

The shortcomings of tocilizumab in COVID-19

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INTRODUCTION

With businesses and schools in many countries across the world reopening, there is tremendous pressure on the scientific community to find treatment for the coronavirus disease 2019 (COVID-19). Among various therapeutics that have been in trials, antivirals and immunomodulatory drugs have had the most attention to date. Among immunomodulatory drugs, IL-6 blockers have gained the spotlight for their benefits in treating cytokine release syndrome (CRS). Tocilizumab, sarilumab, and siltuximab are being investigated in numerous clinical trials for their efficacy in preventing ICU admission, mechanical ventilation, and ultimately death. While several case series, and case reports claim favorable outcomes with the drug, the first phase III clinical trial results for tocilizumab (COVACTA) failed to meet primary and secondary target endpoints [1]. We hypothesize some reasons that might have contributed to this outcome (Figure 1).

Adaptive response or therapeutic target?

Cytokine storm in COVID-19 is thought to be due to supraphysiologic release of cytokines

from immune cells. IL-6 is a key cytokine responsible for the inflammation caused by the coronavirus. Not only has there been a strong correlation ($R=0.902$) between COVID-19 RNAemia and serum IL-6 levels [2], IL-6 is also a reliable prognostic marker of disease outcomes [6]. However, a few authors raised a question whether IL-6 levels are sufficiently raised in COVID-19 pneumonia to warrant treatment with anti-IL6 monoclonal antibodies [3, 4]. Previous studies related to ARDS, influenza and cytokine release syndrome secondary chimeric antigen receptor modified T cell therapy (CAR-T) have reported

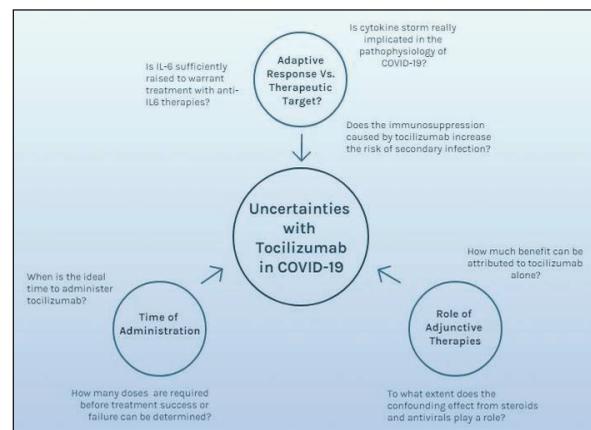


Figure 1 - Infographic summarizing the current gaps in knowledge and possible reasons for the shortcomings of tocilizumab in COVID-19.

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IL-6 levels to be 10-200 times greater than those recently reported in COVID-19 cytokine storm. Sinha et al pose the question whether cytokine storm is even implicated in the pathophysiology of COVID-19 to begin with, suggesting that targeted therapy with drugs such as tocilizumab and sarilumab may be premature with the current understanding of the illness to date [4]. Since serum levels of IL-6 may not be easily available in most hospitals, C-reactive peptide (CRP) is the next best inflammatory marker to assess the extent of inflammation. A study conducted in Spain found that tocilizumab was associated with a decreased rate of death and ICU admission or death in patients with CRP levels >150 mg/L but not <150 mg/L [5]. However, IL-6 and CRP are both well-known inflammatory mediators which are bound to increase in viral illness. The suppression of these markers may also make it more difficult to diagnose secondary infections [7]. Overall, it is still yet to be determined whether IL-6 “merely represents a biomarker of severity or whether it can be targeted for therapeutic interventions” [8]. To add, IL-6 is only one of the cytokines raised in suspected COVID-19 cytokine release syndrome. It may be beneficial to study the contributory value of IL-1, IFN- γ -induced protein (IP)-10 and IL-10 as well [9].

Time of administration

Tocilizumab was considered as a last-ditch effort for many of the patients reported in observational studies. Baseline characteristics were almost always worse in the tocilizumab subjects as compared to control. Tocilizumab was found to be more effective outside of the ICU setting and in non-ventilated patients [10]. Radbel et al state that inhibiting IL-6 too early on in the course of the illness may actually promote increased viral replication [11]. Conversely, waiting until the patient requires ventilation also leads to poor outcomes [10, 12]. The average time from symptom onset to administration of tocilizumab was roughly 10 days or two weeks after treatment with therapeutic care protocol [13, 14]. Since the clinical course of the illness is highly individualized, it is difficult to generalize an ideal time to initiate tocilizumab therapy. Suggesting a cut-off level of IL-6 or CRP does not seem appropriate either due to the risk of indication bias [5]. On a side note, there is discrepancy with regards to dosing as well. While a

case series from Alabama reported no difference between one or two doses, Luo et al in China found that a single dose of tocilizumab failed to show improvement whereas additional doses did [13, 15].

Adjunctive therapies

While most therapeutic care protocols included antivirals, steroids were commonly administered in tocilizumab test subjects on a compassionate care basis. The confounding effect of steroids on clinical improvement should be further explored [7]. An observational single center experience by Mikulska et al. showed the failure-free survival (no intubation or death) at 2 weeks to be 80% (95% CI, 65.1-89.1) in methylprednisolone group, 79.3% (95% CI, 59.6-90.1) in tocilizumab group and 87.5% (95% CI, 75.6-93.8) in combined therapy group with no significant difference between the individual groups [16]. It is unclear how much improvement can be attributed to tocilizumab alone versus glucocorticoids or the synergistic effect of combined therapy. University of Malaya is currently conducting a phase 3 randomized controlled trial (NCT04345445) which may provide some answers. Furthermore, in all relevant published data, it is quite evident that the more critical patients have been treated with tocilizumab. Therefore, it can be inferred that greater efforts would have been made intentionally or unintentionally to manage their disease progression as compared to a less severely affected patient. In a review of ongoing clinical trials, Esposito et al. describe an Italian trial TO-COVID-19 in which it was deemed unethical to randomize patients since the investigators may be restricting them from receiving a potentially beneficial drug [17].

Bias and ‘Desperation Science’

Tensions run high during a global pandemic with an urgency to release working treatment protocols as soon as possible. Rome and Avorn from the Program On Regulation, Therapeutics, And Law (PORTAL) state that there is “an understandable temptation to make unproven therapies widely available and not wait for rigorous clinical trial data” [18]. Kahlil describes the inaccurate but “common interpretation of off-label use and compassionate use of drugs is that if the patient died, they died from the disease, but if

the patient survived, they survived because of the given drug" [19]. In 2009, peramivir was used widely to treat swine flu under emergency use authorization (EUA) until a randomized controlled trial showed no benefit over placebo in severely ill hospitalized patients [18]. While it is important to continue the search for new therapies, it may be wise to optimize current supportive care practices and protect the trust of the general public [20]. Furthermore, there is an observed trend in reporting bias, with more articles favoring compassionate use of tocilizumab during the spring and early summer versus more recently published articles [21, 22].

■ CONCLUSIONS

On July 2, 2020, Sanofi and Regeneron stopped their Kevzara (sarilumab) clinical trial for failing to meet primary and secondary endpoints [23]. Could tocilizumab be the next IL-6 inhibitor to follow suit? The NIH COVID-19 treatment guidelines and IDSA recommendations both discourage the off-label use of tocilizumab outside of clinical trial settings. Although several studies have reported remarkable results with tocilizumab, it would be advisable to wait for further results from other clinical trials before reaching a verdict.

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Conflict of interest

None to declare

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