

Real-World Tocilizumab Use in Pediatric Inpatients

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OBJECTIVES Primary objective: to quantify tocilizumab (TCZ) use in pediatric inpatients. Secondary objectives: to explore safety and clinical outcomes.

METHODS This retrospective cohort study took place in a free-standing, 564-bed children's hospital. Pediatric inpatients who received intravenous TCZ from January 2016 to May 2021 were included. Data collected included demographics, indication, dose, number of administrations, safety events on days 0 to 7 after TCZ, use of extracorporeal support (ES), presence of concurrent infection, and survival to discharge. Exploratory analyses assessed characteristics associated with mortality.

RESULTS A total of 103 TCZ courses (n = 87 patients) were analyzed. Median age was 14 years. Tocilizumab indications included cytokine release syndrome (CRS; 56%), autoimmune disease (27%), graft-versus-host disease (GVHD; 5%), and COVID-19 (4%). The median TCZ dose was 8 mg/kg (IQR, 7.9–11.9), 18% of courses were administered during active infection, and ES was used in 15% of courses. New-onset alanine transaminase (ALT) or aspartate transaminase (AST) levels >3 times upper limit of normal (ULN) occurred in 53% and 60% of courses, respectively. Of 29 courses with evaluable hematologic data, 10% resulted in new-onset neutropenia and 3% in severe thrombocytopenia. Overall survival to discharge was 83%. In multivariable analyses, independent associations with mortality were found for the use of ES (OR, 8.68; 95% CI, 1.85–4.87), oncologic diagnosis (OR, 7.07; 95% CI, 1.14–89.29), and post-TCZ infection (OR, 11.17; 95% CI, 1.50–138.13).

CONCLUSIONS Tocilizumab is used for many pediatric inpatient indications, most commonly CRS. Newly identified transaminitis was common following TCZ administration. Risk factors for mortality are likely confounded by illness severity. Administration during active infection was not independently associated with increased mortality.

ABBREVIATIONS ALT, alanine transaminase; aOR, adjusted OR; AST, aspartate transaminase; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ECMO, extracorporeal membrane oxygenation; ES, extracorporeal support; FDA, US Food and Drug Administration; GVHD, graft-versus-host disease; ICU, intensive care unit; IL, interleukin; IV, intravenous; ONC/M, oncologic diagnosis or receiving myelosuppressive therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab; ULN, upper limit of normal

KEYWORDS cytokines; evidence-based medicine; interleukin-6; patient safety; pharmacology

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Introduction

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody targeted against the interleukin (IL)–6 receptor that inhibits IL–6–mediated signaling.¹ Tocilizumab is currently approved for the treatment of rheumatoid arthritis, giant cell arteritis, and systemic sclerosis–associated interstitial lung disease in adult patients. Additionally, it carries US Food and Drug Administration (FDA) approval for systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, and cytokine release syndrome (CRS) following chimeric antigen receptor (CAR) T-cell therapy in patients 2 years of age and older.²

In June 2021, the FDA granted emergency use authorization for TCZ in patients 2 years of age and older

who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.³ The outbreak of the SARS-CoV-2 pandemic in December 2019 brought renewed attention to the off-label use of TCZ for patients with hyperinflammatory conditions, including critically ill patients. At least 15 studies have assessed the impact of TCZ use in adult patients with severe COVID-19, with an overall signal of decreased mortality.^{4–7} Importantly, multiple studies have found no increase in secondary infection among adult patients with severe COVID-19 who received TCZ.^{8–12}

While additional uses for TCZ are being explored, it is critical to balance any potential benefit with the known risks of the drug. Tocilizumab carries several warnings in its package labeling, including increased risk of infection, hepatotoxicity, and thrombocytopenia.² The current literature surrounding TCZ in pediatric patients is sparse and is largely centered on FDA-approved indications.^{1,2,13–15} We therefore designed a retrospective, single center study to describe intravenous (IV) TCZ use patterns for on- and off-label indications in hospitalized children. We also tested the exploratory hypothesis that clinical characteristics could be identified that are associated with mortality in hospitalized children who receive IV TCZ.

Materials and Methods

A retrospective chart review was performed at a free-standing, 564-bed children's hospital. All patients who received TCZ from January 2016 to May 2021 were identified via query of pharmacy medication orders. Patients were excluded from analysis if TCZ was ordered but not administered, TCZ was administered in an ambulatory setting, or any route of administration other than IV was used. Only patients receiving IV TCZ were included because initial feasibility assessments indicated nearly 98% of inpatient TCZ orders during the inclusion period were administered via the IV route. Each individual patient could contribute more than 1 TCZ course if they were discharged and readmitted to the hospital. All analysis was performed based on TCZ courses unless specified.

Data collected via chart review included demographics, comorbid conditions, TCZ indication, TCZ dose, number of doses administered during hospitalization (i.e., course of therapy), whether TCZ was administered during an active infection, TCZ administration location (intensive care unit [ICU] or general ward), receipt of any extracorporeal therapy during hospitalization (ECMO or any dialysis modality), and survival to discharge. Active infection was defined as a positive microbiologic finding with ongoing organism-directed therapy at time of TCZ administration. Additional safety data collected included new-onset neutropenia, severe thrombocytopenia, transaminitis, or new infection within 7 days after TCZ administration. Neutropenia was defined as an absolute neutrophil count <1500 cells/ μ L, severe thrombocytopenia as a platelet count <50 K/ μ L, and transaminitis as either aspartate transaminase (AST) or alanine transaminase (ALT) levels >3 times the upper limit of normal (ULN) for age. New-onset laboratory abnormalities were defined as having the above laboratory values within the normal range for age for the 7 days prior to TCZ administration, followed by subsequent fulfillment of new-onset abnormality criteria. New infection was defined as a positive microbiologic test result within the 7 days following TCZ administration that received organism-directed therapy for >72 hours.

For patients who died, data on whether death was deemed due to infection or other cause by the clinical team were also collected.

Statistical analysis was performed with R 3.6.3 (R Core Team, 2021). Descriptive data are reported as median (IQR). Categorical data were analyzed by using the Fisher exact test and continuous data by using the Kruskal-Wallis test. To test associations with mortality, univariable analysis was performed on physiologically plausible and clinically available characteristics and outcomes, using the Fisher exact test. Multivariable binomial logistic regression was then performed with characteristics found to be statistically significant on univariable analysis with a p value < 0.05.

Results

A total of 103 TCZ courses, administered to 87 patients, were included for analysis (Table 1). Seventy-five patients received a single dose of TCZ, 10 patients received 2 doses, and 2 patients received 4 doses. The median age was 14.1 years (IQR, 7.1–18.7), and median weight was 50 kg (IQR, 23.3–64.8). The median dose of TCZ administered was 8 mg/kg/dose (IQR, 7.9–11.9) and each course consisted of a median of 1 dose (IQR, 1–2).

Tocilizumab was administered for the treatment of CRS, primary autoimmune disease, graft-versus-host disease (GVHD), and a small number of other indications. The most common indication for TCZ was CRS (56.3%), with 48 (82.7%) of these courses administered on-label in patients who underwent CAR T-cell therapy. The 10 off-label administrations for CRS-related indications included cytokine release secondary to flutetuzumab, dinutuximab, and cytotoxic T-lymphocyte infusions. Of the 26 TCZ courses administered for an autoimmune indication, 20 (76.9%) were for off-label indications including neuromyelitis optica, acute disseminated encephalomyelitis, and Takayasu arteritis. Tocilizumab was administered to patients with a primary oncologic diagnosis or who had received myelosuppressive treatment (ONC/M) in 68 (66%) courses, and 50 (48.5%) TCZ courses were administered in an ICU. There were 19 courses where at least 1 dose was administered during an active infection, and 15 courses where the patient received some form of ECMO during the hospital admission (Table 1).

Evaluable safety data are presented in Table 2 with hematologic data available for 29 (28.2%) TCZ courses. Of those, 3 (10.3%) demonstrated new-onset neutropenia, and 1 (3.4%) new-onset severe thrombocytopenia. Additionally, 45 courses had evaluable pre- and post-TCZ ALT data, with 24 (53.3%) courses demonstrating new-onset ALT elevation. Of the 53 courses with evaluable pre- and post-TCZ AST data, 32 (60.4%) demonstrated new-onset AST elevation. Of these courses with evaluable transaminase data, 13 demonstrated new-onset elevation of both ALT and AST. There were no significant differences between

Table 1. Demographics*

Characteristic	All Courses (N = 103)	Survived (n = 85)	Deceased (n = 18)
Age, yr	14.1 (7.1–18.7)	14.3 (7.1–19.1)	11.9 (7.1–17.2)
Weight, kg	50 (23.3–64.8)	50 (22.8–63.8)	53 (23.2–65.4)
Active oncologic diagnosis or received myelosuppressive treatment	68 (66%)	52 (61%)	16 (88.9%)
• Acute lymphocytic leukemia	50 (48.5%)	43 (50.6%)	7 (38.9%)
• Acute myeloid leukemia	9 (8.7%)	5 (5.9%)	4 (22.2%)
• Other	9 (8.7%)	4 (4.7%)	5 (27.8%)
Tocilizumab dose, mg/kg	8 (7.9–11.9)	8 (7.9–11.8)	8 (8–12)
Number of doses received	1 (1–2)	1 (1–2)	1 (1–3)
Indication for tocilizumab			
• CRS	58 (56.3%)	47 (55.3%)	11 (61.1%)
• GVHD	5 (4.9%)	3 (3.5%)	2 (11.1%)
• Primary autoimmune	26 (25.2%)	25 (29.4%)	1 (5.6%)
• COVID-19	4 (3.9%)	3 (3.5%)	1 (5.6%)
• Other	10 (9.7%)	7 (8.2%)	3 (16.7%)
Received any extracorporeal therapy	15 (15%)	5 (5.8%)	10 (55.6%)
• ECMO only	1	1	0
• CRRT only	8	4	4
• ECMO + CRRT	6	0	6
Received tocilizumab in an ICU	50 (48.5%)	35 (41.2%)	15 (83.3%)
Received tocilizumab during active infection [†]	19 (18.4%)	12 (14.1%)	7 (38.9%)
• Bacterial	8 (7.8%)	5 (5.9%)	3 (16.7%)
• Viral	15 (14.6%)	9 (10.6%)	6 (33.3%)
• Parasitic	2 (1.9%)	1 (1.2%)	1 (5.6%)

CRRT, continuous renal replacement therapy; CRS, cytokine release syndrome; ECMO, extracorporeal membrane oxygenation; GVHD, graft-versus-host disease; ICU, intensive care unit

*Data are reported as median (IQR) or n (%).

[†]Two subjects had concurrent bacterial and viral infections, and 2 subjects had concurrent bacterial, viral, and parasitic infections.

survivors and non-survivors for these outcomes. There were 9 courses, all in different patients, determined to have post-TCZ infections. Of these 9 courses, 2 patients (22.2%) survived to discharge and 7 (77.8%) died. There were 4 courses overall where the cause of death was deemed by the clinical team to be infection, 2 of which had confirmed post-TCZ infections per study criteria.

Overall survival to discharge occurred for 85 (83%) TCZ courses. Clinical characteristics associated with mortality on univariable analysis included receipt of extracorporeal support (ES) (OR, 18.93; 95% CI, 4.62–90.53), ONC/M diagnosis (OR, 5.01; 95% CI, 1.07–47.77), new-onset post-TCZ infection (OR, 24.92;

95% CI, 4.10–273.74), administration of TCZ during active infection (OR, 3.81; 95% CI, 1.04–13.52), and TCZ administration in an ICU (OR, 7.01; 95% CI, 1.80–40.62). On multivariable analysis receipt of ES (adjusted OR [aOR], 8.68; 95% CI, 1.85–44.87), ONC/M diagnosis (aOR, 7.07; 95% CI, 1.14–89.29), and post-TCZ infection (aOR, 11.17; 95% CI, 1.50–138.13) remained as significant risk factors for death (Table 3).

Discussion

Targeted immunomodulation is increasingly being investigated as a therapeutic approach to a range of inflammatory diseases in adult and pediatric patients,

Table 2. Safety Outcomes*

Outcome of Interest	Evaluable Courses	Occurrence of Outcome	Survived	Deceased	p value
New infection in 7 days after TCZ	103	9 (8.7%)	2 (22.2%)	7 (77.8%)	<0.001
New-onset ANC <1500 cells/ μ L after TCZ	29	3 (10.3%)	–	–	–
New-onset platelets <50K cells/ μ L after TCZ	29	1 (3.4%)	–	–	–
New-onset ALT >3 $\times$ ULN after TCZ	45	24 (53.3%)	20 (83.3%)	4 (16.7%)	NS
New-onset AST >3 $\times$ ULN after TCZ	53	32 (60.4%)	26 (81.3%)	6 (18.8%)	NS

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; NS, not significant; TCZ, tocilizumab; ULN, upper limit of normal

*New onset: values within normal range for age for 7 days prior to TCZ administration followed by noted abnormality within 7 days after TCZ administration.

from COVID-19 to inborn errors of immunity to autoimmune encephalopathies.^{10–12,16,17} However, the potential efficacy of TCZ in these novel patient populations must be balanced with a safety assessment for off-label use. This study is the first to describe the real-world use and safety of TCZ across a range of pediatric inpatients, including critically ill children with and without active infection at the time of TCZ administration. Our study demonstrates a wide range of on- and off-label uses of TCZ in pediatric inpatients and suggests that being on extracorporeal life support, having an ONC/M diagnosis, and occurrence of post-TCZ infection represent independent risk factors for mortality in the context of receiving TCZ. Notably, the presence of active infection at the time of TCZ administration was not independently associated with mortality.

In the present study, 19 (18.4%) TCZ courses were administered in the setting of active infection. Most of these courses (78.9%) were administered during an active viral infection. The SARS-CoV-2 pandemic and resultant studies of acute COVID-19–associated respiratory failure demonstrate a role for targeted immunosuppression in acutely infected patients. A recent meta-analysis of 27 clinical trials describing 10,930 adults hospitalized with COVID-19 showed lower mortality in the TCZ-treated subjects ($n = 6449$; OR, 0.86 [95% CI, 0.79–0.95]; $p = 0.003$) with no increased risk of secondary infection in the TCZ group (OR, 0.95; 95% CI, 0.77–1.16).¹⁸ Importantly, among studies that failed to show a mortality benefit of TCZ in adults with COVID-19, the use of TCZ in acutely SARS-CoV-2–infected subjects did not demonstrate harm.^{7,10,19}

Our results complement these studies in the pediatric population, assessing off-label use and clinical characteristics associated with mortality, including administration during active infection. Our finding of a significant association between the use of extracorporeal therapy and mortality suggests that critical illness itself is likely a driver of mortality in our cohort. Similarly, the finding that an ONC/M diagnosis was associated with mortality may be driven by the underlying disease in that population,

specifically with TCZ frequently administered for CRS. Like the association found between ES and mortality, the degree of underlying illness likely contributes to this finding, but additional study is warranted given the increasing use of IL-6 blockade in hyperinflammatory states. Finally, the association between post-TCZ infection and mortality emphasizes the need for infection prevention as well as optimized anti-infective therapy in immunocompromised populations.

While our study could not assess the impact of TCZ use on mortality, we were able to address several important safety outcomes. Adverse events associated with administration of TCZ are well described in prior clinical studies.² Depending on the indication, incidence of AST and ALT elevation >3 times ULN ranged from <1% to 5% and 1.7% to 13%, respectively. This transaminitis was not associated with clinically significant increases in direct bilirubin or clinical evidence of hepatitis or hepatic insufficiency. Additionally, transaminitis resolved with either dose reduction or discontinuation of TCZ. Neutropenia (neutrophil count <1500 cells/ μ L) incidence was reported as high as 15.4% overall, with an incidence of 25.9% in the subgroup of patients <30 kg with polyarticular juvenile idiopathic arthritis. Thrombocytopenia (platelet count <100 K/ μ L) was reported in 1.7% of patients. Because of these adverse events, the package labeling for TCZ includes recommendations to avoid use in patients with an absolute neutrophil count below 2000 cells/ μ L, platelet count below 100 K/ μ L, or those who have AST or ALT levels >1.5 times ULN. The labeling also importantly states that the decision to administer TCZ must consider potential benefits of treating severely ill patients (e.g., those with CRS) versus the risk of short-term TCZ use.²

Our study population's incidence of new-onset neutropenia, thrombocytopenia, and transaminitis was significantly higher than that reported in the package labeling for TCZ. This labeling acknowledges that patients with severe CRS often have cytopenias or transaminitis due to previous chemotherapy or CRS

Table 3. Univariable and Multivariable Analysis of Mortality Risk Factors				
Risk Factor	Survived (n = 85)	Deceased (n = 18)	Univariable Analysis OR (95% CI)	Multivariable Analysis aOR (95% CI)
Received any extracorporeal therapy	5 (5.8%)	10 (55.6%)	18.93 (4.62–90.53)	8.68 (1.85–44.87)
Active oncologic diagnosis or received myelosuppressive treatment	52 (61%)	16 (88.9%)	5.01 (1.07–47.77)	7.07 (1.14–89.29)
Post-tocilizumab infection	2 (2.4%)	7 (38.9%)	24.92 (4.10–273.74)	11.17 (1.50–138.13)
Received tocilizumab during active infection	12 (14.1%)	7 (38.9%)	3.81 (1.04–13.52)	2.98 (0.67–12.80)
Received tocilizumab in an ICU	35 (41.2%)	15 (83.3%)	7.01 (1.80–40.62)	1.60 (0.34–8.60)

aOR, adjusted OR; ICU, intensive care unit

Bolded values represent statistically significant variables

itself, which we attempted to control for by evaluating only patients without preexisting laboratory abnormalities in the 7 days prior to TCZ administration. Laboratory monitoring was not protocolized in our study, with laboratory testing being performed at the discretion of the treating clinicians. Subjects who underwent laboratory testing may therefore have had a higher pre-test probability of having laboratory abnormalities that those for whom testing was not performed. The higher rate of adverse events identified in this study emphasizes the need for additional studies specifically focused on identifying the incidence of these adverse events in critically ill children.

The package labeling for TCZ recommends laboratory monitoring every 2 to 8 weeks, depending on indication, starting with the second dose. Based on the results of our study, it may be prudent to increase monitoring in the period immediately following administration of the first dose, particularly in critically ill children. While reassuring that the primary adverse effects of TCZ resolved in previous studies with either dose reduction or discontinuation, an individualized risk-benefit analysis must be made in patients at high risk of adverse events secondary to TCZ or with pre-existing laboratory abnormalities that may be further exacerbated.

Anti-cytokine therapies have been studied extensively in adults with sepsis, including IL-1 pathway inhibitors, anti-tumor necrosis factor- α therapies, and bradykinin antagonists.^{20–25} These trials nearly uniformly failed to show a mortality benefit, though secondary analyses have repeatedly suggested benefit in the subset of subjects with the most severe systemic inflammation.^{26,27} The REMAP-CAP study, an 803-subject prospective, adaptively randomized study of TCZ in critically ill adults with COVID-19, showed the greatest efficacy of TCZ in subjects in the highest tercile of serum C-reactive protein concentrations.²⁸ It is unclear if a biomarker-driven approach to TCZ use, with TCZ being reserved for patients with marked elevations in

IL-6, could further enhance the safety and efficacy of TCZ in hospitalized children. This is a topic deserving of further study.

Limitations of Study

Our study has several limitations, first of which is its single center, retrospective nature. This design, as well as the lack of a non-TCZ comparator group, prevents causal inferences from being drawn. While multivariable analysis was performed to help account for confounders inherent in any retrospective study, other unmeasured confounders may have influenced our results. Post-TCZ laboratory data were also not available for all patients and data that were available were not collected in a standardized fashion, reducing power to identify safety signals. Additionally, combined analysis of ICU and non-ICU inpatients may suppress safety signals present in either population alone. However, this was done to increase power owing to the limited number of TCZ courses with available data, and patients receiving TCZ for the treatment of CRS were well balanced between the ICU and ward.

Conclusions

Tocilizumab is used for a broad range of indications in pediatric inpatients, the most common being CRS. We found no independent association between administration of TCZ during active infection and mortality, though laboratory abnormalities including transaminase elevation were common. Post-TCZ infection and conditions associated with underlying critical illness, however, were associated with mortality. Based on our findings, surveillance for early transaminitis and neutropenia is warranted in acutely ill children receiving IV TCZ. Future studies of targeted immunomodulation should be considered, focusing on the safety and efficacy of TCZ in pediatric patients with severe inflammation, and these studies should include surveillance for early neutropenia and liver injury.

Article Information

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