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EDITORIAL

Tocilizumab for the treatment of COVID-19

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It has been one year since the first cases of pneumonia caused by the now designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported from Wuhan. Over these past months, clinicians taking care of patients with coronavirus disease 2019 (COVID-19) have learned that the exuberant inflammatory response triggered by the virus acts as a major contributor to the pathogenesis of acute respiratory distress syndrome (ARDS) and multiorgan failure, which occur in most of the fatal cases [1]. In the absence of antiviral drugs that clearly modify the clinical course of the infection, immunomodulation has emerged as the most promising therapeutic approach to COVID-19. The administration of low-to-intermediate-dose corticosteroids (dexamethasone 6 mg daily, equivalent to prednisone 40 mg, for 10 days) is the only treatment to date that have been proven, in the setting of a randomized controlled trial (RCT), to reduce the mortality among patients requiring respiratory support [2]. The early finding that interleukin-6 (IL-6) levels are elevated in severe COVID-19 and independently predict the risk of progression to ARDS and death focused clinical research efforts on this pro-inflammatory and pleiotropic cytokine [3,4]. Existing experience with tocilizumab – a humanized IgG1 monoclonal antibody targeting the IL-6-receptor – for the treatment of the cytokine release syndrome (CRS) in patients receiving chimeric antigen receptor (CAR) T-cell therapy rapidly paved the way for its off-label use in cases of severe COVID-19 since the first weeks of the pandemic [5–7]. Nevertheless, accumulating evidence suggests that the term 'cytokine storm' may be misleading to define the hyper-inflammatory status observed in SARS-CoV-2 infection, since IL-6 levels are actually at least one magnitude order lower than those found in patients with CAR-T-therapy-associated CRS, sepsis, or other causes of ARDS [8]. The desperate need to find an effective therapy to improve the dismal prognosis of severe COVID-19 pneumonia and the well established and acceptable safety profile of tocilizumab led to its widespread use during the first pandemic wave. Indeed, 9.4% of the patients hospitalized through March 17 in a large multicenter registry in Spain received tocilizumab [9], and as many as 17.1% of those admitted to the intensive care unit until April in the US 4 [10]. It should be noted that the supporting evidence was essentially limited during spring and summer of 2020 to small, observational, case series with no control group [5–7]. Now, when the results of RCTs and controlled observational studies have become available, the time has come to critically review the role of tocilizumab in the management of COVID-19.

Various large observational studies have reported marked reductions in the requirement of invasive mechanical ventilation (IMV) or all-cause mortality among COVID-19 patients treated with tocilizumab as compared to the standard of care alone. In a cohort study carried out in three Italian centers (n = 544 patients), Guaraldi et al. found that tocilizumab therapy reduced the risk of death (7.3% versus 20.0%, respectively), although no differences were observed in the progression to IMV (18.4% versus 15.6%). After adjustment for clinical covariates (including duration of symptoms and SOFA score), tocilizumab was associated with a significant reduction in this composite outcome (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.40–0.92) [11]. The SAM-COVID-19 study, that included 778 patients from 60 Spanish centers, reported a 68% decrease after the inverse probability of treatment weight (IPTW) adjustment in the risk of IMV or death for tocilizumab (HR: 0.32; 95% CI: 0.22–0.47) [12]. In the largest observational study published to date (STOP-COVID), Gupta et al. compared 433 critically ill patients that received tocilizumab within the first 2 days from ICU admission and 3,491 patients that did not receive this IL-6 blocker. After a median follow-up of 27 days, the risk of death among patients treated with tocilizumab had decreased by one-third (HR: 0.71; 95% CI. 0.56–0.92). This benefit was more evident in the subgroup with a partial pressure of arterial oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2) <200 and mechanically ventilated at ICU admission, and was not modified by the receipt of corticosteroid therapy [13]. A recently published single-center study also found that tocilizumab therapy improved the alveolar-arterial oxygen and the pulmonary vascular radiologic score (although the lung parenchymal score remained unchanged), favoring the early recovery of pulmonary vascular function [14].

Five RCTs evaluating the efficacy and safety of tocilizumab as immunomodulatory therapy for COVID-19 have been published to date [15–19] (Table 1). All the studies were multicenter and three of them were controlled with placebo [15,16,19]. The number of participants ranged from 126 to 438. Although inclusion criteria varied, all the patients had a molecular or serological (IgM assay) diagnosis of SARS-CoV

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Table 1. Review of RCTs analyzing the efficacy and safety of tocilizumab as immunomodulatory therapy for COVID-19.

	COVACTA [15]	ENVACTA [16]	RCT-TCZ-COVID-19 [17]	CORIMUNO-TOCI-1 [18]	BACC Bay Tocilizumab Trial [19]
Type of RCT	Blinded, placebo-controlled (2:1 ratio)	Blinded, placebo-controlled (2:1 ratio)	Open-label, no placebo-controlled (1:1 ratio)	Open-label, no placebo-controlled (1:1 ratio)	Blinded, placebo-controlled (2:1 ratio)
No. of sites (countries)	67 (Europe, US, Canada)	69 (Mexico, South America, Kenya, South Africa, US)	24 (Italy)	9 (France)	7 (US)
No. of participants	438	389	126	131	243
Age at enrrollment, years (mean ± SD or median [IQR])	60.9 ± 14.6 [TCZ arm]	56.0 ± 14.3	60.0 (54.0–69.0)	64.0 (57.1–74.3) [TCZ arm]	59.8 (45.3–69.4)
Severe disease at enrrollment[a]	301 (68.7%)	100 (26.5%)	Not specified (patients on MV were excluded)[b]	Not specified (patients on MV were excluded)[c]	11 (4.5%)
Days from symptom onset to randomization	11.0 (1.0–49.0) [TCZ arm]	8.0 (0.0–36.0)	8.0 (6.0–11.0)	10.0 (7.0–13.0) [TCZ arm]	9.0 (6.0–13.0)
Use of systemic corticosteroids[d]	106 (36.1%) [TCZ arm], 79 (54.9%) [placebo arm]	200 (80.3%) [TCZ arm], 112 (87.5%) [placebo arm]	None	21 (33%) [TCZ arm], 41 (61%) [SoC arm]	18 (11%) [TCZ arm], 5 (6%) [placebo arm]
Primary outcome	Change in clinical status (on a 7-category ordinal scale) by day 28	Invasive MV, ECMO or death by day 28	Clinical worsening (MV, death and/or PaO_2/FiO_2 ratio <150) by day 14	• MV or death by day 4 • Survival with no MV by day 14	Invasive MV or death (time-to-event analysis)
Main results	Threshold for efficacy not met: OR 1.19 (95% CI: 0.81–1.76; *P*-value = 0.36)	Threshold for efficacy met: HR 0.56 (95% CI: 0.32–0.97; *P*-value = 0.04)	Threshold for efficacy not met: RR: 1.05 (95% CI: 0.59–1.86; *P*-value = 0.87)	• *MV or death by day 4*: threshold for efficacy not met: ARD −9.0% (90% CI: −21.0% – 3.1%) • *Survival with no MV by day 14*: threshold for efficacy met: HR: 0.58 (90% CI: 0.-33–1.00)	Threshold for efficacy not met: HR: 0.83 (95% CI: 0.38–1.81; *P*-value = 0.64)
Selected secondary outcomes (TCZ vs. control arm) and safety signals	No differences in 28-day mortality (19.7% vs. 19.4%)	No differences in 28-day mortality (10.4% vs. 8.6%) Numerically lower rate of serious infection with TCZ	No differences in 14-day (1.7% vs. 1.6%) or 30-day mortality (3.3% vs. 1.6%)	No differences in 14-day (11.1% vs. 8.9%) or 28-day mortality (11.1% vs. 11.9%) Numerically lower rate of SAEs and serious bacterial infection with TCZ	No differences in 14-day (4.4% vs. 1.3%) or 28-day mortality (5.6% vs. 3.8%) Numerically lower rate of serious infection with TCZ

ARD: median absolute risk difference; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; IQR: interquartile range; MV: mechanical ventilation; OR: odds ratio; RCT: randomized clinical trial; SAE: serious adverse event; PaO_2/FiO_2: partial pressure of arterial oxygen/fraction of inspired oxygen; SD: standard deviation; SoC: standard of care; TCZ: tocilizumab.

[a]Patients receiving high-flow oxygen or noninvasive or invasive mechanical ventilation. Definition of severity varied across trials.

[b]Patients were eligible for the RCT-TCZ-COVID-19 trial if they have a PaO_2/FiO_2 ratio between 200 and 300 mmHg. They were allowed to receive oxygen therapy with Venturi mask or high-flow nasal cannula but not invasive or noninvasive mechanical ventilation.

[c]Patients were eligible for the CORIMUNO-TOCI-1 trial if they had a WHO-CPS score of 5 with O_2 levels of 3 L/min or higher but without noninvasive or invasive mechanical ventilation.

[d]Systemic corticosteroids as immunomodulatory therapy for COVID-19.

-2 infection, pneumonia documented by radiologic imaging, and respiratory failure with variable oxygen requirements. Three trials excluded patients on mechanical ventilation at enrollment [16–18]. Of note, only two studies considered the presence of elevated inflammatory markers (serum C-reactive protein or ferritin) as inclusion criteria [17,19]. Quite surprisingly, increased IL-6 levels at baseline were not formally required in any of the trials. It should be remembered, however, that the blockade of the IL-6 receptor is followed by a rapid increase in the levels of the cytokine [7]. Therefore, the monitoring of serum IL-6 is not useful to assess the response to tocilizumab therapy. Study outcomes generally included the improvement in clinical status – assessed by an ordinal scale – or the composite endpoint of IMV or death. The prespecified threshold for efficacy was only achieved in two RCTs. In the ENVACTA trial (which enrolled participants from racial and ethnic minority groups), the cumulative percentage of patients with MV or dead by day 28 was lower in the tocilizumab arm than in the placebo arm (12.0% versus 19.3%, respectively), although the mortality rate at day 28 separately considered did not differ [16]. The CORIMUNO-TOCI-1 assessed two different primary outcomes, only one of which was met. On day 14, 23.8% of the patients treated with tocilizumab and 35.8% receiving standard of care needed mechanical ventilation or had died, accounting for a posterior probability of HR less than 1 of 95.0% [18]. It is important to note that none of the trials was able to show an apparent benefit for tocilizumab in terms of mortality. Finally, no relevant safety signals emerged, and even a lower incidence of infectious complications has been observed within the tocilizumab arm in some trials [18,19].

How to reconcile these apparently contradictory results derived from observational studies and RCTs? Although none of the trials was powered to demonstrate differences in mortality as a separate outcome, it is difficult to accept that no trends would have been observed if differences between arms actually exist, given the amount of decrease in the incidence of study endpoints observed across cohort studies – with reductions that ranged from 30% to 70% [11–13]. The low 28-day mortality observed in the trials by Salvarani et al. [17] and Stone et al. [19] (which not exceeded 6% in any of the study arms) would suggest a baseline COVID-19 severity far below that of observational studies. Therefore, it could be hypothesized that, due to practical reasons, patients approached to be enrolled in RCTs were younger and less sick than those usually seen in clinical practice. The lack of representativeness – in terms of 'real-world patients' – of trial participants has been already discussed [20]. Median age across RCTs was lower than that of the SAM-COVID study (66 years) [12], although in line with the STOP-COVID study (62 years) [13]. On the other hand, it must be emphasized that observational studies investigating the effect of therapies are inherently at risk of bias, from confounding by indication to immortal time. Even if the interpretation of selection bias in this type of studies is not straightforward, it could be presumed that most of them are skewed toward sicker patients. By definition, propensity score and similar techniques (such as IPTW) are exclusively able to adjust for observed differences between treatment groups, but not for unmeasured imbalances. Such unknown confounders due to nonrandom allocation may have been particularly relevant during the first pandemic wave, with overwhelmed healthcare systems across the world and restricted access to ICU resources and drug shortages in numerous European centers. Not surprisingly, none of the 28 observational studies (with 5,776 patients) pooled in a recent meta-analysis was deemed to be at low risk of bias. Thus, the authors were only able to conclude that there is insufficient evidence regarding the efficacy and safety of tocilizumab in the setting of COVID-19 [21].

Expert Opinion

At the present point, how should future intervention and observational studies be designed? The identification of subgroups of COVID-19 patients that would eventually exhibit a greater benefit from the use of tocilizumab should be prioritized. The findings reported by Gupta et al. [13], in addition to the negative results from the RCT-TCZ-COVID-19 [17] and BACC Bay Tocilizumab trials [19], suggest that the effect of immunomodulation may be more evident at more advanced stages of SARS-CoV-2 infection. The potential role of the combination with corticosteroids must be explored. It is noteworthy that the vast majority of patients recruited in the only RCT in which the threshold for efficacy was actually met also received systemic corticosteroid therapy [16], with a similar trend also reported in the CORIMUNO-TOCI-1 trial [18]. Alternative dosing strategies may be evaluated, although no apparent differences have been reported between patients receiving one or more than one tocilizumab doses [16]. The most relevant outcome for RCTs conducted in the setting of COVID-19 (e.g. improvement in clinical status, need of mechanical ventilation, or all-cause or attributable mortality) remains to be defined. Finally, it cannot be completely ruled out that the inhibition of IL-6 provides no meaningful impact on the clinical evolution of COVID-19. The multiplicity and redundancy of inflammatory pathways triggered by SARS-CoV-2 [1] and the lack of outcome differences according to baseline IL-6 levels [19] would point to the existence of escape mechanisms beyond the mode of action of tocilizumab.

One thing is for sure: the search for effective immunomodulation in the setting of severe COVID-19 has not yet said its last word. In view of its overall favorable safety profile and the reasonable expectation of clinical benefit (eventually pending confirmation in future studies), we would still advocate the use of tocilizumab in selected cases of COVID-19 with progressive respiratory failure and sustained inflammatory status despite dexamethasone therapy. Needless to say, the recruitment of such patients in ongoing RCTs should be always prioritized over the off label use of this or other immunomodulatory agents.

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