Interleukin-6 (IL-6)–mediated hyperinflammation may contribute to the mortality of coronavirus disease 2019 (COVID-19). The IL-6 receptor–blocking monoclonal antibody tocilizumab has been repurposed for COVID-19, but prospective trials and dose-finding studies in COVID-19 have not yet fully reported. We conducted a single-arm phase II trial of low-dose tocilizumab in nonintubated hospitalized adult patients with COVID-19, radiographic pulmonary infiltrate, fever, and C-reactive protein (CRP) ≥ 40 mg/L. We hypothesized that doses significantly lower than the emerging standards of 400 mg or 8 mg/kg would resolve clinical and laboratory indicators of hyperinflammation. A dose range from 40 to 200 mg was evaluated, with allowance for one repeat dose at 24 to 48 hours. The primary objective was to assess the relationship of dose to fever resolution and CRP response. Thirty-two patients received low-dose tocilizumab, with the majority experiencing fever resolution (75%) and CRP decline consistent with IL-6 pathway abrogation (86%) in the 24–48 hours following drug administration. There was no evidence of a relationship between dose and fever resolution or CRP decline over the dose range of 40–200 mg. Within the 28-day follow-up, 5 (16%) patients died. For patients who recovered, median time to clinical recovery was 3 days (interquartile range, 2–5). Clinically presumed and/or cultured bacterial superinfections were reported in 5 (16%) patients. Low-dose tocilizumab was associated with rapid improvement in clinical and laboratory measures of hyperinflammation in hospitalized patients with COVID-19. Results of this trial provide rationale for a randomized, controlled trial of low-dose tocilizumab in COVID-19.

Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**
- Many patients with novel coronavirus disease 2019 (COVID-19) develop acute lung injury and hypoxic respiratory failure possibly due to a hyperinflammatory state. Interleukin-6 (IL-6) has been implicated in this process; therefore patients with COVID-19 may benefit from the IL-6 receptor–blocking monoclonal antibody tocilizumab.

**WHAT QUESTION DID THIS STUDY ADDRESS?**
- No dose-finding studies have been performed for tocilizumab in the setting of COVID-19. This prospective phase II clinical trial is, to our knowledge, the first to evaluate different doses of tocilizumab in patients with COVID-19.

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**
- The Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis (COVIDOSE) study, together with retrospective and real-world evidence studies, suggests that tocilizumab is a potential treatment for hyperinflammation among patients with COVID-19. Randomized, controlled trials of tocilizumab, including one of low-dose tocilizumab, in this patient population are ongoing.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**
- Under normal circumstances, application of interventional pharmacoeconomics (IVPE) can help contain drug costs through a reduction in units used. The COVIDOSE study demonstrates how interventional pharmacoeconomic principles can be applied to drug shortages in the context of a global pandemic.
The global pandemic of coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), threatens public health, with quoted mortality among hospitalized patients exceeding 15%. Late-stage COVID-19, marked by hyperinflammation leading to shock and respiratory failure, is associated with high levels of C-reactive protein (CRP) and cytokines, including interleukin-1 (IL-1) and interleukin-6 (IL-6). In patients with severe and critical COVID-19, IL-6–mediated hyperinflammation resembling cytokine release syndrome (CRS) may drive disease mortality, suggesting that repurposing of anti–IL-6 axis monoclonal antibodies such as tocilizumab, sarilumab, and siltuximab, or anti–IL1 therapies such as anakinra, warrant investigation.

Rapid resolution of clinical and biochemical signs of hyperinflammation has been noted following a single 400 mg dose of tocilizumab in patients with severe to critical COVID-19, and multicenter, retrospective case-control studies suggest a 30% to 40% reduction in risk of invasive ventilation or COVID-19–related mortality following tocilizumab. Tocilizumab’s role in moderate, severe, and critical COVID-19, however, remains ambiguous, with prospective data arguing both for and against its use. An investigator-initiated prospective, multi-institutional, randomized, controlled trial evaluating tocilizumab 8 mg/kg in patients with moderate or severe COVID-19 disease (CORIMUNO-TOCI-I (Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients - Tocilizumab Trial)) is positive, while the EMPACTA (A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia) and COVACTA (A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia) studies demonstrated decreased likelihood of death or mechanical ventilation and hospital length of stay, respectively. Other prospective trials, however, have failed to meet diverse prespecified end points such as progression to critical disease, intensive care unit admission, or death and improvement in ordinal clinical status by day 28.

However, a tocilizumab dose lower than the labeled CRS dose of 8 mg/kg may be sufficient to block IL-6 signaling. Prior studies suggest that serum tocilizumab concentrations as low as 1 µg/mL—less than 1% of the peak concentration achieved with the 8 mg/kg dose—can blunt greater than 95% of IL-6 receptor signaling. A tocilizumab dose lower than 400 mg or 8 mg/kg may also be advantageous in COVID-19. In patients with COVID-19, high doses of tocilizumab may increase the risk of secondary bacterial infections (e.g., hospital-acquired and ventilator-associated pneumonias) approximately fourfold. Additionally, IL-6 stimulates B-cell proliferation, plasma cell maturation, and antibody responses. Blocking IL-6 receptor with tocilizumab might impair the generation of antibody responses to SARS-CoV-2. Therefore, administration of tocilizumab too early in the disease has the potential to suppress the adaptive immune response to SARS-CoV-2, and utilization of high doses of tocilizumab would be expected to suppress the immune system of patients for an extended period of time. Finally, using lower doses of tocilizumab may extend available supplies.

To our knowledge, no dose-finding studies have been conducted for tocilizumab in COVID-19. Drawing on lessons from interventional pharmacoconomics (IVYPE), we hypothesized that doses of tocilizumab lower than those used in the outpatient rheumatologic (4–8 mg/kg) or the COVID-19 settings (400 mg or 8 mg/kg) would reduce COVID-19–related inflammation. We developed a titration regimen to administer low-dose tocilizumab to hospitalized patients with COVID-19. We present the results of our phase II study, demonstrating pharmacodynamic and clinical evidence of low-dose tocilizumab activity in hospitalized patients with COVID-19–associated hyperinflammation not requiring mechanical ventilation.

METHODS

Trial design and oversight

Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis (COVIDOSE) was an investigator-initiated, nonrandomized, open-label, single-arm phase II trial performed at a single site within the University of Chicago Medicine (UCM) health system. Details of the low-dose tocilizumab treatment strategy have been described previously. The University of Chicago sponsored and funded the trial, without any industry involvement. The trial was registered with the National Clinical Trials Registry (NCT04331795).

Study participants

Eligible patients were those hospitalized at UCM, aged 18 years or older, and who had (i) positive polymerase chain reaction test for SARS-CoV-2 RNA, (ii) chest radiograph findings such as bilateral ground glass opacities or hazy bilateral infiltrates consistent with viral or atypical pneumonia (as determined by UCM radiologists providing usual clinical care independent of COVIDOSE), (iii) documented fever, defined as temperature ≥ 38.0°C in the 24 hours prior to the time of tocilizumab administration as measured by commonly accepted clinical methods (predominantly oral or axillary), and (iv) CRP ≥ 40 mg/L. Key exclusion criteria included use of invasive mechanical ventilation, scheduled antipyretic medications (as-needed administration of antipyretic following documented fever was allowed), vasopressor medications, active therapy with biologic immunosuppressive or Janus kinase inhibitor medications, and previous receipt of an investigational antiviral agent or off-protocol anti–IL-6 receptor therapy. Full eligibility criteria are available in the trial protocol, available in the Supplementary Material. Patients or their legally authorized representatives provided written or electronic informed consent.
Trial procedures
Enrolled patients were subdivided into two groups (Group A and Group B) based on laboratory signs of hyperinflammation and the presence or absence of risk factors for COVID-19–related mortality (based on extant univariate regressions at the time of study and as agreed to by a multidisciplinary panel of institutional experts). Risk factors, nearly all of which were subsequently validated, included any previous intensive care unit admission; previous nonelective intubation; hospitalization for exacerbation of congestive heart failure or chronic obstructive pulmonary disease in the past 12 months; coronary artery disease requiring percutaneous coronary intervention or coronary artery bypass grafting; stroke with residual neurologic deficit; pulmonary hypertension; home supplemental oxygen use; interstitial lung disease; asthma requiring inhaled corticosteroid use; history of pneumonectomy, lobectomy, or radiation therapy to lung; HIV/AIDS; cancer diagnosis (any stage) receiving nonhormonal treatment; immunodeficiency; end-stage renal disease requiring hemodialysis or peritoneal dialysis; body mass index ≥ 30 kg/m²; and inpatient supplemental oxygen requirement > 6 L/minute at the time of enrollment. Group A patients had CRP ≥ 75 mg/L and at least one risk factor for mortality. Group B patients had CRP of 40–74 mg/L or lacked risk factors for COVID-19–related mortality. This strategy was utilized to justify testing of a lower dose of tocilizumab in patients deemed at lower risk of death from COVID-19.

After group assignment, patients were treated according to the low-dose tocilizumab algorithm, integrated into usual clinical care (Figure S1).17 Group A patients received tocilizumab 200 mg or, later, 120 mg. Group B patients received 80 mg or, later, 40 mg. The study was an adaptive design, and all dosage levels were protocol-based and determined on a cohort basis by the trial operating committee (comprised of the investigators). The study began with 200-mg and 80-mg dose levels. After observing clinical and biochemical responses to the 200-mg and 80-mg dose levels and no safety events, we transitioned to 120-mg and 40-mg dose levels. Vital signs and laboratory studies were monitored per usual clinical care. CRP was evaluated immediately prior to tocilizumab administration (baseline) and approximately 24 hours following tocilizumab administration.

Patients were eligible for re-dosing with tocilizumab. In the originally developed re-dosing schema, the decision was guided strictly by CRP response. In an amended version of the protocol, however, the re-dosing decision was guided by biochemical and clinical parameters. Patients were re-dosed with tocilizumab if signs of clinical worsening (as defined by increased supplemental oxygen requirement or worsening fever curve determined by maximum temperature) were accompanied by CRP decline of < 25% when compared with baseline at the 24-hour assessment (Figure S1). In the COVIDOSE algorithm, treating physicians maintained the option of administering off-protocol tocilizumab (generally 400 mg) as indicated per their clinical judgment. Please see the Supplementary Material for further information.

Patients were followed for the duration of their hospitalization and were contacted 28 days after tocilizumab administration. At the 28-day time-point, survival, clinical status (including admission to a medical or assisted living facility), new or persistent supplemental oxygen requirement, and any notable diagnoses or treatments for secondary infection were documented. The initial planned enrollment was fifty patients, with the goal of determining the lowest pharmacodynamically active dose of tocilizumab (in the context of analyzing the dose–response relationship) for the treatment of COVID-19. After enrolling the thirty-second patient, remdesivir use, the COVIDOSE trial operating committee elected to close the study to further enrollment; it was not closed due to safety concerns.

Outcomes
The primary clinical outcome was resolution of fever in the 24-hour period following tocilizumab, defined as a maximum temperature < 38.0°C. Fever resolution was chosen for its rapid readout and as a proxy for discharge in high-risk patients with COVID-19 who did not require supplemental oxygen (i.e., in the absence of requirement for supplemental oxygen in a high-risk patient, a fever might prevent discharge while its absence might allow discharge). Patients’ requirement for supplemental oxygen was also tracked, so as to inform re-dosing decisions (Figure S1). Originally, the primary biochemical outcomes were rate of and time to CRP normalization, guided by earlier tocilizumab-related work.7,17 During the conduct of the study, it became apparent that CRP normalization would lag behind a patient’s clinical improvement and the patient could be safely discharged before CRP had normalized, making CRP normalization an impractical outcome measure. We therefore report the percentage of patients who achieved biochemical response, defined as a CRP reduction ≥ 25% from baseline in the 24–48 hours after tocilizumab administration, consistent with a decline determined by CRP half-life.22 Secondary outcomes included overall survival at 28 days, survival to hospital discharge, rate and duration of nonelective mechanical ventilation, time to mechanical ventilation, rate and duration of vasopressor/inotropic agent utilization, time to vasopressor/inotropic agent utilization, and number of days spent in intensive care unit. One month after enrollment began, duration of supplemental oxygen requirement greater than a patient’s baseline was added. Definitions of outcomes are provided in the protocol.

Post Hoc evaluation of clinical recovery
Randomized, controlled trials of COVID-19 therapies had not been published at the time of COVIDOSE initiation but were published prior to COVIDOSE data maturity.28 To add context to COVIDOSE results, time to clinical recovery was evaluated post hoc. Using a previously developed seven-point ordinal scale,29 disease severity was assessed daily, with the patient’s worst clinical status and consequent ordinal score recorded for a given day.28,29 Recovery was defined as the first day on which a patient achieved a clinical status of either “hospitalization without need for supplemental oxygen or ongoing medical care” or “not hospitalized.”28,29 Time to recovery was defined as the time in days from study enrollment to achievement of recovery.28 Two independently operating authors (G.W.S. and P.D.R.) adjudicated ratings.

Statistical analysis
We generated descriptive statistics of the clinical and biochemical response rates of patients treated with low-dose tocilizumab. We assessed differences in the clinical and biochemical response rates between different tocilizumab doses using a two-sided Fisher exact test, unadjusted for cohort or other risk factors. A P value of < 0.05 was considered to indicate statistical significance. All analyses were performed using Stata (Stata Corp., College Station, TX). For post hoc analysis, descriptive data summaries are reported as median (interquartile range (IQR)) or percentages.

Ethics approval
The UCM institutional review board (IRB) approved the trial protocol. Given the rapidly evolving landscape of COVID-19, the IRB authorized an internal trial operating committee comprised of investigators to facilitate dose modifications based on incoming data (full details of this operating structure are available in the COVIDOSE trial protocol and Supplementary Material at Clinical Pharmacology & Therapeutics’ website). An internal data monitoring committee oversaw the trial’s progress and adjudicated outcomes, safety signals, and potential protocol deviations in weekly meetings. All authors attest to the validity of the data and adherence to the trial protocol, with reporting of violations where indicated.

RESULTS
Trial population
From April 1 through May 13, 2020, 32 patients consented to participate in COVIDOSE. Twelve were assigned to Group A, 8 of
whom received 200 mg and 4 of whom received 120 mg. Twenty were assigned to Group B, 15 of whom received 80 mg and 5 of whom received 40 mg (Figure 1). Median time from hospital admission to study enrollment was 1 day (IQR, 1–2 days). All patients were included in the statistical analysis of fever resolution, and 29 patients were included in the statistical analysis of CRP response. Characteristics of the COVIDOSE subpopulations are summarized in Table 1. Re-dosing of low-dose tocilizumab is discussed in the Supplementary Materials.

**Clinical outcomes**

The trend of the maximum daily temperature (mean ± standard error of the mean) in COVIDOSE patients is shown in Figure 2a. At 24 hours following tocilizumab administration, 24 COVIDOSE patients (75.0%) were afebrile (maximum temperature < 38.0°C), including 67% of patients in Group A and 80% of those in Group B (Figure 2b). There was no evidence of a relationship between the tocilizumab dose and rate of fever resolution in the first 24 hours (Figure 2c). Ten of the 24 patients (42%) with baseline supplemental oxygen requirement had a decrease in maximum oxygen requirement in the first 24 hours following tocilizumab administration.

**Biochemical outcomes**

The CRP trend (mean ± standard error of the mean) for the COVIDOSE population is shown in Figure 2d. The vast majority (29/32) of patients were evaluable for CRP response, of whom 25 (86%) achieved CRP decrease ≥ 25%. This included 91% of Group A patients and 83% of Group B patients (Figure 2e). There was no evidence of a relationship between tocilizumab dose and likelihood of achieving CRP decrease ≥ 25% (Figure 2f).

**Post hoc evaluation of recovery time and safety**

The 28-day mortality rate was 16% (Table 2). The median time to recovery for the remaining patients was 3 days (IQR, 2–5), and appeared to be associated with the severity of disease at enrollment (Table 2). Culture-proven or clinically suspected ventilator-associated or hospital-acquired pneumonias were identified in 5 (16%) patients.

**Discussion**

Low-dose tocilizumab was clinically and biochemically active in patients with COVID-19 and related hyperinflammation who did not require invasive ventilation, with no apparent relationship between tocilizumab dose and clinical or biochemical improvement over the studied dose range of 40 to 200 mg. Although the minimum effective dose of tocilizumab was not identified in this clinical trial, the COVIDOSE study demonstrated that a tocilizumab dose of 40 mg may be sufficient to blunt the clinical and biochemical signs of COVID-19–related hyperinflammation. Referencing clinical pharmacology

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**Figure 1** Flow of patients in the COVIDOSE trial. Thirty-two eligible patients consented to participate in the COVIDOSE trial, of which 12 were assigned to Group A and 20 were assigned to Group B on the bases of magnitude of C-reactive protein elevation and epidemiologic risk factors for COVID-19 related mortality. Group A patients received either 200 or 120 mg of tocilizumab and were followed for 28 days following drug administration. Group B patients received either 80 or 40 mg of tocilizumab and were followed for 28 days following drug administration. All 32 patients were evaluable for the purposes of primary clinical outcome and 29 were evaluable for biochemical outcome. No patients were lost to follow-up.
arguments, the absence of a dose–response relationship suggests that a dose much lower than those utilized in other COVID-19 studies (400 mg) or approved by regulatory bodies for the treatment of chimeric antigen receptor T-cell–related CRS (4–8 mg/kg) may be sufficient to blunt IL-6–mediated hyperinflammation. The COVIDOSE trial provides proof of concept for a COVID-19 therapeutic strategy centered on the administration of low-dose tocilizumab, with re-dosing guided by readily assessable clinical and biochemical responses.

To our knowledge, COVIDOSE is the first trial to provide prospectively collected evidence of low-dose tocilizumab’s clinical benefit. Marked declines in maximum body temperature and CRP were noted in the 24–48 hours following administration of low-dose tocilizumab—responses that mimic those observed in patients with severe and critical COVID-19 who received tocilizumab 400 mg. Though an increase in CRP after day 4 may be suggested by the data presented, it is not necessarily statistically or clinically significant and is likely attributable to COVIDOSE patients being more chronically ill than other hospitalized patients with COVID-19 and at higher likelihood for secondary issues. The issue will be fully explored in an ongoing randomized, controlled trial. Post hoc analysis of COVIDOSE patients’ clinical trajectories provides encouraging evidence of low-dose tocilizumab’s benefit. Patients requiring supplemental oxygen at enrollment experienced median time to recovery of 4 days. This is an encouraging finding in the context of a median time to recovery of approximately 7 days in a similarly risked subpopulation receiving remdesivir. Notably,

### Table 1 Demographic, clinical, and laboratory characteristics of patients enrolled on COVIDOSE

| Characteristic                                      | COVIDOSE Group A n = 12 | COVIDOSE Group B n = 20 | Overall COVIDOSE Population n = 32 |
|----------------------------------------------------|-------------------------|-------------------------|-----------------------------------|
| Age, median (IQR), years                           | 70 (51, 73)             | 66 (41, 73)             | 69 (41, 73)                       |
| Male sex, n, (%)                                   | 7 (58.3%)               | 9 (45.0%)               | 16 (50.0%)                       |
| Race, n, (%)                                       |                         |                         |                                   |
| White                                              | 1 (8.3%)                | 0 (0%)                  | 1 (3.1%)                         |
| Black                                              | 9 (75.0%)               | 16 (80.0%)              | 25 (78.1%)                       |
| Hispanic/Latinx                                    | 2 (16.7%)               | 1 (5.0%)                | 3 (9.4%)                         |
| Multiracial, other, prefer not to identify         | 0 (0.0%)                | 3 (15.0%)               | 3 (9.4%)                         |
| Comorbidities per patient, n, (%)                  |                         |                         |                                   |
| None                                               | 0 (0%)                  | 4 (20.0%)               | 4 (12.5%)                        |
| 1                                                  | 2 (16.7%)               | 6 (30.0%)               | 8 (25.0%)                        |
| 2                                                  | 4 (33.3%)               | 6 (30.0%)               | 10 (31.3%)                       |
| 3 or greater                                       | 6 (50.0%)               | 4 (20.0%)               | 10 (31.3%)                       |
| Epidemiologic risk factors from risk group stratification per patient, n, (%) |                         |                         |                                   |
| None                                               | 1 (8.3%)                | 12 (60.0%)              | 13 (40.6%)                       |
| 1                                                  | 5 (41.7%)               | 5 (25.0%)               | 10 (31.3%)                       |
| 2                                                  | 5 (41.7%)               | 3 (15.0%)               | 8 (25.0%)                        |
| 3 or greater                                       | 1 (8.3%)                | 0 (0%)                  | 1 (3.1%)                         |
| Medications, at baseline, n, (%)                   |                         |                         |                                   |
| Hydroxychloroquine                                 | 4 (33.3%)               | 6 (30.0%)               | 10 (31.3%)                       |
| Azithromycin                                        | 5 (41.7%)               | 8 (40.0%)               | 13 (40.6%)                       |
| Lopinavir-Ritonavir                                 | 1 (8.3%)                | 3 (15.0%)               | 4 (12.5%)                        |
| Systemic corticosteroid (within 24h of enrollment) | 0 (0%)                  | 0 (0%)                  | 0 (0%)                           |
| Supplemental O₂ Requirement at enrollment (eligibility), n, (%) |                         |                         |                                   |
| None                                               | 2 (16.7%)               | 6 (30.0%)               | 8 (25.0%)                        |
| Low-flow oxygen                                     | 9 (75.0%)               | 13 (65.0%)              | 22 (68.8%)                       |
| Noninvasive ventilation or high-flow oxygen         | 1 (8.3%)                | 1 (5.0%)                | 2 (6.5%)                         |
| C-Reactive Protein, baseline, mean (SEM), mg/L      | 175 (24)                | 138 (17)                | 152 (14)                         |
| D-dimer, baseline, mean (SEM), pg/mL               | 1.98 (0.50)             | 2.2 (0.96)              | 2.12 (0.62)                      |
| Ferritin, baseline, mean (SEM), pg/mL              | 2022 (458)              | 1151 (308)              | 1478 (264)                       |
| COVID-GRAM risk prediction score, median (IQR)      | 126.8 (113.5, 151.8)    | (102.3, 158.9)          |                                   |

IQR, interquartile range.
the COVIDOSE population had higher likelihood of comorbid-
ities associated with poor COVID-19–related outcomes.28 The
COVIDOSE data add context to the emerging real-world evidence
for tocilizumab’s benefit and will add context to the interpreta-
tions of the COVACTA, CORIMUNO-TOCI, and Randomised
Evaluation of COVID-19 Therapy (RECOVERY) tocilizumab
trials once these studies are published.8,9,32,33 Care needs to be
taken in interpreting these studies given significant heterogeneity

Figure 2 Temperature and CRP decrease rapidly following administration of low-dose tocilizumab. (a) Temperature values for COVIDOSE patients following eligibility (mean ± standard error of mean). (b) Percentage of COVIDOSE (dark gray), COVIDOSE Group A (light gray), and COVIDOSE Group B (white) patients meeting the primary outcome of $T_{\text{max}24\text{ hours}} < 38.0°C$. (c) Relationship between tocilizumab dose and probability of achieving fever resolution. Percentage of COVIDOSE patients at the noted tocilizumab dose levels achieving the outcome of $T_{\text{max}24\text{ hours}} < 38.0°C$. Bars denote one-sided Fisher exact test for difference in proportions. P values are as shown in the panel. (d) Representative CRP values for COVIDOSE patients following eligibility (mean ± standard error of mean). (e) Percentage of COVIDOSE (dark gray), COVIDOSE Group A (light gray), and COVIDOSE Group B (white) patients meeting the primary biochemical outcome of CRP decline of ≥ 25% at 24 hours. (f) Relationship between tocilizumab dose and probability of achieving CRP decline of ≥ 25%. Percentage of COVIDOSE patients at the noted tocilizumab dose levels achieving CRP decline of ≥ 25%. Bars denote one-sided Fisher exact test for difference in proportions. P values are as shown in the panel figure. CRP, C-reactive protein; $T_{\text{max}24\text{ hours}}$, maximum temperature within 24 hours following drug administration.

Table 2 Post hoc clinical outcomes in the overall COVIDOSE study population

| Ordinal Score at Baseline | Risk Group Stratification at Baseline |
|--------------------------|--------------------------------------|
| 1 | 2 | 3 | 4 | 5 | Recovery | Risk Group A | Risk Group B |
| Overall | NIV, HHFNC (n = 4) | Low-flow oxygen (n = 17) | No supp. oxygen (n = 11) |
| 3 | 2 | 15 | 10 |
| Median time to recovery (IQR), days | 3 (2–5) | 11.5 (10.75–12.25) | 4 (3–5) |
| 2 | 10 | 4.5 (2.5–6.75) |
| 17 | 3 (2–4) |
| Mortality | No. of deaths by day 28 | 5 | 2 | 2 | 2 | 3 |

Post hoc clinical outcomes in the overall COVIDOSE study population, according to baseline ordinal clinical status and risk group assignment. HHFNC, heated high-flow nasal cannula; IQR, interquartile range; NIV, noninvasive ventilation; supp., supplemental.
More relevant moving forward is where tocilizumab fits into a COVID-19 treatment paradigm that consists of remdesivir with the possible addition of corticosteroids for patients who require mechanical ventilation and, depending on local institutional standards, supplemental oxygen. \textsuperscript{34,35} The field lacks evidence-based, highly efficacious treatment for patients with severe (but not critical) COVID-19—the confidence interval of the hazard ratios for corticosteroids in this clinical scenario ranges from 0.73 to 1.00. \textsuperscript{34} Strategies including drugs that are both accurate and precise—Janus kinase inhibitors or IL–6-targeted drugs, for example—may be beneficial in patients who are not yet intubated, as suggested by early press releases describing the possible efficacy of baricitinib in COVID-19. \textsuperscript{36} Tocilizumab’s role in moderate, severe, and critical COVID-19 remains ambiguous. \textsuperscript{11} Benefit has been identified in the prospective EMPACTA and CORIMUNO-TOCI-1 randomized controlled trials,\textsuperscript{12,13} with these studies meeting their primary end points of death or mechanical ventilation and survival without mechanical ventilation, respectively. The COVACTA study demonstrated a marked decrease in hospital length of stay, but failed to meet its primary end point of improvement in ordinal clinical status at day 28. \textsuperscript{14} Recently published studies, though likely underpowered, failed to meet their primary end points of progression to death, intensive care unit admission, or critical disease, respectively. \textsuperscript{15,16} Trials that have not yet reported include A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia (REMDACTA) and our own Low-Dose Tocilizumab Versus Standard of Care in Hospitalized Patients With COVID-19 (COVIDOSE-2) study. \textsuperscript{30,37} The latter of these studies allows for concomitant remdesivir and/or corticosteroids and allows for enrollment on one of two substudies at the discretion of clinicians—one substudy evaluates against a tocilizumab-free control arm while the other evaluates against a comparator of the standard 400 mg dose of tocilizumab. \textsuperscript{30} As this body of evidence develops, the COVIDOSE data will become particularly compelling.

The data presented in COVIDOSE suggest that a threefold to 10-fold tocilizumab supply expansion may be possible due to lower dosing regimens. In this trial, we administered a total of 4,120 mg of tocilizumab, corresponding to 37 doses for 32 patients. In comparison, 12,800 mg would have been administered had each patient received 400 mg. \textsuperscript{5,33} The EMPACTA, CORIMUNO-TOCI-1, and COVACTA trials utilize a dose of 8 mg/kg. \textsuperscript{12-14} Rapid, global scaling is necessary for tocilizumab to become a safe, effective, and equitable therapy for hospitalized patients with COVID-19, and an IVPE-based approach is one possible strategy for extending supplies.\textsuperscript{17,22}

Beyond sustainability, low-dose tocilizumab may be clinically advantageous over higher dosages. Utilizing lower doses of tocilizumab may lessen the depth and duration of its immunosuppressive effect while retaining clinical benefit, as evidenced by declines in maximum temperature and CRP. Despite a rate of secondary bacterial infection fourfold of that observed in COVIDOSE, mechanically ventilated patients who received tocilizumab 8 mg/kg derived survival benefit. \textsuperscript{34,35} How the prospectively collected rates of secondary infections compare between low-dose tocilizumab–treated, tocilizumab 8mg/kg–treated, and dexamethasone-treated patients, as well as the combination of dexamethasone and tocilizumab, remains to be seen, but lower doses of tocilizumab may be advantageous. \textsuperscript{2} A priori rationale for the safety of combining corticosteroid and tocilizumab can be found in the treatment of giant cell arteritis.\textsuperscript{38} Finally, in biological studies conducted in parallel with COVIDOSE, no statistically significant differences in anti–SARS-CoV2 antibody production between patients treated with any dose of tocilizumab, remdesivir, or supportive care alone were identified. \textsuperscript{39} Carefully constructed prospective trials with appropriate biological correlative studies are needed.

The COVIDOSE trial is not without limitations. It was a small, single-center study conducted at a tertiary care center with active research efforts in COVID-19–related supportive care. The absence of a randomized control arm limits formal conclusions about low-dose tocilizumab’s safety and efficacy. The rapidly changing understanding of COVID-19 and local practice prevented trending CRP to normalization, leading to the need for reporting of a different biochemical outcome than originally expected. The COVIDOSE study, however, provides proof of concept as well as valuable lessons that are being incorporated into a randomized, controlled trial evaluating the clinical efficacy of low-dose tocilizumab in COVID-19. \textsuperscript{30}

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

ACKNOWLEDGMENTS
The authors wish to thank Spring Maleckar for her assistance and contributions in creating the REDCap database and Bethany Martell for her expertise throughout aspects of the COVIDOSE trial’s proceedings. We also thank Athalia Pyzer, MD, Yuanyuan Zha, Blake Flood, Glee Li, Hongyuan Jiao, Apameh Pezeshk, Lara Kozloff, Randy Sweis, MD, and the Human Immunologic Monitoring core facility of the University of Chicago Comprehensive Cancer Center for contributions to the COVID-19 biobanking project.

FUNDING
This trial was funded and sponsored by the University of Chicago. The institution had no role in the design, execution, or analysis of this trial. There was no industry involvement in COVIDOSE.

CONFLICT OF INTEREST
G.W.S. is supported by the Richard and Debra Gonzalez Research Fellowship at the University of Chicago (established through philanthropy by Abbott Laboratories; Lake Bluff, Illinois, USA). B.L.H. is funded by the T32 GM007019 grant from the National Institute of General Medical Sciences. M.E.S. reports research grants from Boehringer Ingelheim and Genentech. M.J.R. reports other support including the following: personal fees from multiple generic companies, personal fees from Cyclacel, personal fees from Aptevo, personal fees from Shionogi, other from Dicerna,
personal fees and other from Genentech, other from Biogen, other from AbbVie, other from Corvus, other from Bristol-Myers Squibb, other from Xencor, outside the submitted work. In addition, M.J.R. has a patent US6935481B1 with royalties paid to Mayo Medical, a patent EP1629111B1 with royalties paid to Mayo Medical, a patent US8877238B2 issued, a patent US9617583B2 issued, and a patent provisional patent pending and Director and Treasurer, Value in Cancer Care Consortium. G.W.S., B.L.H., P.D.R., and M.J.R. are coinventors of a filed provisional patent on the use of low-dose tocilizumab in viral infections. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

G.W.S., M.J.R., and P.D.R. wrote the manuscript. G.W.S., B.L.H., J.A.T., C.E., I.B.V., N.N.P., B.K.P., J.P., M.E.S., T.F.G., M.J.R., and P.D.R. designed the research. G.W.S., B.L.H., J.A.T., J.Y., A.J.K., R.C.W., A.K.K., K.D., E.F.H., J.C.B., A.C., and P.D.R. performed the research. G.W.S., A.J.K., T.G.K., T.F.G., M.J.R., and P.D.R. analyzed the data. E.F.H. and A.W. contributed new reagents/analytical tools.

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