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THEMED ISSUE ARTICLE

Single dose tocilizumab for COVID-19 associated cytokine storm syndrome: Less is more

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Aims: We aim to evaluate the clinical pharmacokinetics of a single dose interleukin-6 (IL-6) antibody tocilizumab (TCZ) in methylprednisolone (MP)-treated COVID-19 patients with cytokine storm syndrome (CSS).

Methods: MP pre-treated patients with COVID-19-associated CSS, defined as at least two elevations of C-reactive protein (CRP) >100 mg/L, ferritin >900 μg/L or D-dimers >1500 μg/L, received intravenous TCZ (8 mg/kg, max. 800 mg) upon clinical deterioration. A nonlinear-mixed effects model was developed based on TCZ serum concentrations and dosing information. Population pharmacokinetic parameters were estimated and concentration–time profiles were plotted against individual predicted values. Fixed dose simulations were subsequently performed based on the final model.

Results: In total 40 patients (mean [SD] age: 62 [12] years, 20% female, body weight: 87 [17] kg) with COVID-19 induced CSS were evaluated on pharmacokinetics and laboratory parameters. A biphasic elimination of TCZ serum concentration was described by a homogeneous population pharmacokinetic model. Serum TCZ concentrations above the 1 μg/L target saturation threshold were covered for 16 days in all evaluated patients treated with a single dose of 8 mg/kg. In a simulation with TCZ 400 mg fixed dose, this condition of full IL-6 receptor occupancy at minimum serum concentration was also met.

Conclusions: A single dose (8 mg/kg, max. 800 mg) is sufficient to cover a period of 16 days of IL-6-mediated hyperinflammation in COVID-19-induced CSS in MP-treated patients. Based on body weight PK simulations, a fixed-dose tocilizumab of 400 mg should be considered to prevent overtreatment, future drug shortage and unnecessary drug expenditure.

KEYWORDS
COVID-19, cytokine storm syndrome, dose rationale, pharmacokinetics, tocilizumab

The authors confirm that the principal investigator of this paper is Remy L. M. Mostard and that he had direct clinical responsibility for the patients.

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1 | INTRODUCTION

At the time of the first virus outbreak in 2020, the cytokine storm syndrome (CSS) caused by COVID-19 pneumonia induced autoimmune dysregulation in up to 20% of the admitted patients and led to acute respiratory distress syndrome (ARDS), multi-organ failure and hence high morbidity and mortality.[1]

The severe clinical deterioration of patients with CSS as a result of COVID-19 virus infection prompted physicians to treat patients with anti-inflammatory drugs.[1,2] COVID-19 patients with CSS have elevated plasma levels of pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNFα), interleukins (IL)1β, **interleukine-6** (IL-6), inducible protein 10 (IP-10), interferon gamma, macrophage inflammatory protein (MIP) and VEGF.[3,4]

Given the broad pallet of inflammatory mediators involved, the use of broad-spectrum glucocorticoids can be designated as cornerstone therapy for COVID-19-induced CSS.[2,5] In the COVID High-intensity Immunosuppression in Cytokine storm syndrome (CHIC) study, we reported that patients with CSS who showed severe respiratory deterioration despite treatment with high-dose methylprednisolone (MP) had benefit from subsequent TCZ treatment. Patients without sufficient clinical improvement or respiratory deterioration after Day 2 of MP were treated with a single dose of 8 mg/kg tocilizumab (max. 800 mg), as occurred in 43% of these patients.[5] Methylprednisolone was chosen based on experiences in rheumatological systemic autoimmune diseases and its high affinity for glucocorticoid receptors.[5] Based on the clinical experiences with TCZ as a drug to treat rheumatoid arthritis (RA), among others, a pre-dose serum concentration of >1 μg/mL normalizes C-reactive protein and is sufficient to antagonize all soluble IL-6 (sIL-6).[6]

Tocilizumab is a humanized IL-6 antibody that competitively inhibits IL-6 signalling by targeting both membrane-bound and sIL-6 receptors. At the start of the COVID-19 pandemic, TCZ had proved its effectiveness and safety in therapy for RA and several CSS disorders, such as induced by Chimer Antigen Receptor (CAR) T-cell therapy.[7] In CAR T-cell therapy-induced CSS, up to three additional TCZ doses of 8 mg/kg (≥30 kg body weight, max. 800 mg) with a minimum interval of 8 h is the label recommendation, but it was never subject to a formal posology study. It was rather based on pharmacokinetic (PK) simulations derived from trials in RA, where the regimen for CAR T-cell-induced CSS therapy was expected to yield TCZ serum levels below what was observed in former RA trials and was confirmed to be safe.[8]

In order to verify whether targeted IL-6 inhibition may potentially be an effective and safe way to reduce mortality of COVID-19, 21 Chinese COVID-19 patients were treated with tocilizumab therapy after severe or critical diagnosis.[9] At the clinical introduction of TCZ in the treatment of COVID-19-induced CSS, its non-labelled application sparked controversy.[10] In accordance with our findings based on clinical routine care patients that were included in the CHIC study, the beneficial effects of treating COVID-19-induced CSS with tocilizumab in critically ill (ICU) patients were also confirmed by a randomized controlled study (REMAP-CAP) in critically ill, organ support receiving patients admitted to the ICU and a meta-analysis.[11,12] In this recent meta-analysis of 19 trials, which included 10 930 patients hospitalized for COVID-19, a lower 28-day all-cause mortality was associated with administration of tocilizumab compared with usual care or placebo. The association between treatment with IL-6 antagonists and a lower mortality rate was more marked in patients receiving concurrent glucocorticoids.[12]

The majority (93%) of the patients included in the REMAP-CAP study were pre-treated with glucocorticoids (dexamethasone), and subsequently with 8 mg/kg (max. 800 mg) TCZ upon clinical deterioration. Patients in the REMAP-CAP study were given a first TCZ dose of 8 mg/kg (max. 800 mg) and one third of these patients received a second dose after 12–24 h at the discretion of the treating clinician if clinical improvement was insufficient.[11] The recent meta-analysis concluded a wide variety on applied dosages of low (4 mg/kg), high (>4 mg/kg) and multiple TCZ administrations.[12] Until a study by Moes et al., no formal TCZ posology has been studied for this new application in COVID-19-induced CSS. This pharmacokinetic characterization after a single weight-based dosage of TCZ in dexamethasone-treated patients concluded that there is no rationale for weight-based dosing while a fixed dose of 600 mg offers more practical and cost-efficient benefits.[13] Shortly after the publication of the study by Moes et al., the European Medicines Agency (EMA) approved TCZ in COVID-19-induced CSS where patients receive 8 mg/kg (max. 800 mg) TCZ in a maximum of two doses with concomitant systemic glucocorticoid treatment.[7] The aim of our pharmacokinetic study was to evaluate population pharmacokinetics of tocilizumab after a single weight-based dose in COVID-19-induced CSS patients. The population described in this study differed from the study by Moes et al.

What is already known about this subject

- Tocilizumab (TCZ) treatment is established as potentially beneficial in COVID-19 patients with cytokine storm syndrome (CSS).
- The rationale for current TCZ dosing regimens in COVID-19-induced CSS is under-researched and varies in clinical application, while the drug is expensive and scarce.

What this study adds

- A single fixed dose of TCZ in COVID-19 patients with CSS is sufficient to cover adequate TCZ serum levels for 16 days in patients treated with intravenous high dose methylprednisolone.
- Pre- or concomitant treatment with glucocorticoids, including the type of glucocorticoid, may influence TCZ clearance and the amount of fixed dose needed.

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concerning the cotreatment with more pharmacological potent high-dose MP.[13] The secondary objective was to investigate alternative dosing strategies allowed by cotreatment with high-dose MP.

2 | METHODS

2.1 | Patients and follow-up

In this TCZ population pharmacokinetic evaluation study, patients with COVID-19-induced CSS were followed in the period between March 2020 and January 2021. According to the CHIC study protocol, COVID-19-associated CSS was defined as rapid respiratory deterioration (detection of diffuse interstitial pneumonia and/or bilateral infiltrates on chest x-ray or CORADS score 4 or 5 on the basis of CT thorax findings, including oxygen saturation at rest in ambient air ≤94% or tachypnoea >30/min) plus at least two out of three of the biomarker elevations (C-reactive protein [CRP] >100 mg/L; ferritin >900 μg/L; D-dimers >1500 μg/L). Patients were evaluated daily on their clinical performance status and laboratory outcomes by a multidisciplinary team consisting of pulmonologists, intensivist, internist and rheumatologists who decided on the administration and precise timing of MP and subsequent administration of TCZ and additional medical interventions.[5] Patients were studied on pharmacokinetics from their first dose of TCZ, defined as study Day 0, for a period of 30 days unless they were discharged or died. Consenting patients received high-dose intravenous MP per protocol (i.e., first loading dose 250 mg MP and 80 mg MP per day on five consecutive days) before, or parallel with, TCZ treatment. Upon subsequent clinical deterioration a single TCZ dose of 8 mg/kg body weight (max. 800 mg) was administered.

Patient demographic data (age, gender, body weight, height, body mass index smoking status), the laboratory findings at baseline (serum albumin, CRP, ferritin, D-dimers, creatinine, total bilirubin, serum albumin, urea) and the TCZ serum concentrations, CRP values and additional laboratory findings (creatinine, total bilirubin, serum albumin, urea) during follow-up were extracted from electronic patient dossiers. The study protocol was reviewed and approved by the local medical ethics committee of Zuyderland Medical Center, and Zuyd Hogeschool (METC Z) approval was granted under number Z2020077.

2.2 | TCZ serum sampling and analysis

TCZ serum samples were drawn per protocol at Day 1, 3 and 10 (after TCZ administration) to assess unbound TCZ serum concentrations with a validated enzyme-linked immunosorbent assay (ELISA) by Sanquin Laboratories (Amsterdam, The Netherlands), as described previously.[13] Serum was obtained after centrifugation and stored at −20°C until analysis.

The lower limit of quantification was 0.2 μg/mL and the range of measurement 0.2–250 μg/mL. Samples above the upper limit of quantification of 250 μg/mL were diluted per standard operating procedure of Sanquin Laboratories.

In January 2021, after the first step in the pharmacokinetic modelling process, additional serum samples of four patients were drawn 10 days after TCZ dosing to verify and optimize the pharmacokinetic model.

2.3 | Statistical and pharmacokinetic modelling procedures

A nonlinear-mixed effects model was developed based on all concentration time data to characterize TCZ pharmacokinetic parameters using NONMEM (v. 7.4.4) in conjunction with Pirana (v. 2.9.8) for model interpretation.[14–17] This model was based on first order model assumption with an interaction approach. During model development, candidate models were evaluated for their decrease in objective function value (OFV) calculated as the −2 log likelihood. A decrease in OFV of ≥6.63 was considered significant (chi-square = 1 degree of freedom [df], $P < 0.01$). In addition, goodness-of-fit (GOF) plots were assessed. Furthermore, parameter precision, shrinkage and interindividual variability (IIV) were considered during the modelling process. The final model was checked by means of a prediction-corrected visual predictive check (pcVPC) based on 500 Monte Carlo simulations. In addition, the precision of the parameter estimates was further assessed by means of a nonparametric bootstrap with resampling the dataset ($n = 1000$ times). Analysis of concentration dependent total clearance, consisting of linear and parallel non-linear clearance, was performed to determine the supposed and theoretical serum concentration under maximal IL-6 receptor occupancy in COVID-19-induced CSS patients.

Individual pharmacokinetic parameters area under the curve ($AUC_{0\text{-}inf}$), C_{max} were estimated and TCZ concentration–time observations were plotted against the individual predicted concentrations to visualize the complete TCZ concentration–time curve. The time above the concentration of theoretical soluble IL-6 receptor saturation was evaluated by means of a pharmacokinetic approach analysing the ratio between linear and non-linear clearance *vs.* the TCZ serum concentration. This threshold analysis of the serum concentration is common to establish optimal dosages and yielded a value of 1 μg/mL TCZ in a former study in patients with RA and Castleman disease.[6,18] Exploratory statistics and graphics were performed with R statistics.[19]

Body weight, serum albumin concentration and CRP are well known factors of potential influence on pharmacokinetics of biologics, including TCZ.[6,8] Covariate analysis based on patient demographics at baseline (age, gender, body weight, height and BMI) was performed, including an additional time-dependent disease covariate analysis (creatinine, total bilirubin, serum albumin, urea) to determine whether patient variables influenced pharmacokinetics and drug clearance.

A covariate was included only if it significantly (chi-square = 1 df, $P < 0.01$) improved the model fit after evaluation by back and forward elimination method.

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2.4 | Fixed dose and potential drug savings

Based on the derived population-kinetic model, and as proposed by Wang et al., fixed dose fits (200, 400, 600 and 800 mg) of TCZ were simulated to ensure adequate IL-6 receptor occupancy in the interest of dosing efficiency and minimal drug spillage.[20]

In order to estimate the exponent of body weight, to be able to compare the exponent with the range of 0–1, the body weight (BW) was tested as a covariate to the model as shown in Equation (1)

$$CL = CL \times (BW/\text{median}\,BW)\ \text{exp} \quad (1)$$

As explained by Wang et al., the question as to which dosing approach is better depends on how steep the relationship is between CL and body size, that is, the value of the exponent.[20] Fixed dosing provides less variability in exposure when exp < 0.5, while this is true for body weight-based dosing when exp > 0.5. Various fixed dose simulations of 200, 400, 600 and 800 mg were run based on pharmacokinetic modelling data derived from the single 8 mg/kg dose scheme and the subsequently measured serum samples among patients over time.

Drug expenditure was calculated based on the current national Dutch list price.[21]

3 | RESULTS

In total, 40 patients with COVID-19-induced CSS received TCZ per protocol upon clinical deterioration after pre- or concurrent treatment with high-dose MP. The included patients (mean age 66 [18.2] years, 80% male gender, body weight 87.2 [17] kg, body mass index 28.1 [4.9] kg/m^2) delivered a total of 108 TCZ serum samples for the pharmacokinetic evaluation of TCZ dose and serum concentration. Patient demographics and clinical characteristics at baseline are presented in Table 1.

In the cohort of included patients, 10 patients died because of COVID-19 infection. Eight patients died during the study follow-up period of 30 days. Two patients died, one upon readmission and another patient died after hospital discharge. Two patients received a second dose of TCZ: among them one patient on Day 5 who died on Day 8, another patient was re-dosed on Day 6 and died on Day 21 after the first dose. The assessment of TCZ pharmacokinetics after two or more doses is outside the scope of this study.

3.1 | Body weight-based tocilizumab dosing

Pharmacokinetic (PK) modelling, including a covariate analysis, resulted in a one-compartment disposition model with parallel first order (linear) and Michaelis–Menten (nonlinear) elimination kinetics as depicted in Figure 1. The model building process is summarized in Table S1 and comprised the evaluation of a one-compartment model with and without parallel linear and non-linear clearance and a two-compartment model with parallel linear and non-linear clearance.

TABLE 1 Baseline demographic and clinical characteristics.

Parameter	COVID-19 patients with CSS ($n = 40$)
Age (years)	66.0 (18)
Female gender, *n* (%)	8 (20)
Smoking status	
Never smoker	32.5%
Ex-smoker	55.0%
Current smoker	12.5%
BMI (kg/m^2)	28 (5)
Weight (kg)	87 (17)
Height (m)	177 (9)
Albumin mmol/L	34 (6)
CRP (mg/L)[a]	105 (80)
Ferritin (μg/L)[b]	1672 (961)
D-dimers (μg/L)[c]	4937 (8225)
TCZ treatment	
TCZ dosage (mg)	679 (100)
TCZ dose (days) after start with MP treatment (median, range)	4 (4)

Note: *n* (%) for categorical variables. Demographic data and baseline characteristics of methylprednisolone pre-treated patients with COVID-19-induced CSS treated with tocilizumab and included in the pharmacokinetic model. Baseline characteristics were presented as means ± SD and as number of patients with corresponding percentage for categorical variables.
Abbreviations: BMI, body mass index; CSS, cytokine storm syndrome; CRP, C-reactive protein; MP, methylprednisolone IV treatment; TCZ, tocilizumab.
[a] $n = 38$ patients.
[b] $n = 36$ patients.
[c] $n = 35$ patients.

GOF plots indicated a good model performance for the prediction of TCZ serum concentrations on both individual and population level (Figure S1). None of the examined baseline or time-dependent covariates, including body weight, were found to significantly affect the model. Pharmacokinetic parameters derived from this model are presented in Table 2.

The mean AUC was 658 (400–973) μg/mL*days and the maximal concentration amounted 137 (85–219) μg/mL after one dose. The elimination half-life of the terminal linear part was 3.5 (2.3–4.1) days.

In order to evaluate the direct pharmacological effect of IL-6 antagonism on TCZ, the inflammatory biomarker CRP was measured in parallel with TCZ serum samples after the initial TCZ dose. All patients reached serum CRP levels <20 mg/L on Day 4. Five patients showed re-increased CRP levels between TCZ therapy Day 5 and 12 after an initial decline upon MP and TCZ treatment and despite adequate TCZ serum levels. Two out of these five patients showed re-increased CRP levels above 100 mg/L, three patients showed a moderate rise of CRP levels between 50 and 100 mg/L.

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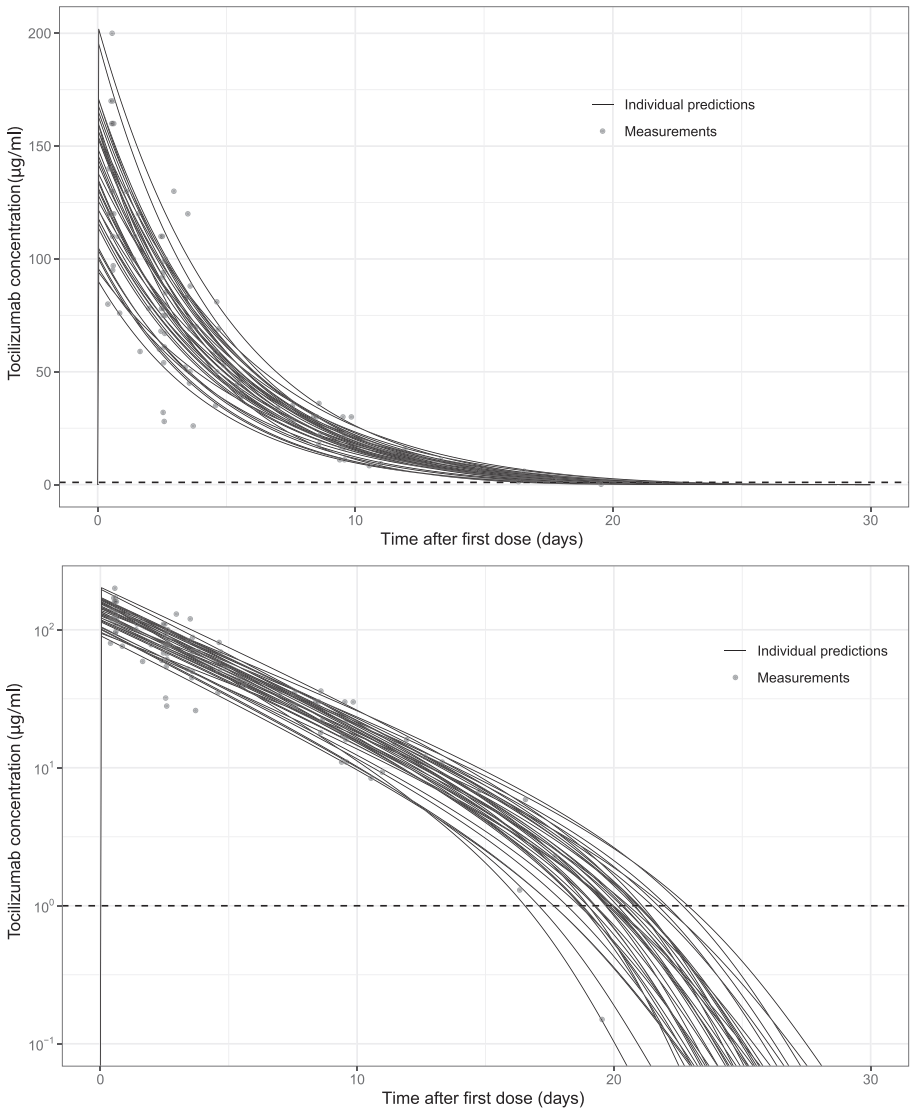

FIGURE 1 Observed and predicted concentration–time profiles of single dose (8 mg/kg) tocilizumab in COVID-19-induced CSS both in normal scale and semi-log scale. Predicted concentration–time profiles of one single dose TCZ (8 mg/kg, max 800 mg) in 40 high-dose methylprednisolone pre-treated patients with COVID-19-induced cytokine storm syndrome. Dashed horizontal line: Theoretical maximum IL-6 receptor occupancy concentration of 1 µg/mL; Black solid line: simulated concentration decay per patient; transparent black dots: tocilizumab serum measurements in individual patients.

TABLE 2 Population pharmacokinetic parameters and bootstrap results of tocilizumab based on pharmacokinetic modelling of 40 patients.

Final model				1000 bootstrap runs results	
	Mean value	RSE (%)	Shrinkage (%)	Median value (95% CI)	
CL (L/day)	0.98	3		0.98	0.87–1.09
V_d (L)	4.97	3		4.97	4.43–5.30
V_{max} (mg/day)	2.15	16		2.29	0.62–5.28
K_m (mg/L)	0.811	21		0.92	0.13–3.85
Interindividual variability					
CL (CV%)	21.5	26	15	21.0	12.3–34.2
V_d (CV%)	21.2	39	22	21.5	10.8–44.7
Random residual variability					
Proportional (CV %)	17.6	20	21	15.4	10.7–22.4
Additive (µg/mL)	0.0186	45	21	0.01	0.00025–0.12

Note: Population pharmacokinetic modelling parameters of weight-based single dose tocilizumab in COVID-19 patients with CSS ($n = 40$).
Abbreviations: CL, clearance V_d volume of distribution; V_{max} maximum elimination rate; K_m, concentration at half saturated elimination pathway; RSE, relative standard error; CV%, coefficient of variation (%); CI, confidence interval.

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3.2 | Minimal serum concentration

Based on the population pharmacokinetic model information, the graphical intersection was determined between the maximum concentration driven non-linear clearance and the maximum linear clearance rates, as depicted in the total clearance *vs*. the TCZ serum concentration plot in Figure 2. In this PK modelling analysis, the maximum systemic IL-6 receptor occupancy is effectuated, and hence is saturated, when serum concentrations are above 1 μg/mL. This condition was met in all included patients during 16 days after TCZ initiation.

3.3 | Body weight dosing *vs*. fixed dosing

The exponent was estimated to be as low as 0.075, meaning no clinically relevant effect at all on clearance (CL). Furthermore, the inclusion did not lead to a statistically significant improvement of the model, nor did it reduce the interindividual variability in CL. Figure 3 shows the simulated fixed doses in different panels. $AUC_{0\text{-infs}}$ decreased proportionally by the descending doses, while the minimum concentration for maximum IL-6 receptor occupancy is still covered between 8 and 16 days after TCZ fixed dose administration for doses varying between 200 and 800 mg, respectively. A semi-log representation of serum concentration over time after several fixed doses is provided in Figure S2.

3.4 | Drug savings on fixed dose regimen

The optimal fixed dose of 400 mg was determined based on the observed 16-day coverage of TCZ serum concentration above 1 μg/mL for all patients. The washout effect of the drug surplus increased with fixed doses above 400 mg up to 800 mg.

In the studied population of 40 patients who received a TCZ weight-based dosage, a fixed dose of 400 mg TCZ would have resulted in a potential saving of 11 600 mg (41% less) and €10 556 in drug expenditure.[21]

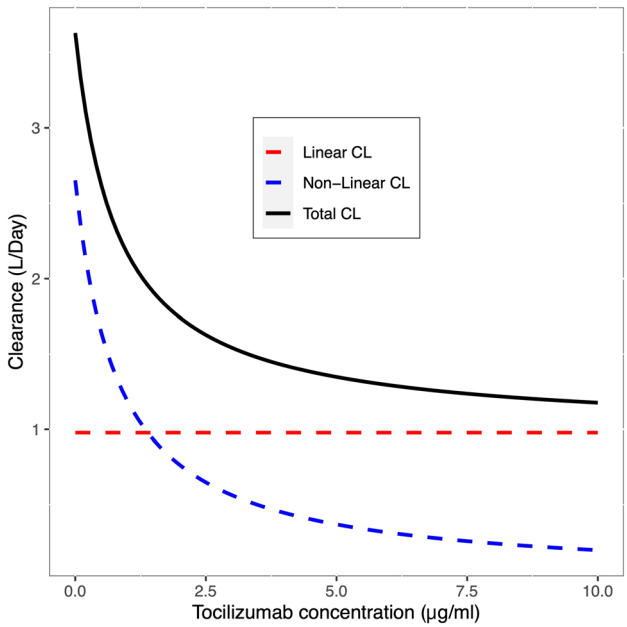

FIGURE 2 Clearance *vs*. tocilizumab serum concentration. Total clearance, non-linear (blue dotted line) and linear clearance (red dotted line) *vs*. tocilizumab concentration, based on the derived pharmacokinetic model after weight-based dosing. CL, clearance.

4 | DISCUSSION

In this pharmacokinetic evaluation of TCZ in patients with COVID-19-associated CSS that were concomitantly or pre-treated with MP, we have shown that a single dose of 8 mg/kg (max. 800 mg) is sufficient to cover a minimum serum concentration above 1 μg/mL for a period of 16 days. In addition, this minimal serum concentration of 1 μg/mL was confirmed to be necessary for maintaining complete IL-6 systemic receptor occupancy in COVID-19 patients with CSS based on studied pharmacokinetics.

This finding can be generalized to all MP (pre-)treated patients since we have established a homogeneous population pharmacokinetic model in the absence of any clinical or pharmacokinetic covariate having potential influence on TCZ clearance. Importantly, body weight in the studied patient population was not determined to be a covariate for TCZ drug distribution and clearance which provided the rationale for fixed dosing.

The benefit from a single dose can be explained on the basis that patients were MP (pre-)treated resulting in reduced sIL-6 as a target for TCZ and the fact that an average episode of CSS lasts for approximately 6 days.[22] Based on our findings, this makes repeated TCZ administration, at least within 7–10 days, as used by other tocilizumab COVID-19 treatment protocols, unnecessary.[10–12]

Based on the performed population PK simulations, a single fixed dose of 400 mg TCZ in general will most likely be sufficient for the treatment of COVID-19-induced CSS as confirmed by our PK study in patients (pre-)treated with MP. Concentration–time profiles of simulated fixed TCZ dosages above 400 mg showed only higher drug deposition during the distribution phase as a result of weight-based dosages, which leads to unnecessary drug expenditure and drug shortages.[23]

In a small subgroup of patients ($n = 5$) we observed a re-increase in CRP levels after an initial decline upon TCZ administration despite the presence of sufficient free TCZ drug concentration. The benefit and therapeutic rationale for a second TCZ dose in these rare occasions should prompt further research for the following reasons: first, additional suppression of CRP potentially leads to increased susceptibility for bacterial and fungal infections and could thereby harm patients[24,25]; and second, the question is whether intervention via IL-6 inhibition is still indicated under these circumstances. Moreover, the clinical event of a CSS occurs in a relatively short window of time and given the sustained serum concentration >1 μg/mL after the first dose, a second dose seems irrational even when CRP is still elevated.

Our study has a few limitations. In this observational pharmacokinetic study, we primarily focused on the pharmacokinetics of TCZ in

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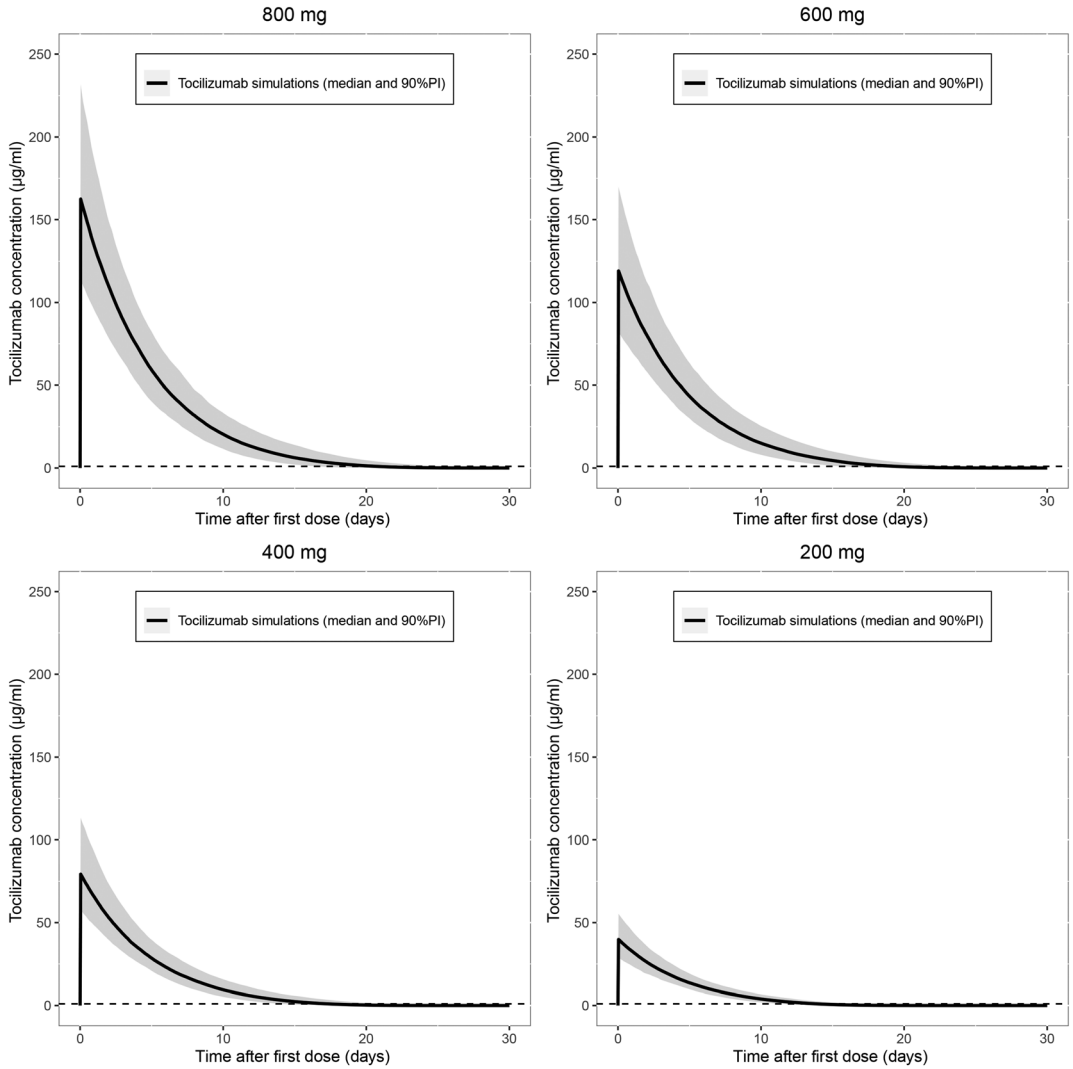

FIGURE 3 Predicted concentration–time profiles of fixed tocilizumab doses. Fixed dose simulations of 800 mg, 600 mg, 400 mg and 200 mg based on 8 mg/kg single dose pharmacokinetics. Vertical dashed line: Point in time (days) after a single simulated fixed TCZ dose at which one of the included patients reaches a TCZ serum concentration below 1 µg/mL.

patients with COVID-19-associated CSS who did not respond sufficiently to high-dose MP treatment as a complementary analysis to the CHIC study. Consequently, the pharmacodynamic and safety perspectives on reported pharmacokinetic data are lacking. In addition, our findings including the single fixed TCZ dose of 400 mg can only be generalized to pre- or cotreated patients with potent glucocorticoids like MP within the studied weight range. Nevertheless, the CHIC study reported beneficial effects of TCZ which was later confirmed by other groups.[5,9–11] A study by Kumar et al. corroborated similar pharmacokinetic-pharmacodynamic effects on sIL-6-R, IL-6, CRP and ferritin over time upon different treatment groups after 4 and 8 mg/kg dosing confirming complete IL-6 antagonism at a lower dose of 4 mg/kg, which is in line with our findings indicating that higher dosing is not necessary.[26]

The effect of various glucocorticoid types and their different relative affinities for the glucocorticoid receptor and the influence on the total TCZ clearance and the rationale for a single dose needs to be clarified in future studies. Our reported pharmacokinetic parameters (i.e., total clearance, fraction non-linear and linear elimination and AUC) were observed in patients with COVID-19-associated CSS (pre)-treated with high-dose MP, which potentially may have influenced TCZ clearance in our study population since MP has the highest glucocorticoid receptor affinity in the class of glucocorticoids. Therefore, it is possible that results of the dose simulations we performed cannot directly be extrapolated to COVID-19 patients co-treated with other less potent glucocorticoids or lower dose regimes.

The concentration at which maximum IL-6 receptor occupancy occurred in our studied population was at a TCZ serum concentration of 1 µg/mL and corresponds with the findings of Nishimoto et al. in RA and Castleman disease.[6] Interestingly, in the study by Moes et al., where an identical PK modelling approach was used, an IL-6 receptor saturation value of 5 µg/mL with a corresponding higher fixed dose of 600 mg TCZ was concluded to be sufficient. In this study, TCZ pharmacokinetics in COVID-19-associated CSS was evaluated in

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dexamethasone (6 mg once daily) pre-treated patients with higher CRP levels (mean 146 [13–309] mg/L) at the start of TCZ therapy as compared to our population with a CRP value of 105 mg/L before TCZ infusion.[13] The difference compared to our study can be explained by the difference in patient population and the potency of glucocorticoid treatment that most likely led to differences in sIL-6 target expression, also referred to as target-mediated drug disposition, which is derived from the ratio between linear and non-linear clearance, and was smaller in our study compared to the study by Moes et al.

Disease severity of COVID-19 infection had a major impact on TCZ elimination rate as confirmed by PK studies supporting the recently acquired TCZ label indication of CSS treatment upon COVID-19 infection in adults who are receiving systemic glucocorticoids.[27] In contrast, in these studies the type of glucocorticoid treatment had no impact on TCZ clearance, where no distinction could be made in type and potency of glucocorticoid treatment.

In conclusion, the present population pharmacokinetic study in hospitalized patients co-treated with high-dose MP for severe COVID-19-induced CSS demonstrated that a single weight-based TCZ dose of 8 mg/kg is adequate to maintain TCZ serum levels >1 μg/mL for at least 16 days. Based on our findings, an additional TCZ dose, as suggested on the TCZ label, is in our opinion therefore not indicated; however, it depends on both the severity and duration of disease and type of systemic glucocorticoid pre- or cotreatment. Pharmacokinetic modelling showed that TCZ clearance in COVID-19-induced CSS is independent of body weight. Based on PK simulations we suggest a fixed tocilizumab dose of 400 mg to treat MP (pre-)treated patients with COVID-19-induced CSS to prevent overtreatment, future drug shortage and unnecessary drug expenditure.

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CONTRIBUTORS

N.W.B., D.J.M. and D.W. had full access to all the data and take responsibility for data integrity and the accuracy of the data analysis. N.W.B., D.J.M. and D.W. were involved in the data processing and analysis. N.W.B., D.J.M., S.R., R.M., R.L. and D.W. were involved in the study design and writing of the manuscript. All authors contributed to the critical revision and final approval of the manuscript.

COMPETING INTERESTS

None.

DATA AVAILABILITY STATEMENT

Datasets generated during this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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