

Tocilizumab Induces Rapid, Sustained Improvement of Inflammatory Markers in COVID-19, With Clinical Improvement in Most Patients

To the Editor:

The novel coronavirus, SARS-CoV-2, the causative agent of COVID-19, has caused enormous morbidity and mortality worldwide. Clinical manifestations of COVID-19 range from asymptomatic and mild infection to severe disease with pneumonia, acute respiratory distress syndrome, and multiorgan failure.

Currently, remdesivir is the only FDA-approved drug to treat COVID-19. Multiple agents are currently under investigation, such as tocilizumab, an

anti-IL-6 receptor monoclonal antibody originally approved for treatment of rheumatoid arthritis and later chimeric antigen receptor T-cell-induced cytokine release syndrome (CRS)¹ CRS is a complex disorder characterized by an increase in pro-inflammatory cytokines, including IL-6, which triggers a hyperinflammatory syndrome.² Although recent data have shown that corticosteroids may provide benefit in COVID-19, it is unclear whether other forms of immunomodulatory therapy improve clinical outcomes.³

Table 1. Demographics, past medical history, and clinical outcomes for the 19 patients receiving tocilizumab for COVID-19.

Patient	Age/Sex	PMHx	Ordinal scale for clinical improvement (OSCI) after TCZ			Discharge status
			Day 0	Day 7	Day 14	
1	70 M	HTN, HLD, DM, CAD	7	7	4	Acute rehab day 19
2	67 M	None	7	6	6	Deceased day 24
3	58 M	HLD	7	6	4	Home day 26
4	51 M	HTN, HLD, OB	7	4	3	Home day 24
5	62 M	CAD	7	7	7	Acute rehab day 27
6	66 M	HTN	4	4	—	Home day 11
7	64 M	CAD, DM, HTN	7	8	8	Deceased day 3
8	84 M	HTN, COPD	3	—	—	ALF (returned) day 6
9	45 M	None	4	2	—	SNF day 5
10	44 M	Tob	7	4	3	Home day 15
11	64 M	HTN, Asth	4	4	—	Home day 11
12	79 F	CKD	4	8	8	Deceased day 1
13	56 M	HTN, HLD, OB	7	8	8	Deceased day 6
14	91 F	HTN, HF	4	8	8	Deceased day 5
15	58 F	CAD	7	6	6	LTAC day 20
16	46 M	None	4	3	—	Home day 7
17	86 F	HTN	7	4	8	Deceased day 10
18	94 F	HTN, HLD, DM	4	—	—	Rehab day 3
19	53 F	HTN, DM, OB	6	4	3	Rehab day 13

PMHx: CAD, coronary artery disease, CKD, chronic kidney disease, COPD, chronic obstructive pulmonary disease, DM, diabetes mellitus, HF, heart failure, HLD, hyperlipidemia, HTN, hypertension, Tob, Tobacco smoking history, OB, Obesity. Discharge Status: LTAC, long term acute care facility, SNF, skilled nursing facility, ALF, assisted living facility.

Table 2. Ordinal scale for clinical improvement.

0	No clinical or virological evidence of infection
1	No limitation of activities in the ambulatory setting
2	Limitation of activities in the ambulatory setting
3	Hospitalized without oxygen therapy (mild disease)
4	Hospitalized and requiring oxygen by mask or nasal cannula (mild disease)
5	Hospitalized and requiring non-invasive ventilation of high-flow oxygen (severe disease)
6	Hospitalized and requiring intubation and mechanical ventilation (severe disease)
7	Hospitalized and requiring ventilation and additional organ support such as vasopressors, renal replacement therapy or extracorporeal membrane oxygenation (severe/critical disease)
8	Death

Here, we describe the clinical response to tocilizumab (TCZ) in the first 19 consecutive patients with moderately severe to critical COVID-19 at our facility. We analyzed objective clinical response, temperature curves, changes in inflammatory markers, and short-term patient outcomes. All patients were diagnosed with SARS-CoV-2 infection in March through May of 2020 and received at least one dose of TCZ during hospital admission. TCZ was given to patients at the discretion of the infectious diseases consultant when there was clinical determination of moderately severe-to-critical COVID-19 with evidence of CRS such as persistent or rising fever and/or rising inflammatory markers more than a week into symptomatic infection. Clinical outcomes were recorded on days 7 and 14 after receiving TCZ, recovery and discharge home, partial recovery and discharge to a rehabilitation facility, or death. The ordinal scale for clinical improvement (OSCI), as recommended by the WHO R&D expert group, was used to measure clinical outcomes on days 7 and 14 post-tocilizumab administration

(Table 1).⁴ CRP and temperature were analyzed before and after TCZ. Statistical significance was assessed by the Wilcoxon Signed-Rank test.

Of 246 inpatients admitted to our hospital with documented COVID-19 from March through May of 2020, 19 received TCZ. The median age was 64 years (range 44–94, 6 women and 13 men). Sixteen patients received one dose of TCZ 400 mg IV, 2 patients received 2 doses of 400 mg IV, and one patient received one dose of 660 mg. 7 patients had recovery to the level of being discharged home or to an assisted-living facility, 6 patients had recovery to the level of discharge to a rehabilitation or long-term acute care facility, and a total of 6 patients died with 5 of those dying within 2 weeks of receiving TCZ (Table 2). Of the patients who died, 4 patients had critical disease with OSCI scores of 7, 1 patient died a day after receiving TCZ, and 1 patient died from acute respiratory failure in the setting of an aspiration event on day 24 after TCZ administration. One patient who received TCZ was included for demographic data but excluded from analysis (patient 12), because the patient expired the day after receiving the first dose.

Mean interval from onset of symptoms to dose of TCZ was = 11.5 ± 5 days. The median value of IL-6 level was 137.9 pg/mL (range = 33.1–4518.5 pg/mL). Median peak temperature (T_{max}) of the 18 analyzed patients before TCZ was 38.2°C and 37.1°C after TCZ ($P < 0.001$) (Figures 1, 2). The median CRP before TCZ was 207.5 mg/L which was reduced to 55.0 mg/L after TCZ ($P = 0.001$) (Figures 1, 2). By Ordinal Scale for Clinical Improvement (OSCI), 11 of 19 patients (57.9%) showed improvement by at least one point at 7 days after TCZ administration, and 13 of 19 patients (68.4%) showed improvement by at least one point at 14 days.

Lack of proven effective therapies poses an ongoing challenge in the management of COVID-19. Although most patients with SARS-CoV-2 infection have a mild and self-limited disease, a significant number

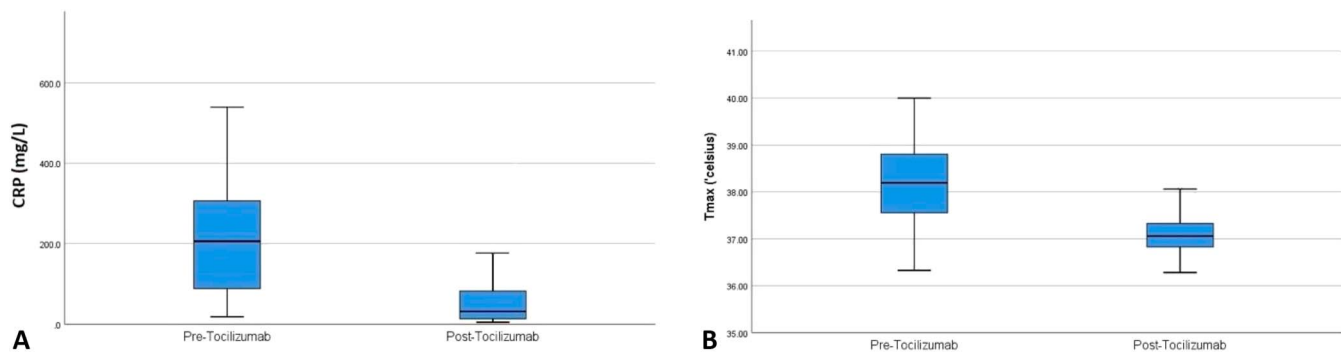


FIGURE 1. CRP (A) and temperature (B) levels pre- and post-tocilizumab. Boxplot shows total and interquartile ranges. Difference for CRP and T_{max} pre-TCZ and post-TCZ significant with $P < 0.001$.

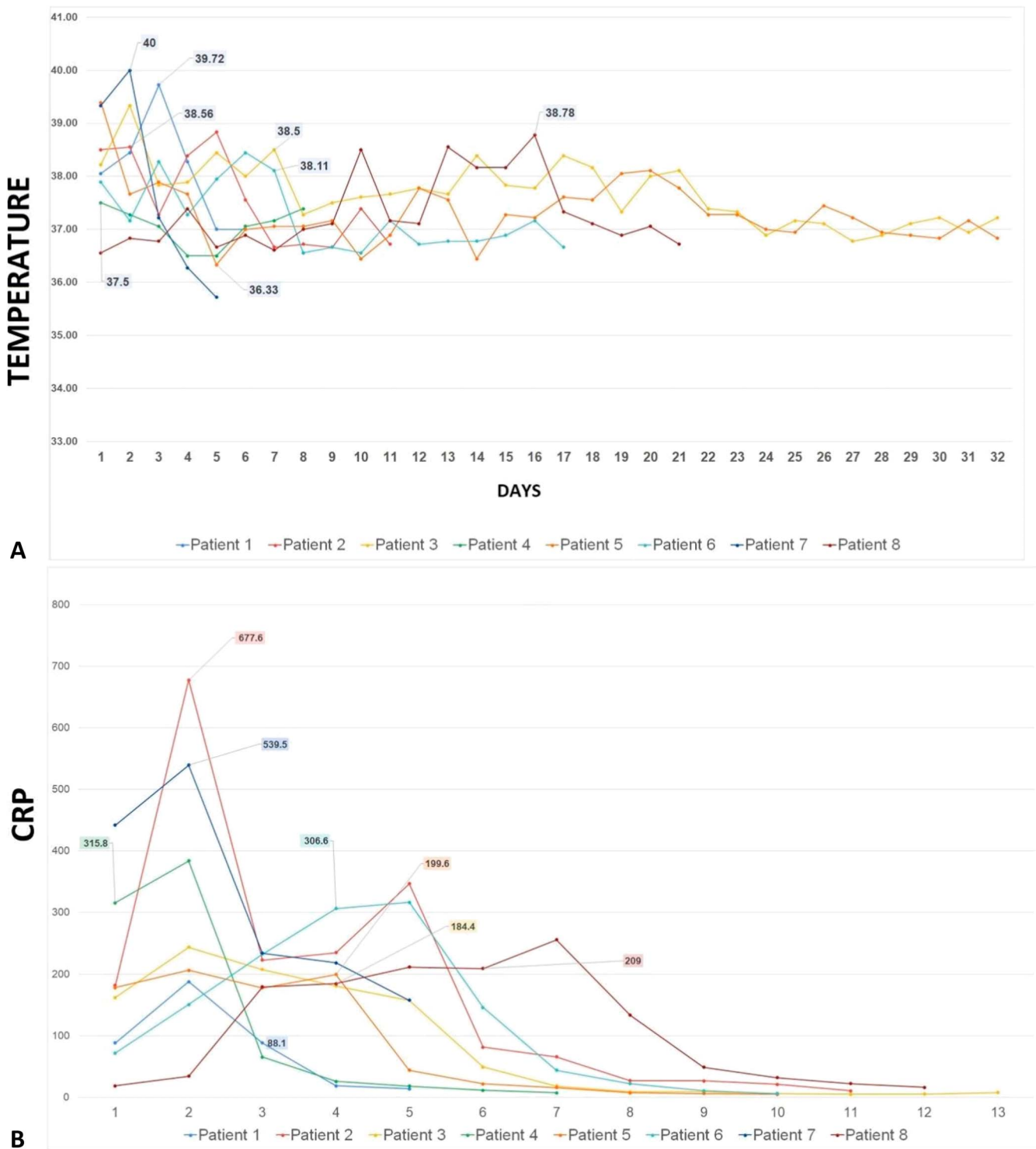


FIGURE 2. Trend over time for temperature (A) and CRP (B). Only first 8 patients are plotted for clarity of visualization. Figure highlights the points when tocilizumab was given to the patient.

experience worsening illness with rising inflammatory signs late after onset, suggestive of CRS.⁵ For these patients, suppression of IL-6 presents an attractive target for intervention.

TCZ has been reported to reduce the requirement for supplemental oxygen and to be associated with clinical improvement in patients from China with severe COVID-19.⁶ Of note, 53% of patients received

Methylprednisolone in combination with TCZ. Similar results were reported in a study from Italy.⁷ Prepublication results from the open-label CORIMUNO-TOCI trial suggested significantly lower mortality and need for ventilator support in patients treated with TCZ with moderate to severe COVID-19.⁸ Interim analysis of a study of the anti-IL-6 monoclonal, siltuximab, reported a lower 30-day mortality rate in patients requiring ventilatory support. There was a trend toward a reduced need for invasive mechanical ventilation in the siltuximab-treated patients on noninvasive ventilation.⁹ Other more recent studies have not found significant benefits.^{10–12} These medium-sized, randomized prospective trials failed to show benefit (or harm) in mortality or disease progression, although the confidence intervals remain large. In RECOVERY (Randomized Evaluation of COVID-19 thERapY) Trial, dexamethasone for 10 days reduced 28-day mortality.¹² In our patients, the most improvement resulted from decreased invasive mechanical ventilation, vasopressors, dialysis, and supplemental oxygen. (Detailed inpatient clinical summaries are provided in the see **supplementary data. File A, Supplemental Digital Content 1**, <http://links.lww.com/AJT/A101>).

One patient experienced posterior reversible encephalopathy syndrome (PRES) during the inpatient treatment with full recovery after the aggressive treatment of labile hypertension. PRES has been described in cases of TCZ administration.^{13,14}

In this retrospective case series of COVID-19 patients with moderately severe-to-critical disease and evidence of CRS late after the onset of symptoms, we observed rapid and dramatic reductions in fever and inflammatory markers after administration of TCZ, and overall improvement of clinical status (OSCI). Although currently published data do not support a general role for TCZ in treatment of COVID-19, the fulminant inflammatory response seen late in the illness in some patients, and the rapid, dramatic diminution in this response after administration of TCZ leave open the possibility that a subset of patients may benefit. This hypothesis will need to be addressed in more targeted trials.

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Inaccurate Real-World Data Does Not Provide Real-World Answers

To the Editor:

We would like to congratulate Kory et al¹ for their article. From the beginning of the COVID-19 pandemic, there emerged the need to find a drug that could alter the course of severe infection and reduce mortality, was easily accessible, and was inexpensive. Ivermectin, among others, is a potential drug with these properties.

Numerous studies on the subject, of variable quality, have been published, but evidence of the effectiveness of ivermectin is inconclusive. The review article by Kory et al attempted to consolidate the existing evidence on ivermectin to justify its recommendation.

The authors used real-world data from 3 South American countries, Brazil, Paraguay, and Peru.

A more detailed and in-depth analysis of these data shows us that they do not provide enough evidence of effectiveness of ivermectin because there are discrepancies from the official data and the previous use of lockdown and other preventive public health measures was not adequately considered.

Data from Brazil published in the article differ from the official data.² As shown in Table 1, the number of cases of COVID-19 did not decrease after the introduction of ivermectin, as shown by the authors of the

Table 1. Comparison of number of COVID-19 cases in Brazilian cities with and without Ivermectin distribution campaigns.

	June	July	August	Change from June to August (%)
Itajaí	1385 (2123)	1891 (2854)	2733 (998)	97% (–53%)
Chapecó	1583 (1760)	1337 (1754)	1926 (1405)	22% (–20%)
Macapá	7960 (7966)	2501 (2481)	1742 (2370)	–78% (–70%)
Ananindeua	1620 (1520)	1523 (1521)	991 (1014)	–39% (–30%)
Natal	8695 (9009)	7497 (7554)	3304 (1590)	–62% (–82%)
João Pessoa	9939 (9437)	8032 (7963)	5555 (5384)	–41% (–43%)

Source: Brazilian Health Ministry- <https://covid.saude.gov.br/>.

The cities shown in bold distributed ivermectin; the neighboring regional cities below did not. Percent difference (% difference between June and August). The number of cases published in Kory’s article is shown in parentheses.