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The Return of Tocilizumab for Patients with COVID-19 Pneumonia

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Abstract

The COVID-19 pandemic has been devastating for many for over one year. Vaccination has helped decrease the number of cases, but there are still multiple challenges to end the pandemic, such as the advent of variants, vaccine hesitancy, access to vaccines, and the impaired efficacy of vaccines in immunocompromised persons. Due to the hyperinflammatory state of SARS-COV-2 infections, research has been done on treatments that curtail the hyperinflammation. One such drug is tocilizumab, an interleukin-6 receptor inhibitor used to treat rheumatoid arthritis and chimeric antigen receptor T (CAR T) cell induced cytokine release syndrome. Much has been done to study the possible benefits of tocilizumab in COVID-19 management. Although some studies have conflicting results, it seems that tocilizumab may be beneficial for those with severe hyperinflammatory states, those who use it in conjunction with corticosteroids, and patients requiring at least high flow oxygenation therapy but not mechanical ventilation.

Keywords: Tocilizumab, COVID-19, SARS-CoV2

Introduction

The COVID-19 pandemic has now impacted the global population for over a year. It has been devastating for many and has challenged us all in many ways. While the advent of vaccinations looks to curtail the number of cases, multiple challenges to ending the pandemic remain, including the advent of variants, vaccine hesitancy, access to vaccines, and the impaired efficacy of vaccines in immunocompromised persons. Thus, it is still essential to continue investigating treatments for COVID-19.

SARS-COV-2 infections can result in severe hyperinflammatory states. This has led to an increased interest in the use of anti-inflammatory agents and immune modulators in the management of severe and critical COVID-19 disease. Interleukin-6 (IL-6) is one cytokine that has garnered much attention with this disease. Elevated IL-6 has been associated with a number of inflammatory conditions. In patients with acute lung injury, IL-6 has been associated with morbidity and mortality [1]. Elevated IL-6 has been correlated with the progression of severe COVID-19 [2]. IL-6 blockade has been used in the management of cytokine release syndrome associated with CAR T cell therapy used in some cancer therapies.

Tocilizumab is an interleukin-6 receptor inhibitor monoclonal antibody that has been studied in the treatment of severe COVID-19 pneumonia since the beginning of the pandemic in late 2019. Opinions about the utility of tocilizumab has changed over the course of this pandemic. In late 2020, we reported our experiences in the beginnings of the pandemic in

the United States of America with tocilizumab in mechanically ventilated patients with PCR confirmed COVID-19 pneumonia, finding no clear benefit in this population [3]. Our knowledge about the management of COVID-19 and potential role of various therapeutics has grown considerably since then. Here, we review the trials using tocilizumab in the treatment of severe COVID-19 since our reported experience.

Trials

The study of Rosas et al. [4] suggested lack of clinical condition improvement and mortality at 28 days with tocilizumab when compared to placebo. This randomized controlled trial analyzed 438 patients in Europe and North America. Adults with COVID-19 pneumonia on laboratory work and imaging with an oxygen saturation of ≤ 93% or a PaO2/FiO2 <300 mmHg were included. Patients were randomized in a 2:1 ratio of tocilizumab 8 mg/kg or placebo. A second dose was administered if no improvement was observed within 24 hours of the initial dose. Patients were also given standard of care at that time, which included antivirals, glucocorticoids, and convalescent plasma. 19.4% of patients received glucocorticoids in the tocilizumab group compared to 28.5% in the placebo group. 24.1% of patients received antivirals in the tocilizumab group compared to 29.2% in the placebo group.

Use of tocilizumab did not improve clinical condition or mortality at 28 days, but there was a possible benefit in shortening the time in the intensive care unit and hospital stay. One of the limiting factors of this study was that standard treatment was different across trial sites. Antiviral therapies included hydroxychloroquine and lopinavir-ritonavir. There were more patients on glucocorticoids in the placebo group than in the tocilizumab group. Those who received glucocorticoids seemed to have higher mortality in each group, which may reflect a worse overall clinical condition. However, more clinical data published after this study period has demonstrated the benefit of corticosteroid use in hypoxic patients with COVID-19 [5]. This confounding factor was evident in various studies, such as in Fisher et al. [3], Somers et al. [6] and Biran et al. [7] which had 77%, 25%, and 43% of their overall patients on steroids respectively.

Stone et al. [8] studied the efficacy of tocilizumab in hospitalized patients with moderately severe COVID-19 pneumonia. The outcome of this study suggested that tocilizumab is not effective at preventing intubation or death. All patients in this study required less than 10 liters of supplemental oxygen. Patients received remdesivir, but only 11% of the tocilizumab group and 6% in the placebo group received glucocorticoids. Of the 161 patients who received tocilizumab and 81 patients who received placebo, 17 patients from the tocilizumab (10.6%) and 10 (12.5%) from the placebo group were intubated or died within 28 days (hazard ratio 0.83 (95% confidence interval [CI], 0.38 to 1.81; P=0.64)). This randomized double-blind control trial did not suggest benefits in using tocilizumab for moderate COVID-19 pneumonia in preventing intubation or death. Limitations of this study was that it was conducted early in the pandemic when treatments that are now standard of care were still being investigated.

In the retrospective observational study by Huang et al. [9], fewer deaths were seen in patients treated with tocilizumab compared to non-treatment. Most of the tocilizumab treated patients needed mechanical ventilation (80% vs 37%, P<0.001); some were intubated prior to the start of treatment or within one day of treatment, which may suggest a more severe disease in this group compared to the non-treatment group. The median time to treatment was two hospital days (0-16 days). In contrast, despite the advanced disease, fewer deaths occurred in both the overall (15% vs 37%; P=0.02) as well as the intubated (14% vs 60%; P=0.001). Only 1 patient in each group was treated with dexamethasone and although more patients in the tocilizumab treatment group concurrently received remdesivir, their reported data still shows a statistically significant decrease in death.

In the study of Mariette et al. [10] treatment with tocilizumab was shown to be beneficial only when CRP levels were greater than 15.0 mg/dL. This randomized clinical trial investigated patients between March 31, 2020 to April 18, 2020. 131 patients were recruited from nine hospitals in France. Patients in this study were hospitalized, required ≥ 3L oxygen, but did not require high flow or mechanical ventilation. 64 patients received tocilizumab (8 mg/kg) with standard of care while 67 patients received only standard of care [11]. Standard of care at that time included antibiotics, antivirals, steroids, and anticoagulants. 16% of patients in the tocilizumab group and 18% in the standard of care group were taking glucocorticoids. The primary endpoint of the study were patients who required noninvasive ventilation, mechanical ventilation, or death. In patients treated with tocilizumab with CRP levels greater than 15.0 mg/dL, 18% of patients received noninvasive or invasive ventilation or died compared to 57% with those in the standard of care groups (HR, 0.18; 95% CI, 0.06-0.59). 90-day mortality was 9% in the tocilizumab group and 25% in the usual care group (HR, 0.18; 95% CI, 0.04-0.89). Limitations in this study include different standard of care among centers. This trial suggests the benefit of administering tocilizumab for patients with elevated CRP.

Recently, tocilizumab has reemerged as a treatment for patients with severe COVID-19 pneumonia due to a large, randomized controlled trial in the United Kingdom with the RECOVERY Collaborative Group [12]. In this trial, it was found that those who received tocilizumab were less likely to require mechanical ventilation or reach death and were more likely to be discharged from hospitalization within 28 days. The study enrolled 4116 adults who had an oxygen saturation <92%

Table 1: Comparison of studies with tocilizumab compared to standard of care.

	Trial (intervention/control)						
	Fisher et al. 2020	Rosas et al. 2021	Stone et al. 2020	RECOVERY Collaborative Group 2021	REMAP-CAP 2021	Mariette et al. 2021	Huang et al. 2021
Study Type	Single center, retrospective cohort	Multicenter, randomized, double blinded, placebo controlled	Multicenter, randomized, double blinded, placebo controlled	Multicenter, randomized, double blinded, placebo controlled	Multicenter, randomized, double blinded, placebo controlled	Multicenter, open label, randomized trial	Single Center, retrospective cohort
No. of patients	45/70	294/144	161/81	2022/2094	353/402	63/67	55/41
Age, mean (years)	56.2/60.6	60.9/60.6	61.6/56.5	63.3/63.9	61.5/61.1	64/63.3	66.6/63.2
CRP, median (mg/L)	195/176	157.2/150.3	116/94.3	143/144	150/130	119.5/127.0	122.3/122.5
IL-6, median (mg/L)	81.6/92.3	88.1/71.2	26.3/25.4	Not reported	Not reported	Not reported	42.7/28.5
Antiviral use* (%)	0	23.1/24.3	33/29	3/3	33**	11.1/23.9	14.5/2.4
Glucocorticoid use (%)	73.3/78.6	19.4/28.5	11/6	82/82	93**	46/73.1	1.8/2.4
Conclusion	No difference in 30-day mortality, extubation within 14 days, or discharge within 30 days	No mortality benefit	No benefit in preventing intubation or death	Mortality benefit, decreased intubation, increased likelihood of discharge within 28 days	Improved in hospital mortality, organ support-free days, 90-day survival	Improved 90-day survival if CRP>150 mg/L	Mortality benefit overall and in patients requiring mechanical ventilation

*Antivirals used: lopinavir-ritonavir, remdesivir
**Percentage represents all patients in the study

on room air or required oxygen therapy and had laboratory evidence of systemic inflammation, defined as a CRP ≥ 75 mg/L. The mean CRP was 143. Patients received varying degrees of oxygenation- from simple oxygen therapy to mechanical ventilation. During the second randomization, 45% of patients received simple oxygen therapy, 41% received non-invasive respiratory support, and 14% of patients received mechanical ventilation. Patients were either assigned to standard of care alone or standard of care with weight-based dosing of tocilizumab (400-800 mg) in a 1:1 ratio. A second dose of tocilizumab was given 12-24 hours later at the clinician's discretion. 82% of patients in both the usual care and tocilizumab groups received corticosteroids. Results showed that 31% of patients who received tocilizumab compared to 35% in the usual care group reached 28-day mortality (95% CI, 0·76–0·94; p=0·0028). 57% of patients who received tocilizumab versus 50% in the usual care group were discharged from the hospital within 28 days (1·12–1·33; p<0·0001). 35% of patients who received tocilizumab compared to 42% in the usual care group progressed to mechanical ventilation or death (95% CI 0·77–0·92; p<0·0001).

From March 2020 through November 2020, the REMAP-CAP Investigators [13] analyzed two IL-6 receptor antagonists (tocilizumab and sarilumab) in their international open-label trial that showed favorable results for both IL-6 inhibitors as compared to standard of care. Standard of care included glucocorticoids (>80% of patients) and remdesivir (33% of patients) This trial ultimately enrolled 895 patients from 113 centers from 6 countries. Adult patients were ≥ 18 years old, had clinically suspected or confirmed COVID-19 infection and were admitted to the intensive care unit requiring either respiratory support (at least high flow nasal cannula with flow rate more than 30 L/min and fraction of inspired oxygen >40%) or cardiovascular support (intravenous vasopressor or inotrope). For those on respiratory support, 29% required high flow nasal cannula, 42% noninvasive ventilation, and 29% invasive mechanical ventilation. 19% of patients required vasopressors. 353 patients received weight-based tocilizumab (8 mg/kg), 48 patients received sarilumab, and 402 patients received standard of care within 24 hours of starting respiratory or cardiovascular support. Median CRP level of participants was 136 µg/ml. Primary outcome of this study investigated days free from respiratory and cardiovascular support at 21 days. Patients who received tocilizumab had a median of 10 days free from organ support and those who received sarilumab had a median of 11 days. Patients who received either tocilizumab or sarilumab had improved 90-day survival.

Limitations include different standard of care among centers especially since tocilizumab and sarilumab were approved at different timeframes. In addition, not all patients had confirmed COVID-19 infection as those suspected to have COVID-19 infection were included in the study.

Conclusion

Numerous studies have investigated the detrimental effects of markedly elevated inflammatory cytokines and a dysregulated immune system resulting in severe respiratory disease [1,9]. The research summarized here varies in study designs with some being randomized controlled trials and others being observational studies (Table 1). All took place during a dynamic year where the standard of care differed in each hospital and every month as new data emerged from around the world. Of these studies, some suggest efficacy of tocilizumab [9,10,12,13] while others have proposed the contrary [4,5,8,14].

Some conclusions can be drawn from the above studies. First, timing looks to be critical. No substantial benefit was seen in persons using supplemental low flow oxygen and in those on prolonged mechanical ventilation or ECMO. Persons entering the hyperinflammatory phase of COVID-19 as evidenced by high oxygen requirements and elevated inflammatory serum markers appeared to benefit the most from tocilizumab. Second, IL-6 blockade by itself is not enough. Tocilizumab should be combined with corticosteroids to derive the most benefit for patients.

Questions remain regarding the use of tocilizumab. Is there a benefit to repeat dosing of tocilizumab? While some of the above studies allowed for a second dose if there was no clinical improvement, this variable was not controlled. Are there long-term consequences to the use of tocilizumab in persons with COVID-19?

Tocilizumab has now become a recommended intervention in certain persons with COVID-19 pneumonia. Patient selection is crucial to maximizing the benefits. Further research is needed to better define the best timing for tocilizumab to improve morbidity and mortality.

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