Tocilizumab and Thromboembolism in COVID-19: A Retrospective Hospital-based Cohort Analysis

Kok Hoe Chan (kokhoedelcos.chan@gmail.com)
Saint Michael's Medical Center
Bhavik Patel
Saint Michael's Medical Center
Bishnu Podel
Saint Michael's Medical Center
Maria E Szabela
Saint Michael's Medical Center
Hamid S Shaaban
Saint Michael's Medical Center
Gunwant Guron
Saint Michael's Medical Center
Jihad Slim
Saint Michael's Medical Center

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Abstract

Background: Tocilizumab, an IL-6 receptor antagonist has been used in patients with Coronavirus Disease 2019 (COVID-19) as an anti-cytokine agent. IL-6 also plays a complex role in hemostasis and thrombosis. We observed a transient elevation of D-dimer in our patients who received Tocilizumab, which triggered the current study.

Methods:A retrospective hospital-based cohort analysis of patients with confirmed COVID-19 who received Tocilizumab during the study period of 03/15/2020 to 05/20/2020. We retrieved demographic, clinical and laboratory data, we excluded patients who were receiving therapeutic anticoagulation therapy prior to Tocilizumab administration. Descriptive analysis was performed, the cause of death and trends of D-dimer and inflammatory markers were studied.

Results: Out of the 436 confirmed COVID 19 patients admitted during the study period, 24 met the inclusion criteria. Their median age was 47.5 years old. They were 18 males and 6 females; 15 patients survived, and 9 expired. Of the group that survived, 12 received therapeutic anticoagulation. Of the 7 patients who did not receive therapeutic anticoagulation, 4 expired, 1 from sepsis and 3 probably from thromboembolic complications, compared to 5 deaths in the 17 patients who received therapeutic anticoagulation with 4 dying from sepsis, and one possibly from thromboembolic complications.

Conclusions: The interplay between IL-6, IL-6 receptor antagonist and venous thromboembolism are complex. We observed a transient elevation of D-dimer in COVID-19 patients who received Tocilizumab, and a trend toward increased death secondary to thromboembolism. This observation is novel and highlights the potential thrombophilic side effects of Tocilizumab.

Introduction

Coronavirus Disease 2019 (COVID-19) is a major public health emergency. COVID-19 has multifaceted presentations and while the majority of patients are asymptomatic or present with mild disease, there is a subgroup of patients who tend to present with severe disease. Cytokine storm mediated by proinflammatory cytokines such as IL-6 and TNF- α is probably the culprit for severe COVID-19 [2]. Exuberant inflammatory response with complications related to cytokine release syndrome have been observed and proposed as leading to critical and fatal illness [3,4].

Currently, there are two recombinant humanized monoclonal antibodies targeting the IL-6 receptor, that are FDA approved in the USA, they are Sirukumab and Tocilizumab. There are multiple case reports and observational studies reporting use of Tocilizumab in patients with COVID-19 from around the world [5-7]. In the observational study by Xu et al., 21 patients with severe or critical COVID-19 infections showed rapid fever reduction and reduced oxygen requirement after receiving Tocilizumab [6], highlighting the potential role of IL-6 in modulating the disease activity.

To the best of our knowledge, Tocilizumab has not been shown to increase the risk of thrombosis or hypercoagulable state. Nonetheless, we have observed an elevation of D-dimer in the patients receiving Tocilizumab while the rest of inflammatory markers (ferritin, LDH and CRP) were down-trending, with an increased mortality related to thrombo-embolism, raising the possibility that Tocilizumab may be promoting a prothrombic state. In this retrospective, hospital-based cohort study, we are reporting the clinical outcomes and dissecting the potential interplay between Tocilizumab and thrombosis.

Methodology

A retrospective analysis was done on patients admitted to our hospital between March 15th and May 20th, 2020. Inclusion criteria were: 1) positive SARS-CoV-2 RT-PCR; 2) received Tocilizumab as part of their COVID-19 regimen. The only exclusion criteria was prior anticoagulation use.

Demographic analysis was performed, and data was expressed as counts, percentages or median. Death was determined as thromboembolic disease if the patient expired with increasing D-dimer while Ferritin and CRP were decreasing; Septic shock if cultures were positive, increasing vasopressor requirement and/or increasing CRP and/or Ferritin. Dealth was unlikely due to thromboembolic if D-dimer <1,500 at the time of death. The trends of D-dimer and inflammatory markers of the patients who did not receive anticoagulation were plotted and demonstrated in Figure 1. A waiver of HIPAA privacy authorization has been obtained through the hospital local institutional review board.

Results

Between March 15th to May 20th, 2020, 24 SARS-CoV-RT-PCR tested positive patients received 400 mg IV Tocilizumab one dose. Patient's demographic and outcomes are tabulated in Table 1. Their median age was 47.5 years old (range from 32 to 67 years old). They were 18 males and 6 females. As for ethnicity; 17 were Hispanic (74%), 2 African American (9%), and 4 had other ethnicities (17%). Of the 24 patients, 15 patients (65%) survived and 9 patients (35%) expired. Therapeutic anticoagulation with either low molecular weight heparin or unfractionated heparin were given to 17 patients (71%). Of the 15 patients who survived, 12 patients (80%) received therapeutic anticoagulation. Only 5 patients (56%) in the expired group received therapeutic anticoagulation. The 4 patients who were not anticoagulated and expired, 1 from sepsis and 3 probably from thromboembolic complications, compared to 5 deaths in the 17 patients who received therapeutic anticoagulation with 4 dying from sepsis, and one possibly from thromboembolic complications.

Eighteen out of 24 patients (75%) had elevation of D-dimer after Tocilizumab administration, while all the inflammatory markers (ferritin, LDH and CRP) were trending down. Moreover, the elevation was more pronounced in the group who expired and not on therapeutic anticoagulation (Figure 1).

Discussion

The association of Tocilizumab and thrombosis, to our knowledge, have never been reported. We observed the elevation of D-dimer after Tocilizumb administration. Moreover, of those 4 patients who were not anticoagulated that expired, there were a profound elevation of D-dimer and 3 of them expired probably secondary to thromboembolic events. As compared to those who were anticoagulated, most of them expired due to sepsis and only one who expired likely secondary to thromboembolic event.

The interplay between IL-6, IL-6 receptor antagonists and the venous thromboembolism are complex. IL-6 is a proinflammatory cytokine that is involved in inflammation, autoantibody production, endothelial regeneration and permeability, as well as hematopoiesis [15]. IL-6 is produced by a variety of cells including T-lymphocytes, monocytes, endothelial cells and fibroblasts [15]. Stone et. al. has demonstrated the increase risk of deep vein thrombosis with tumor derived IL-6 in the mouse model of ovarian cancer via the induction of hepatic thrombopoietin, promoting thrombus formation [12]. Moreover, IL- 6 has been reported to contribute to deep vein thrombosis by dysregulation of miR-338-5p expression [16].

On the contrary, Nosaka et al has recently published a research article in Feb 2020, highlighting the role of IL-6 in thrombus resolution, in which suppression of IL-6 may in fact result in the growth of the thrombus as demonstrated in the rat model [17]. Moreover, IL-6 antagonist has been associated with a reduced level of Factor XIII, chimerin and plasminogen activator inhibitor [18]. The pivotal role of Factor XIII is in fibrin stabilization, thus the decrease of Factor XIII as a result of IL-6 antagonist will lead to thrombus instability, which may also contribute to this thrombophilic state.

Thrombosis is a complex phenomenon, the hemostasis balance between thrombus formation rate and resolution is important. IL-6 in this context seems to play a complex role, both in thrombus formation and resolution. This assumption has been strengthened by the observations that the administration of Tocilizumab, an IL-6 antagonist, transiently elevated the D-dimer, which is a marker of coagulability. Though more studies are needed to understand the pathophysiological role of IL-6 in hemostasis and thrombosis. Our observation would suggest that it may be beneficial to use therapeutic anticoagulation in COVID 19 patients receiving Tocilizumab, since they already are at high risk of thrombosis.

Conclusion

The interplay between IL-6, IL-6 receptor antagonist and venous thromboembolism are complex. We observed a transient elevation of D-dimer in COVID-19 patients who received Tocilizumab. This observation is novel and highlights the potential thrombophilic side effects of Tocilizumab. Prospective randomized controlled trials will need to measure this effect in order to come up with a firm clinical recommendation in the future.

Declarations

Conflicts of Interest: All authors including Kok Hoe Chan, Bhavik Patel, Bishnu Poudel, Maria E Szabela, Hamid S Shaaban, Gunwant Guron, and Jihad Slim declare no competing conflict of interest

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Tables

No	Age	Gender	Race	No of days of symptoms	No of days from symptoms to Tocilizumab	Therapeutic anticoagulation	Outcome	Cause of Death
1	38	Male	Hispanic	7	11	Yes	Survived	-
2	41	Male	Hispanic	3	3	Yes	Survived	-
3	43	Female	Hispanic	9	11	Yes	Survived	-
4	44	Male	Other	10	10	Yes	Survived	-
5	44	Male	Hispanic	7	11	Yes	Survived	-
6	46	Male	Hispanic	7	9	Yes	Survived	-
7	50	Male	Other	14	19	Yes	Survived	-
8	57	Male	Hispanic	14	16	Yes	Survived	-
9	60	Female	AA	7	10	Yes	Survived	-
10	60	Female	Hispanic	7	10	Yes	Survived	-
11	61	Female	Other	14	15	Yes	Survived	-
-12	67	Male	AA	5	10	Yes	Survived	-
13	34	Male	Hispanic	7	10	No	Survived	-
14	44	Female	Other	3	3	No	Survived	-
15	60	Female	Hispanic	7	7	No	Survived	-
16	37	Male	Hispanic	2	3	Yes	Expired	Septic Shock with acute rise of CRP/Ferritin
17	42	Male	Hispanic	5	9	Yes	Expired	AHRF likely thromboembolic event
18	49	Male	Hispanic	7	8	Yes	Expired	Septic Shock and multiorgan failure (increasing pressor requirement (3 pressors)
19	52	Male	Hispanic	7	9	Yes	Expired	Septic Shock (Blood culture positive for Neisseria sicca)
20	62	Male	Hispanic	7	14	Yes	Expired	Septic Shock with increasing CRP/Ferritin
21	35	Male	Hispanic	14	18	No	Expired	AHRF likely thromboembolic event
22	39	Male	Hispanic	7	8	No	Expired	AHRF likely thromboembolic event
23	52	Male	Hispanic	5	7	No	Expired	Septic Shock and Severe *Clostridiodes Difficile*
24	60	Male	Hispanic	7	10	No	Expired	AHRF likely thromboembolic event

Table 1: Demographic, clinical outcomes and cause of death after Tocilizumab.
AHRF (acute hypoxic respiratory failure), AA (African American)

Figures

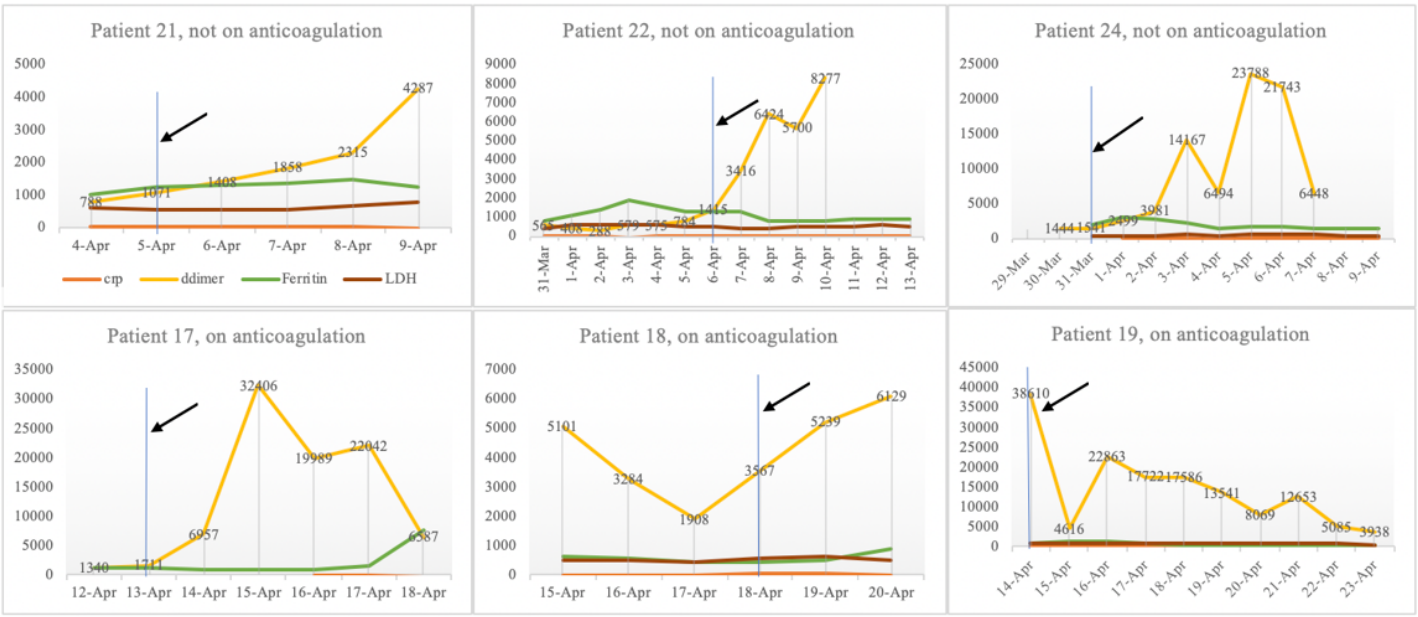

Figure 1

Trend of D-dimers and inflammatory markers (CRP, LDH and Ferritin) of the patients who expired (Blue line and black arrow indicated the time of the Tocilizumab given, orange line – CRP, yellow line – D-dimer, green line – Ferritin, brown line - LDH)