	"There is an immense need for treatment strategies to help combat this contagious disease" (p.1). Assess outcomes associated with TCZ treatment in patients with COVID-19.	Multiple studies. 6 articles met inclusion criteria. Inclusion criteria: studies involved humans with COVID-19 receiving TCZ that included clinical findings. 21 patients got TCZ treatment in the retrospective studies. Luo study had 15 patients, Xu study had 21. 4 case study patients received TCZ (one had been on it chronically).	Systematic review. Included studies: 2 retrospective analyses (by Luo and Xu) and 4 case reports. Review was done using the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Search engines used: Embase, PubMed, Web of Science and Scopus. Key words used: "tocilizumab," "COVID-19," and "interleukin 6" or "IL-6" (p.1).	Luo study: 47% critical, 40% serious, 13% moderate. 53% received steroids. 67% saw a rise in IL-6 levels after TCZ but decrease after. Death in 20%, 80% still hospitalized at press. Xu study: 19% critical, 80% serious. All received steroids and an antiviral. No deaths, 10% hospitalized, 90% discharged at press. In the case studies, all patients alive at press, 3 of the 4 had recovered from COVID-19.	"TCZ is an option for compassionate use in patients with COVID-19" (p.4)" More safety profiles need done and more Phase II trials need studied. IL-6 may be an important level to gauge efficacy of TCZ therapy. Limitations: no studies were randomized, small sample size, dosing of TCZ was inconsistent	Screening for latent TB is necessary before use. Same CRS biomarkers seen in severe COVID IL-6 is important biomarker Concurrent steroid use Concurrent antiviral use	IV

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Campochiaro, C., Della-Torre, E., Cavalli, G., De Luca, G., Ripa, M., Boffini, N., Tomelleri, A., Baldissera, E., Rovere-Querini, P., Ruggeri, A., Monti, G., De Cobelli, F., Zangrillo, A., Tresoldi, M., Castagna, A., & Dagna, L. (2020). Efficacy and safety of tocilizumab in severe COVID-19 patients: A single-center retrospective study. *European Journal of Internal Medicine, 76*, 43-49. doi.org/10.1016.j.ejim.2020.05.021 PubMed	Treatment of COVID-19 is lacking research. The aim of this study was to compare the efficacy of TCZ treatment to standard treatment for patients with severe COVID-19 pneumonia	San Raffaele Hospital in Milan, Italy 65 patients total, all hospitalized outside of ICU with COVID-19 Inclusion: hyper-inflammatory state, severe respiratory involvement on Xray or CT, and a P:F ratio of ≤ 300. Exclusion: existing bacterial infection, liver enzymes > 5x baseline, or any other immuno-suppressive medication use	Retrospective study using a control group. All pts received antivirals, antibiotics, and enoxaparin. Assessed daily for 28 days using a six-category scale from 1) live discharge to 6) death. Clinical improvement noted if patient decreased their number by 2 points on the scale. Survival and improvement analyzed using Kaplan-Meier approach, log-rank tests, and proportional hazard Cox regression models.	By day 28, 16% died in TCZ group and 33% in control group (p = 0.150). 63% of TCZ group and 49% of control group discharged from the hospital by day 28 (p = 0.32). Clinical improvement reached in 69% of TCZ group and 61% of control group (p = 0.61). Adverse events occurred in 25% of TCZ group and 27% of control group. No significant differences noted at day 28 between groups.	Higher baseline P:F ratio was associated with more promising outcome. Concern for opportunistic infections needs considered in patients treated with TCZ. Retrospective design and small cohort size are limitations. No evidence to suggest that TCZ treatment was more effective.	No steroid use allowed in this study. No statistically significant results found. Infection risk. CRS is result of uncontrolled immune reaction Timely inhibition of IL-6 could help this population	III

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Dastan, F., Saffaei, A., Haseli, S., Marjani, M., Moniri, A., Abtahian, Z., Abedini, A., Kiani, A., Seifi, S., Jammati, H., Hashemian, S., Toutkaboni, M., Eslaminejad, A., Heshmatnia, J., Sadeghi, M., Nadji, S., A., Dastan, A., Baghaei, P., Varahram, M., … Tabarsi, P. (2020). Promising effects of tocilizumab in COVID-19: A non-controlled, prospective clinical trial. *International Immunopharmacology, 88,* 1-7. doi.org/10.1016/j.intimp.2020.106869 CINAHL	"Data is particularly needed on treatments able to reduce mortality and the number of critically ill patients" (p. 397).	Dr. Masih Daneshvari Hospital in Tehran, Iran. 76 assessed, 42 selected. All positive for COVID-19. Inclusion: Severe (RR > 30, SpO2 < 90, progressive lung infiltrate, critical (ICU or intubated), no improvement for over 72h Exclusion: pregnant, bacterial infection, use of anti-inflammatory agents, CKD, liver disease, did not receive 72h of care.	Prospective study, non-controlled trial. One 400mg TCZ dose given. Standard care was oxygen delivery and an antiviral drug. Patients evaluated for 28 days. Clinical improvement: weaning from oxygen/discharge from hospital. Xray and CT done at baseline and Day 14. Statistical analysis of survival via Kaplan-Meier estimator.	72h in, 20 were severe stage and 22 critical. No statistically significant difference in time-to-death in severe vs. critical patients (p = 0.06) but survival rate higher in severe group. 28 patients demonstrated significant improvement on lung imaging. Overall mortality rate was 49% on patients admitted to ICU.	Severe TCZ patients had better outcomes which may suggest greater efficacy of earlier administration of TCZ. Limited by small size and lack of control group. "There may be an ideal time point for initiating tocilizumab therapy, and all efforts should be made to administer it during the early stages of SARS-CoV-2 infection before deterioration of clinical conditions" (p.5).	3 patients experienced adverse effects post-TCZ No steroid use. No statistically significant improvement. CRS occurs after inflammatory cascade activation TCZ binds to IL-6 receptors and inhibits signal transduction Screen for latent TB	IV

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Klopfenstein, T., Zayet, S., Lohse, A., Balblanc, J., Badie, J., Royer, P. Toko, L., Mezher, C., Kadiane-Oussou, N.J., Bossert, M., Bozgan, A., Charpentier, A., Roux, M., Contreras, R., Mazurier, I., Dussert, P., Gendrin, V., & Conrozier, T. (2020). Tocilizumab therapy reduced intensive care unit admission s and/or mortality in COVID-19 patients. *Medecine et Maladies Infectieuses, 50,* 397-400. doi.org/10.1016/j.medmal.2020.05.001 Science Direct	To study whether TCZ is an effective treatment for COVID-19.	Nord Franche-Comte Hospital in France. 20 patients in TCZ group, 25 in control. Inclusion: no CI to TCZ, failure of standard treatment, elevated inflammatory markers, >25% lung damage on CT scan, oxygen needs >/= 5L/min Exclusion: those with only moderate disease presentation and those that received other meds not normally in standard treatment.	Retrospective case-control study with control group. Endpoint was determined to be death and/or ICU admission. Groups were compared via Charlson comorbidity index, as well as statistical analyses. No statistical differences between groups, however the TCZ group had a higher comorbidity index (p = 0.014) and higher age (p = 0.036). No statistical differences between groups at admission.	Endpoint of death or ICU admission, however, was higher in the standard group than TCZ group (72% vs 25%, p = 0.002) and the standard group needed mechanical ventilation more often (32% vs 0%, p = 0.006). Mortality difference not statistically significant but higher in standard group (48% vs 25%, p = 0.066).	Limitation of small sample size and retrospective design. The data "strongly suggests that TCZ may reduce the number of ICU admissions and/or mortality in patients with severe SARS-CoV-2 pneumonia" (p.398). "TCZ could be key in the treatment of COVID-19 cases to reduce ICU admissions" (p.397).	Positive outcomes Cytokine storm causes the multi-organ failure seen in this population	III

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Lan, S., Lai, C., Huang, H., Cheng, S., Lu, L., & Hsueh, P. (2020). Tocilizumab for severe COVID-19: A systematic review and meta-analysis. *International Journal of Antimicrobial Agents, 56*, 1-7. doi.org/10.1016/j.ijantimicag.2020.106103 Science Direct	To "assess the efficacy of tocilizumab for the treatment of severe coronavirus disease 2019 (COVID-19)" (p.1).	592 total patients: 240 in TCZ groups and 352 control groups. Inclusion: comparing TCZ against control regarding at least one of the following: all-cause mortality, ICU admission, and requirement of mechanical ventilation. Exclusion: Case reports, studies without a control, studies that did not report a required outcome.	Systematic Review and Meta-Analysis of seven retrospective studies. Done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Two authors assessed articles separately to avoid bias. Pool analysis was done on the seven studies. Bias was assessed using the Newcastle-Ottawa scale.	All-cause mortality rate of the TCZ group was 16.3% which was lower than the 24.1% of the control group, but not statistically significant (*RR* = 0.62). 5 studies reported ICU admission and 3 reported ventilator requirements - all reported similar risks between groups. "Tocilizumab could not provide any additional benefit for the clinical outcome of severe COVID-19" (p.2).	Limitation: the number of doses and route of administration varied between studies. TCZ group had higher Charlson comorbidity index and higher inflammatory markers at baseline ($p < 0.00001$) Other studies that matched their groups better showed better outcomes for the TCZ groups. Timing/dosing could affect outcome. Bias rated 6 out of 7 scale.	No better outcome for TCZ group vs control group Studies carry heavy limitations. "The tocilizumab group had more severe clinical outcomes compared with the control group and may explain why no additional benefit of tocilizumab was found in this meta-analysis" (p.6). IL-6 is most important cytokine in CRS	III

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Mady, A., Aletreby, W., Abdulrahman, B., Lhmdi, M., Noor, A., Alqahtani, S., Soliman, I., Alharthy, A., Karakitsos, D., & Memish, Z. (2020). Tocilizumab in the treatment of rapidly evolving COVID-19 pneumonia and multifaceted critical illness: A retrospective case series. *Annals of Medicine and Surgery, 60*, 417-424. doi.org/10.1016/j.amsu.2020.10.061 Science Direct	To analyze the critical course of critically ill COVID-19 patients and evaluate whether IV TCZ would be associated with more favorable patient outcomes.	King Saud Medical City in Riyadh, Saudi Arabia. 61 patients met inclusion criteria. Inclusion: ICU admission with at least one of: MV, RR > 30, SpO2 < 90% on RA, P:F ratio < 300 and given TCZ. Exclusion: pregnant, known immune suppression, CI to TCZ use.	Retrospective, single-arm, single-center observational study. All patients got antivirals, antibiotics, steroids, and enoxaparin (unless CI). All patients received 2 doses of TCZ during the study. Data was statistically analyzed as appropriate. Proportional hazard model was adjusted for variables deemed important.	Mortality rates were 24.6% on day 14 post-ICU admission and 31.1% on day 30. TCZ was found the be a safe adjunct therapy but no control group to compare outcomes. Comparison between pts receiving MV and non-MV had significantly longer ICU and hospital stays ($p = 0.04$ and $p = 0.01$).	"The administration of TCZ per se as an adjunct therapy did not have any effect of the mortality of critically ill COVID-19 patients" (p.419). Study was small and underpowered. With no control group, the results were not very helpful.	Steroids used. Secondary infections were not correlated with mortality. Higher comorbidity and critical illness in this study compared to some others.	IV

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Malekzadeh, R., Abedini, A., Mohsenpour, B., Sharifipour, E., Ghasemian, R., Javad-Mousavi, S. A., Khodashahi, R., Darban, M., Kalantari, S., Abdollahi, N., Salehi, M. R., Hosseinabadi, A. R., Khorvash, F., Valizadeh, M., Dastan, F., Yousefian, S., Hosseini, H., Anjidani, N. & Tabarsi, P. (2020). Subcutaneous tocilizumab in adults with severe and critical COVID-19: A prospective open-label uncontrolled multicenter trial. *International Immunopharmacology, 89*, 1-11. doi.org/10.1016/j.intimp.2020.107102 Pub Med	To evaluate the use of SQ TCZ in adult patients with severe or critical COVID-19 on patient outcomes	8 tertiary care centers in Iran. 126 patients, 86 severe and 40 critically ill. Inclusion: febrile, cough, RR > 30, O2 sat < 93 on RA, IL-6 level of 3x normal Exclusion: hx of hepatitis, immune suppression, CI to TCZ, pregnancy, concurrent infection Wt-based doses of SQ TCZ. All received antivirals, antibiotics, and interferon beta-1a	Prospective, multi-center, uncontrolled study. Outcomes measured were all-cause mortality, oxygen support use, O2 saturation, RR, and lab values. Drug safety was also evaluated. Patients followed up until discharge or death. Assessed change on a 6-point scale from 1) no oxygen to 6) death. All data between groups were statistically analyzed.	All-cause mortality was much higher (60%) and statistically significant in critical patients vs severe patients ($p < 0.001$). No TCZ-related adverse events occurred. Rapid improvements to RR, body temperature, and blood oxygenation were seen after 3 days of TCZ and sustained throughout treatment. Results with high dose SQ TCZ were similar to that of IV TCZ.	Better results in severe patients and high mortality of critical patients suggest that earlier TCZ may provide more benefit. Uncontrolled design was a limitation. "Subcutaneous tocilizumab might be capable of reducing the risk of death, particularly if used the in the early stages of respiratory failure" (p.8). SQ TCZ may be an appropriate substitute for IV if the IV TCZ is not available.	No steroids used. Cytokine storm. SQ TCZ	IV

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Menzella, F., Fontana, M., Salvarani, C., Massari, M., Ruggiero, P., Scelfo, C., Barbieri, C., Castagnetti, C., Catellani, C., Gibellini, G., Falco, F., Ghidoni, G., Livrieri, F., Montanari, G., Casalini, E., Piro, R., Manusco, P., Ghidorsi, L., & Facciolongo, N. (2020). Efficacy of tocilizumab in patients with COVID-19 ARDS undergoing noninvasive ventilation. *Critical Care, 24,* 589. doi.org/10.1186/s13054-020-03306-6 CINAHL	To evaluate the safety and efficacy of TCZ in patients with COVID-19 ARDS on noninvasive mechanical ventilation.	Pulmonary unit of Azienda USL of Reggio Emilia – IRCCS. 79 patients with severe/ worsening disease. 41 in the TCZ group, 38 in control group Inclusion: pts all needed NIV and had P:F ratios of 100 to 200 despite Venturi mask. The control group represented patients admitted when no TCZ was available.	Retrospective case-control study, control group. TCZ route determined by availability (28 IV, 13 SQ) TCZ given at the start of NIV. Improvement measures: P:F ratio increased by 30%, FiO2 < 50%, RR < 30, PEEP < 8, and able to keep TV > 5ml/kg body weight with PS < 10. Outcomes measured: in-hospital mortality, intubation, post-TCZ infections. Data was statistically analyzed.	CRP levels significantly lower in TCZ (p = 0.02 and p = 0.001). Overall probability of dying significantly lower in both TCZ groups (p = 0.092). Probability of dying or being intubated was also significantly lower in the TCZ groups (p = 0.036). Adjusted for sex and age, significantly less chance of intubation and death in TCZ groups but not overall mortality (p = 0.022 vs. p = 0.192)	TCZ group significantly younger, lower Charlson comorbidity index, got more HCQ Results lost significance in the SQ group versus control, implying that IV may be more effective. “Results suggest that TCZ could be an effective therapeutic option for the treatment of critically ill COVID-19 patients receiving NIV” (p. 7). Small sample size	Control group IV vs SQ Secondary infections did not affect mortality Heterogeneous route of TCZ may have muddied results Suggests combining TCZ and steroids for better treatment.	III

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Perrone, F., Piccirillo, M.C., Ascierto, P.A., Salvarani, C., Parrella, R., Marata, A.M., Popoli, P., Ferraris, L., Marrocco-Trischitta, M., Ripamonti, D., Binda, F., Bonfanti, P., Squillace, N., Atripaldi, L., … & Chiodini, P. (2020). Tocilizumab for patients with COVID-19 pneumonia. The single arm COVID-19 prospective trial. *Journal of Translational Medicine, 18*, 405. doi.org/10.1186/s12967-020-02573-9 CINAHL	To evaluate the efficacy of TCZ "while controlling the highly increasing off-label use of the drug" (p. 2).	Multicenter Italian trial, 301 patients. 59.8% received TCZ Validation cohort added due rapidly increasing pts – 920 patients Inclusion: O2 sat </= 93 on RA or requiring NIV/MV (intubated within 24 hours of inclusion) Exclusion: bacterial infection, GI/other CI to TCZ, ALT/AST > 5x normal, low neutrophils/ Platelets	Single-arm study with 2% 14 day and 35% one-month mortality rate as null hypothesis and a TCZ group 10% reduction at 14 and 30 days as alternative hypothesis. Data was statistically analyzed for both cohorts separately	TCZ significantly lowered need for respiratory support (p = 0.03 and 0.08 at 14d and 30d). Null hypothesis rejected at 30d but not at 14d (p < 0.001 and p = 0.52). Mortality rates higher for older patients, those with lower P:F ratios. Mortality rates lower for those treated with both TCZ and steroids and statistically significant at 14d (p = 0.004).	Variable delay between registration and drug administration due to availability Younger and critical patients given preferential treatment. "The possible effect of tocilizumab might be greater among patients not requiring mechanical ventilation" (p. 5). Single-arm study limited ability to draw conclusions Selection and immortal time bias	Study "supports the use of tocilizumab" (p. 9). Missing data due to the massive influx of patients Steroid use Addresses safety and exclusion criteria	III

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Price, C., Altice, F.L., Shyr, Y., Koff, A., Pischel, L., Goshua, G., Azar, M.M., Mcmanus, D., Chen, S-C., Gleeson, S., Britto, C., Azmy, V., Kaman, K., Gaston, D., Davis, M., Burello, T., Harris, Z., Villanueva, M.S., Aoun-Barakat, L., … & Malinis, M. (2020) Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus disease 2019. *Chest journal, 158*, 4. doi.org/10.1016/j.chest.2020.06.006 CINAHL	To determine if tocilizumab treatment could positively impact patients hospitalized with COVID-19	Single hospital study in Connecticut, USA. Inclusion: severe disease: >/= 3L oxygen, critical: needing MV, and evolving CRS Disease severity determined at admission	Observational study, chart review 239 patients, 21-day observation period, 21-day follow-up period. 104 deemed severe at admit. 13-point scale measured changes in oxygenation status Measured over 14 days	Severe disease: higher mortality ($p < 0.001$), need for MV ($p < 0.001$), longer time spent on MV ($p = 0.003$). Pt surge, but no parallel surge in the need for MV during the study Survival significantly lower in white patients vs Black and Hispanic pts, ($p = 0.002$). "use of tocilizumab may result in lower-than-expected mortality in a subgroup of patients with evidence of CRS" (p. 1407)	Early administration may slow disease progression and monitoring of CRP/CRS biomarkers may be helpful Reducing need for MV helps hospitals cope with patient surge Elevated DDimer levels may indicate that TCZ only helps part of the CRS state Survival rate in this TCZ group was higher than other studies	Race differences in mortality Unable to establish causality No adverse events with TCZ Steroids may be useful D-dimer levels icreased Treating CRS was focus of therapy	IV

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Rossotti, R., Travi, G., Ughi, N., Corradin, M., Baiguera, C., Fumagalli, R., Bottiroli, M., Mondino, M., Merli, M., Bellone, A., Basile, A., Ruggeri, R., Colombo, F., Moreno, M., Pastori, S., Perno, C.F., Tarsia, P., Epis, O.M., & Puoti, M. (2020). Safety and efficacy of anti-il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: A comparative analysis. *Journal of Infection, 81,* 11-17. doi.org/10.1016/j.jinf.2020.07.008 CINAHL	"To evaluate the efficacy of TCZ in severe and critical COVID-19 subjects comparing survival and hospital discharge with controls matched for disease severity" (p. 12). To evaluate the safety of TCZ in terms of clinical recovery and infectious events	Hospital in Milan, Lombardi Region, Italy 74 patients in TCZ group, 148 matched controls Inclusion: RR >/= 30, O2 sat </= 93 on RA, or P:F ratio </= 300, intubation, ICU treatment Exclusion: ALT > 5x normal, low neutrophils or platelets, bacterial infection, GI CI to TCZ	Retrospective, single-center analysis Chinese Guidelines for management of COVID-19 determined severity Clinical/lab features assessed at baseline and Days 1, 3, 5, 7. Each TCZ patient had 2 matched controls: age/sex/severity as well as P:F ratio, Charlson comorbidity index, time to symptoms and admission Data was statistically analyzed	No significant differences between TCZ and their matched controls Significant survival advantage of TCZ over control (p = 0.035) TCZ associated with longer hospital stay (p = 0.019). DDimer continued to rise even in the TCZ group The sharp rise in IL-6 after TCZ could lead to rapid decline due to hyper-inflammation	"This study confirms the potentially effectiveness of TCZ on COVID-19 – especially in critically ill patients" (p. 17). Longer hospital stay may be due to respiratory or infectious complications "Our data indicate that the risk of thrombotic complications after treatment might not be completely reduced" (p. 16). Concurrent steroid use could prevent worsening CRS after TCZ	Selection bias cannot be ruled out Steroid use D-dimer > 1.5 mcg/mL was considered inflammatory marker IL-6 plays a role in lung diseases CRS and overproduction of inflammatory mediators affects clinical severity	III

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Salvati, L., Occhipinti, M., Gori, L., Ciani, L., Mazzoni, A., Maggi, L., Capone, M., Parronchi, P., Liotta, F., Miele, V., Annuziato, F., Lavorini, F., & Cosmi, L. (2020). Pulmonary vascular improvement in severe COVID-19 patients treated with tocilizumab. *Immunology Letters, 228*, 122-128. doi.org/10.1016/j.imlet.2020.10.009 Science Direct	Evaluate the imaging and clinical response one week after TCZ treatment in patients with severe COVID-19 requiring intensive care	Careggi University Hospital in Florence, Italy 33 patients: 20 in TCZ group and 13 in control group	Retrospective, observational, single-center study Variables: age, gender, oxygen support, outcome, adverse events, multiple lab biomarkers, CXR Lung parenchyma scored by 2 independent radiologists. 4-point scale with 0 = no lung involvement and 4 = more than 75% involvement on CXR Data was statistically evaluated.	Mortality was lower in TCZ group than control at 28d (21% vs 46%) TCZ group: significant reduction in FiO2 (p = 0.005) and increase in P:F ratio (p = 0.026) after 7d. CRP, fibrinogen, and ferritin levels also significantly decreased. No significant reduction in inflammatory biomarkers were seen in control group after 7d. Radiographic score: lower in TCZ group after 7d where control group increased.	TCZ may be beneficial in severely ill patients by decreasing the inflammatory immune response TCZ promoted earlier pulmonary vascular recovery Vascular improvement was less dramatic than lung parenchymal score, indicating that there is still some vascular risk Selection bias	Long-term outcomes need evaluated No steroids used	III

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Tleyjeh, I.M., Kashour, Z., Damlaj, M., Riaz, M., Tlayjeh, H., Altannir, M., Altannir, Y., Al-Tannir, M., Tleyjeh, R., Hassett, L., & Kashour, T. (2020). Efficacy and safety of tocilizumab in COVID-19 patients: A living systematic review and meta-analysis. *Clinical Microbiology and Infection*, 1-13. doi.org/10.1016/j.cmi.2020.10.036 Pub Med	To execute a systematic review of the literature regarding the efficacy and toxicity of tocilizumab in patients with COVID-19	1325 patients from the 5 chosen RCTs and 10, 021 from 19 cohort studies were evaluated. Single-center and multicenter studies were included Multiple countries were included Data is updated every 3 months ("living systematic review").	Followed Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines 9 databases were reviewed. Eligible studies chosen by 8 reviewers in groups of 2. Discrepancies resolved by 2 senior reviewers. The 5 RCTs had low bias per the ROB 2 scale, 18 cohorts at moderate bias risk Heterogeneity between studies were statistically evaluated. Data statistically analyzed	The RCTs did not show that TCZ had an effect on mortality For the cohort studies, the absolute risk difference in mortality when compared to the 27.3% from the International Severe Acute Respiratory and Emerging Infection COVID-19 database was -11.5% "Tocilizumab reduces the risk of mechanical ventilation in hospitalized COVID-19 patients" (p.11).	Sample size for an RR of 0.73 on mortality would need a TCZ group size of 4506 (2253 in each arm) patients, so the RCT sample size of 772 in TCZ group and 553 in control group is too low for determination. Studies varied greatly and the overall quality of evidence was low due to moderate risk of bias TCZ had low risk for infection or adverse events Bias risk	Possible efficacy Safety includes elevated infection risk CRS responsible for the organ damage in severe COVID-19 No steroids mentioned	I

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., Zhou, Y., Zheng, X., Yang, Y., Li, X., Zhang, X., Pan, A., & Wei, H. (2020). Effective treatment of severe COVID-19 patients with tocilizumab. *Proceedings of the National Academy of Sciences of the United States of America, 117(20)*, 10970-10975 doi.org/10.1073/pnas.2005615117 Pub Med	To assess the efficacy of tocilizumab on severe COVID-19 patients	Anhui Provincial Hospital and Anhui Fuyang Second People's Hospital in China 21 patients: 17 severe by: RR ≥ 30, O2 sat ≤ 93 on RA, P:F ratio ≤ 300. 4 critical be needing ICU admission for MV, shock, organ failure All patients were febrile and had abnormal, ground-glass opacities via chest CT on presentation.	Retrospective, observational study Evaluated via clinical manifestation, CT imaging, lab results	Temperatures returned to normal within a day of TCZ administration and remained stable 75% had lower oxygen requirements by Day 5. CRP significantly decreased and returned to normal in 84.2% of patients by Day 5. CT scans: vast improvement in 90.5% of patients. IL-6 levels rose in the short term after TCZ	No control group Small sample size "Tocilizumab effectively improves clinical symptoms and represses the deterioration of severe COVID-19 patients." (p. 10974). No p values were given Potential bias	Followed temperatures and inflammatory lab values No adverse events were found post-TCZ Cytokine storm seen is similar to SARS-CoV-1 or MERS-CoV	IV

Citation/ Search Engine	Purpose/ Objective	Population/ Sample/ Setting	Study Design/ Variables/ Instruments	Results/ Main Findings	Implications/ Critiques	Comments/ Themes	Level of Evidence
Zhao, J. & Tian, B-P. (2020) Efficacy of tocilizumab treatment in severely ill COVID-19 patients. *Critical Care, 24(524)*, 1-4. doi.org/10.1186/s13054-020-03224-7 CINAHL	To examine the efficacy of TCZ treatment in patients with severe COVID-19	10 studies included, 1675 severe COVID-19 patients One RCT and 9 retrospective cohort studies America, Europe and India 600 TCZ group, 1000 control group TCZ was IV or SQ and doses/timing varied Varied steroid use	Systematic review and meta-analysis 5 databases searched and two independent reviewers selected eligible studies Discrepancies evaluated by group discussion Studies were then statistically compared	Significant difference in mortality between TCZ group and control ($p < 0.00001$)	The reduction in mortality suggests that TCZ is an effective treatment for severe COVID-19 Significantly high heterogeneity was observed ($p < 0.0001$) The low quality of studies and variable diagnostic criteria for severe COVID-19 were limiting	Variable steroid use Uncontrolled immune activation leads to cytokine storm CRS appears as overproduction of cytokines or chemokines	I

Table 3

Levels of Evidence

Level of Evidence	Description
Level I	Evidence via systematic review or meta-analysis of relevant RCTs (randomized controlled trial) or clinical practice guidelines created from systematic reviews of RCTs or three or more RCTs of good structure with similar results.
Level II	Evidence via at least one well-designed RCT.
Level III	Evidence via well-designed controlled trials with no randomization (quasi-experimental).
Level IV	Evidence via well-designed case-control or cohort studies.
Level V	Evidence via systematic reviews of descriptive and qualitative studies (meta-synthesis).
Level VI	Evidence via a single descriptive or qualitative study.
Level VII	Evidence via the opinion of authorities and/or expert committees.

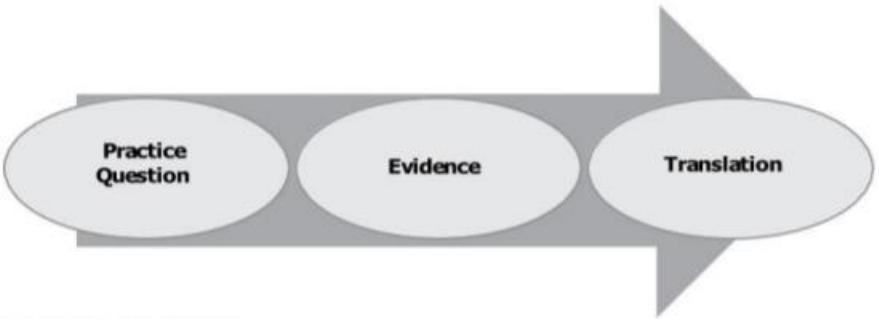
(Ackley, et al., 2008.)

Table 4

Theme Matrix for Literature Review of tocilizumab use for severe COVID-19

	Themes Identified				
Citation	**CRS/ Cytokine Storm**	**Route IV vs. SQ**	**Steroid Use**	**Safety/ Screening**	**Efficacy/ Recommendation**
Alzghari & Acuna, 2020	X	IV	Some	X	X
Campochiaro, et al., 2020	X	IV	No	X	
Dastan, et al., 2020	X	IV		X	X
Klopfenstein, et al., 2020	X		Some		X
Lan, et al., 2020	X	Both		X	
Mady, et al., 2020	X		All	X	X
Malekzdeh, et al., 2020	X	SQ	No	X	X
Menzella, et al., 2020	X	Both	Some	X	X
Perrone, et al., 220	X		Some		X
Price, et al., 2020	X	IV	Some		X
Rossoti, et al., 2020	X	IV		X	X
Salvati, et al., 2020	X	IV	No		X
Tleyjeh, et al., 2020	X			X	X
Xu, et al., 2020	X			X	X
Zhao, Cui, & Tian, 2020	X	Both	Some		

Appendix A Johns Hopkins Nursing Evidence Based Practice Model



PRACTICE QUESTION

Step 1: Recruit interprofessional team
Step 2: Define the problem
Step 3: Develop and refine the EBP question
Step 4: Identify stakeholders
Step 5: Determine responsibility for project leadership
Step 6: Schedule team meetings

EVIDENCE

Step 7: Conduct internal and external search for evidence
Step 8: Appraise the level and quality of each piece of evidence
Step 9: Summarize the individual evidence
Step 10: Synthesize overall strength and quality of evidence
Step 11: Develop recommendations for change based on evidence synthesis

- Strong, compelling evidence, consistent results
- Good evidence, consistent results
- Good evidence, conflicting results
- Insufficient or absent evidence

TRANSLATION

Step 12: Determine fit, feasibility, and appropriateness of recommendation(s) for translation path
Step 13: Create action plan
Step 14: Secure support and resources to implement action plan
Step 15: Implement action plan
Step 16: Evaluate outcomes
Step 17: Report outcomes to stakeholders
Step 18: Identify next steps
Step 19: Disseminate findings