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Reduced fixed dose tocilizumab 400 mg IV compared to weight-based dosing in critically ill patients with COVID-19: A before-after cohort study

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Summary

Background Interleukin-6 inhibitors reduce mortality in severe COVID-19. British Columbia began using tocilizumab 8 mg/kg (maximum 800 mg) in January 2021 in critically ill patients with COVID-19, but due to drug shortages, decreased dosing to 400 mg IV fixed dose in April 2021. The aims of this study were twofold: to compare physiological responses and clinical outcomes of these two strategies, and examine the cost-effectiveness of treating all patients with 400 mg versus half the patients with 8 mg/kg and the other half without tocilizumab.

Methods This was a single-centre, before-after cohort study of critically ill COVID-19 patients treated with tocilizumab, and a control cohort treated with dexamethasone only. Physiological responses and clinical outcomes were compared between patients receiving both doses of tocilizumab and those receiving dexamethasone only. We built a decision tree model to examine cost-effectiveness.

Findings 152 patients were included; 40 received tocilizumab 8 mg/kg, 59 received 400 mg and 53 received dexamethasone only. Median CRP fell from 103 mg/L to 5.2 mg/L, 96 mg/L to 6.8 mg/L and from 81.3 mg/L to 48 mg/L in the 8 mg/kg, 400 mg tocilizumab, and dexamethasone only groups, respectively. 28-day mortality was 5% (n=2) vs 8% (n=5) vs 13% (n=7), with no significant difference in all pair-wise comparison. At an assumed willingness-to-pay threshold of $50,000 Canadian per life-year, utilizing 400 mg for all patients rather than 8 mg/kg for half the patients is cost-effective in 51.6% of 10,000 Monte Carlo simulations.

Interpretation Both doses of tocilizumab demonstrated comparable reduction of inflammation with similar 28-day mortality. Without consideration of equity, the net monetary benefits of providing 400 mg tocilizumab to all patients are comparable to 8 mg/kg to half the patients. In the context of ongoing drug shortages, fixed-dose 400 mg tocilizumab may be a practical, feasible and economical option.

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Research in context

Evidence before this study

We searched Pubmed for articles published from inception up to Jan 3, 2022, using the kewords "coronavirus", "COVID-19", "tocilizumab", "sarilumab", "interleukin-6" with no language restrictions. The existing evidence at the time of our study consisted of observational studies of lower dose tocilizumab and pharmacological modeling studies suggesting that doses lower than 8 mg/kg may be effective in COVID-19.

Added value of this study

To the best of our knowledge, the present study is the most comprehensive comparison of physiological parameters (CRP, ferritin, PaO_2/FiO_2) and clinical outcomes (ICU stay, short term mortality) between fixed dose 400 mg IV and 8 mg/kg (maximum 800 mg) IV. It is also the first study to examine cost effectiveness of these two strategies, and is one of the few studies done in a critically ill population with a low overall mortality < 20%.

Implications of all the available evidence

Although no randomized studies comparing tocilizumab doses have been done, this study adds to the body of observational data that lower doses of tocilizumab such as the 400 mg IV fixed dose strategy used in this study increases the number of patients who benefit from the medication in a situation of drug scarcity.

Introduction

The severe acute respiratory coronavirus 2 (SARS-CoV-2) induces a maladaptive cytokine storm characterized by evasion of the type I/III interferon response followed by inflammatory hypercytokinemia and respiratory failure.[1] Interleukin (IL)-6 is one of the key cytokines driving respiratory failure and death,[2,3] and IL-6 inhibition reduces mortality.[4] The most widely studied IL-6 inhibitor, tocilizumab, is now scarce in many jurisdictions due to high global demand and limited manufacturing capacity.[5]

In the Canadian province of British Columbia, tocilizumab entered widespread use for critically ill COVID-19 patients on Jan 8, 2021, shortly after online publication of the Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial.[6] From January to April, a single dose of 8 mg/kg IV (up to 800 mg), as per the REMAP-CAP and Randomized Evaluation of COVID-19 Therapy (RECOVERY) protocols, was used.[6] However, in the spring of 2021, shortages of tocilizumab became a major issue in Canada, and British Columbia switched to fixed dosing 400 mg IV for patients over 50 kg.

The reasoning for this decision was that 400 mg would likely provide an equivalent short-term anti-inflammatory effect to 8 mg/kg while allowing nearly twice as many patients to receive tocilizumab. This assumption was based on several observations. First, the REMAP CAP trial demonstrated that sarilumab 400 mg IV fixed dose is equivalent to tocilizumab 8 mg/kg.[7] Both sarilumab and tocilizumab work by binding the IL-6/IL-6 receptor complex.[8] While sarilumab has higher affinity for the IL-6/IL-6 receptor complex than tocilizumab, the level of on receptor drug is similar, so in principle, fixed dose tocilizumab 400 mg should have a very similar biological effect to sarilumab.[8]

Second, observational studies have found lower doses of tocilizumab to be biologically active in COVID-19. In one of the earliest reports of tocilizumab in COVID-19 out of Italy, patients received either fixed dose 400 mg or 324 mg subcutaneously.[9,10] The phase II COVIDOSE study found similar resolution of fever and decline in CRP in 32 patients receiving doses of tocilizumab ranging from 40 to 200 mg.[11] A retrospective Turkish study that defined low dose as < 200 mg and high dose as ≥ 200 mg found slightly lower mortality (30 vs 37.5%, $p = 0.008$) in the low dose group.[12]

Third, the pharmacokinetics of IL-6 blockade support a lower dose of tocilizumab for short-term control of inflammation. In a pharmacokinetic study of 29 patients with COVID-19 receiving tocilizumab, Monte Carlo simulations using a non-linear mixed effects model demonstrated that a 400 mg fixed dose of tocilizumab achieved drug levels above 1 μg/mL for at least 15 days which was comparable to 8 mg/kg dosing across patients weighing between 60 kg to 100 kg.[13]

We conducted a retrospective cohort study in critically ill patients at our center to compare outcomes in those who received 8 mg/kg before April 9, 2021 with those who received 400 mg IV fixed dose after that

date, as well patients who received dexamethasone only (Aug 1-Dec 31, 2020) as a control group. The aims of this study were to compare physiological responses and clinical outcomes of 400 mg IV fixed dose tocilizumab compared to 8 mg/kg. We also examined the cost-effectiveness of treating all patients with 400 mg versus half the patients with 8 mg/kg and the other half no tocilizumab, in the context of a limited medication supply.

Methods

The study was approved by the University of British Columbia Clinical Research Ethics Board (H20-00971) and registered on ClinicalTrials.gov (NCT04363008). All research was conducted in accordance with the principles of the Helsinki declaration and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study design and participants

Patients in the present study were enrolled as part of a prospective COVID-19 biomarker study as previously described.[2] Adult patients admitted to the intensive care unit (ICU) at Vancouver General Hospital, an 800-bed quaternary care center with 34 ICU beds, with a diagnosis of pneumonia secondary to SARS-CoV-2 infection who received dexamethasone alone prior to tocilizumab becoming standard of care at our centre (Aug 1 to Dec 31 2020) or in combination with tocilizumab (Jan 9 to June 24 2021) were eligible for the study. Patients were excluded if: COVID-19 was an incidental finding on or during admission (e.g. admitted to ICU primarily for trauma), if COVID-19 was determined to be nosocomial in origin, or if patients were transferred from another ICU (please see the Supplemental Figure for the study inclusion flow diagram). In addition to standard supportive care, all patients received dexamethasone 6 mg po daily up to 10 days or equivalent corticosteroid as per the RECOVERY trial.[14] No patients received remdesivir, monoclonal antibodies targeting the spike glycoprotein, or baricitinib during the study period and none of the patients had received a COVID-19 vaccination. In the province of British Columbia, patients were eligible for tocilizumab if they met REMAP-CAP criteria: high flow oxygen (> 30 L/min and FIO2 > 0.4W or invasive or non-invasive ventilation or vasopressor or inotropic support).[6] Tocilizumab was administered within 24 h of initiation of life support measures (high flow oxygen support > 30 L/min and FiO2 > 0.4 or invasive or non-invasive ventilation or vasopressor or inotropic support). Between Jan 9 and April 9, 2021, patients received 8 mg/kg (up to 800 mg) of tocilizumab IV; from April 10 to June 24 2021, patients received 400 mg IV fixed dose. This change in dosing was made based on provincial treatment guidelines in response to medication shortages.

Outcomes and procedures

Demographics pertaining to age, sex, medical comorbidities and date of: symptom onset, hospital and ICU admission, tocilizumab administration, initiation and cessation of mechanical ventilation, and ICU and hospital discharge and death were collected. Clinical laboratory values including: C-reactive protein (CRP), D-dimer, complete blood count (WBC count and differential, hemoglobin concentration, and platelet count), ferritin, creatinine, liver enzymes, and bilirubin and median daily measurement of PaO_2/FiO_2 were recorded. Data were collected in the 24h prior to tocilizumab administration as well as 5–7 days (target range 4-10 days) following. Differences in CRP, ferritin, lymphocyte count, and PaO_2/FiO_2 were calculated in patients with paired pre and post tocilizumab values. For dexamethasone controls, initial data was collected upon ICU admission and study enrollment, with follow-up data collected 5-7 days later.

The following interventions were recorded if they ever took place during the participants' ICU stay: mechanical ventilation, venous-venous extra corporeal membrane oxygenation (VV-ECMO), acute respiratory distress syndrome (ARDS), as defined by the Berlin criteria, shock, continuous renal replacement therapy (CRRT), prone position, inhaled nitric oxide (iNO), or medically induced paralysis The main clinical outcome of interest was 28-day mortality, defined as 28 days from receipt of tocilizumab as per the RECOVERY trial. Other outcomes include all-cause in-hospital mortality, length of mechanical ventilation, ICU stay, and hospital stay.

Statistical analysis

Descriptive statistics, including median, interquartile ranges (IQRs), and frequency, were used to describe continuous and categorical variables, respectively. Group differences were tested using a Mann-Whitney U test (two groups) or Kruskal-Wallis with Dunn's Multiple Comparison Test for continuous variables, or Fisher's exact test for categorical variables. Paired-longitudinal data was analyzed using the Wilcoxon signed rank test. All statistical tests were two-sided and a p value of less than 0.05 was considered significant. Statistical analyses for biochemical and clinical outcomes were completed using GraphPad Prism (Version 7.03).

Economic analysis

We examined the cost-effectiveness of two treatment strategies in the context of a limited medication supply: treating all patients with 400 mg versus a randomly selected half of patients treated with 8 mg/kg tocilizumab and the other half receiving no tocilizumab. We incorporated the relevant parameters from our study to create a decision tree model that examined these two strategies. In the context of limited resources, the

utilization 400 mg per patient allows up to double the amount of patients to be treated. Rather than utilize retrospective data from our own prior cohort of patients who did not receive tocilizumab and to minimize time-varying confounding in comparing patients receiving tocilizumab to no tocilizumab across different periods of the pandemic, we determined *a priori* to utilize data from two large, prospective, randomized control trials (RECOVERY and REMAP-CAP). Here the number needed to treat is readily calculated and corresponds to an additional 4-8 deaths per 100 people for the trial arm of patients not receiving any tocilizumab as compared to 8mg/kg tocilizumab. These additional deaths inform the counterfactual that we would have expected in half of our 8 mg/kg cohort of patients after running out of tocilizumab. The corresponding base-case mortality probability in the 8 mg/kg cohort is then an average of the mortality in this cohort (10%) and the expected additional 4-8 deaths per 100 people above this baseline. Assuming an average of 6 additional deaths per 100 people corresponds to a mortality of 16% in those patients not receiving tocilizumab, which together with the 10% mortality of those receiving 8 mg/kg tocilizumab comes to an average of 13%. Separately, the mortality probability in our fixed dose cohort is 15.2%. For length of stay we utilized the same approach and, after accounting for the counterfactual cohort median time to discharge, estimated the length of stay in the 8mg/kg tocilizumab cohort to be 22.5 days. The length of stay in the fixed dose tocilizumab cohort is 17 days. The average cost of hospitalization inclusive of ICU stays in British Columbia is $2,330 per day and is based on data from the Canadian Institute for Health Information (https://www.cihi.ca/en/covid-19-hospitalization-and-emergency-department-statistics), being higher in the 8 mg/kg group based on a longer length of stay. Other base-case parameters include lifetime health costs and life expectancy that we weighted to match the age and gender demographics in our cohort, with a median start age of 62 years and a gender prevalence of 40% female and 60% male. Age- and gender-weighted life expectancy for survivors of 22.3 life years is derived from data available with Statistics Canada (https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310013401) while age- gender-weighted annual health care cost of $13,617 CAD per survivor is based on the 2019 Health Expenditure Trends in British Columbia (https://www.cihi.ca/en/national-health-expenditure-trends) with annual rate assumed to be at the most expensive rate in the highest age bracket in this analysis (80−84). The cost of tocilizumab in British Columbia is per milligram and is $2.29/1 mg. Costs and life-years were discounted at 3% annually.[15] We constructed our model using TreeAge Pro Healthcare 2021, assumed a health system perspective, and a lower-end willingness-to-pay of $50,000 CAD (TreeAge Software, Williamstown, MA).[16]

Economic analyses- sensitivity analysis

Each of the base-case probabilities of mortality, lifetime health expenditures and tocilizumab costs were varied +/-50% with this uncertainty propagated by assigning appropriate probability distributions and varying all model parameters within their respective distributions by simulating 10,000 Monte Carlo iterations. We used Beta (β)-PERT and Gamma (γ) distributions for clinical probabilities and costs, respectively (Supplemental Table).

Role of the funding source

The funders had no role in the design, analysis or reporting of the study.

Results

A total of 152 patients were included. Forty patients received tocilizumab 8 mg/kg (maximum 800 mg) between Jan 9 and April 9, 2021 and 59 patients received 400 mg fixed dose between April 10 and Jun 25, 2021. Fifty-three patients who received dexamethasone only (Aug 1-Dec 31, 2020) were included as a control group. Baseline demographics and clinical characteristics are shown in Table 1. Overall, there were no significant demographic differences between the groups. On average, patients presented to hospital 5-8 days following the onset of symptoms and were given tocilizumab and admitted to ICU in the 1-2 days following. Based on the group median and IQR for weight (77 kg in the 8 mg/kg group and 78 kg in the 400 mg group), 400 mg of tocilizumab equates to 5.1 mg/kg (IQR 3.5, 7.1].

Baseline respiratory physiology and blood laboratory measures are summarized in Table 2. Before administration of tocilizumab, patients were severely hypoxemic, with 20% requiring mechanical ventilation. In the dexamethasone only group, 60% were ventilated at baseline, but the PaO_2/FiO_2 ratio was also significantly higher so some of these differences may related to the disease stage in which the data was derived. As per standard care during the different time periods of this study, the dexamethasone only cohort were enrolled while already in the ICU, whereas 20-25% of patients in the tocilizumab cohort were on the ward on high flow oxygen at the time of drug administration. All three cohorts were lymphopenic, with elevated levels of D-dimer, C-reactive protein, and ferritin.

Changes in CRP, ferritin, lymphocyte count, and PaO_2/FiO_2 (P/F) ratio are shown in Figure 1 and summarized in (Table 3). The median [IQR] time to follow-up was 5 days [4,7] in the 8 mg/kg tocilizumab group, 5 days [3,6] in the 400 mg tocilizumab group, and 4 days [4,5] in the dexamethasone control group, with no statistical difference between groups ($p = 0.06$). There was a dramatic anti-inflammatory response in the days following tocilizumab administration, with a decrease in CRP and ferritin and an increase in

	Tocilizumab 8 mg/kg (n=40)	Tocilizumab 400 mg (n=59)	Dexamethasone control (n=53)	Kruskal Wallis test[a]	P-values pair-wise comparisons[b]
Demographics					
Male, n (%)	24 (60)	38 (64)	31 (58)	–	0.68/>0.99/0.56
Female, n (%)	16 (40)	21 (36)	22 (42)		
Age, y, median [IQR]	62 [52, 74]	59 [49, 67]	62 [50, 74]	$p = 0.20$	0.38/>0.99/0.38
Weight, kg, median [IQR]	77 [74, 82]	78 [72, 89]	77 [73, 83]	$p = 0.72$	>0.99/>0.99/>0.99
BMI, kg/m^2, median [IQR]	30.5 [27, 34]	30 [26, 34]	31 [28, 34]	$p = 0.75$	>0.99/>0.99/>0.99
Tocilizumab dose, mg/kg, median (min, max)	–	5.1 (3.5, 7.1)	–	–	–
Comorbidities, n (%)					
HTN	17 (43)	28 (47)	26 (49)	–	0.68/0.67/>0.99
Diabetes	17 (43)	17 (29)	21 (40)	–	0.20/0.83/0.24
Dyslipidemia	15 (38)	25 (43)	19 (36)	–	0.68/>0.99/0.45
CKD	1 (3)	3 (5)	6 (11)	–	0.64/0.23/0.31
CAD	4 (10)	5 (9)	8 (15)	–	>0.99/0.55/0.38
COPD	2 (5)	5 (9)	6 (11)	–	0.70/0.46/0.75
Smoking	7 (18)	11 (19)	10 (19)	–	>0.99/>0.99/>0.99
Presentation to ICU					
Presenting symptoms, n (%)					
Fever	30 (77)	36 (65)	40 (75)	–	0.36/>0.99/0.30
Cough	36 (92)	46 (87)	47 (89)	–	0.51/0.73/>0.99
Dyspnea	37 (85)	54 (93)	50 (94)	–	>0.99/>0.99/>0.99
Myalgias	0 (0)	7 (12)	8 (15)	–	0.039/0.019/0.78
Diarrhea	22 (56)	22 (41)	23 (43)	–	0.14/0.29/0.85
Headache	3 (8)	3 (6)	4 (8)	–	0.69/>0.99/0.71
Duration, days, median [IQR], between:					
Symptoms and hospital admission	6 [5, 7]	8 [5, 10]	5 [3, 8]	$p = 0.0005$	0.026/>0.99/0.0005
Hospital admission and tocilizumab	1 [0, 3][c]	1 [0, 2][d]	–	$p = 0.16$[e]	–
Symptoms and tocilizumab	7 [5, 10]	9 [7, 11]	–	$p = 0.026$ [e]	–
Symptoms and ICU admission	7 [5, 9]	9 [7, 11]	7 [5, 9]	$p = 0.0028$	0.067/>0.99/0.003

***Table 1*: Comparison of demographics and clinical characteristics for COVID-19 patients admitted to the ICU between Jan 9 2021 and Jun 24 2021, based on the dose of tocilizumab administered, and Aug 1 and Dec 31 2020 (dexamethasone control group).**

[a]Continuous variables were compared using a Kruskal Wallis Test.

[b]pair wise comparison of 8mg/kg vs 400 mg toci / dex vs 8 mg/kg/ dex vs 400mg/. Categorical variables were analyzed using Fisher's Exact test; continuous variables were analyzed using Dunn's Multiple Comparison test that followed the group wise Kruskal Wallis Test.

[c]10/40 received tocilizumab on the hospital ward, the remaining 30/40 received tocilizumab in the ICU.

[d]13/59 participants received tocilizumab on the hospital ward, the remaining 46/59 received tocilizumab in the ICU.

[e]groups were compared using Mann Whitney U test

lymphocyte count after administration tocilizumab with dexamethasone at both doses, as well as dexamethasone alone. Median CRP fell from 103 mg/L to 5.2 mg/L (95% decrease, $p < 0.0001$) and from 96 mg/L to 6.8 mg/L (93% decrease, $p < 0.0001$) in the 8 mg/kg and 400 mg groups, and from 81.3 mg/L to 48.0 mg/L (41% decrease, $p = 0.014$) in the dexamethasone only group (Figure 1A, E, I). Ferritin likewise decreased from 919 µg/L to 700 µg/L ($p < 0.0001$), 1298 µg/L to 953 µg/L ($p < 0.0001$), and from 1126 µg/L to 760 µg/L ($p < 0.0001$) respectively (Figure 1B, F, J). Lymphocyte counts improved significantly in both tocilizumab groups, from 0.8×10^9/L to 1.5×10^9/L ($p < 0.0001$), and 0.7×10^9/L to 1.1×10^9/L ($p = 0.0006$), and from 0.8×10^9/L to 1.0×10^9/L ($p = 0.0006$) in the dexamethasone only group (Figure 1C, G, K). Last, we compared PaO_2/FiO_2, a simple measure of hypoxemic respiratory failure, whose improvement is an important marker of clinical recovery. The PaO_2/FiO_2 improved from a group median of 114 to 141 ($p = 0.0006$) and 105 to 167 ($p = 0.0004$) in the tocilizumab 8 mg/kg and 400 mg groups, respectively (Figure 1D, H). In contrast, there was no significant improvement in PaO_2/FiO_2 in the dexamethasone control (Figure 1L).

In order to compare the magnitude of change between treatment groups, the biomarker difference (day 5 − day 0) was calculated for each patient, and the resulting group median of differences was analyzed statistically (Table 3). There was a significant group difference ($p = 0.0005$) in the change of CRP; the median of differences in CRP was significantly larger in the 8 mg/kg tocilizumab versus dexamethasone (-98 vs -22 mg/L, $p = 0.0014$) and in the 400 mg tocilizumab versus dexamethasone (-84 vs -22 mg/L, $p = 0.004$).

	Tocilizumab 8 mg/kg (*n*=40)	Tocilizumab 400 mg (*n*=59)	Dexamethasone control (n=53)	Kruskal Wallis test[a]	*P*-values pair-wise comparisons[b]
Respiratory Data					
PaO2/FiO2, median [IQR]	114 [78, 154]	108 [78, 150]	153 [128, 196]	$p < 0.0001$	>0.99/<0.0001/<0.0001
Ventilated, n (%)	8 (20)	11 (19)	32 (60)	–	>0.99/0.0001/<0.0001
Clinical laboratory results (reference range, male/female)					
Basic cell count, median [IQR]					
WBC count, x10^9/L (4-11)	10 [6.4, 15.8]	7.4 [5.5, 10]	9.7 [6.4, 12.7]	$p = 0.0071$	0.0089/>0.99/0.08
PMN count, x10^9/L (2-7)	8.2 [5.5, 12.5]	6.2 [4.8, 9.0]	7.7 [5.3, 10.8]	$p = 0.12$	0.12/>0.99/0.73
Lymphocytes, x10^9/L (1.2-4)	0.8 [0.6, 1.1]	0.7 [0.5, 1.0]	0.8 [0.6, 1.0]	$p = 0.56$	0.85/>0.99/>0.99
Hemoglobin, g/L (135-170/120-155)	126 [103, 138]	140 [124, 148]	125 [115, 131]	$p = 0.0002$	0.0046/>0.99/0.0005
Platelets, x10^9/L (150-400)	273 [218, 345]	223 [179, 275]	256 [196, 358]	$p = 0.041$	0.063/>0.99/0.16
Coagulation, median [IQR]					
PTT, s, median [IQR] (25-38)	32 [28, 36]	33 [30, 36]	30 [28, 33]	$p = 0.063$	0.56/>0.99/0.06
INR, median [IQR] (0.9-1.2)	1.1 [1.1, 1.2]	1.1 [1.1, 1.2]	1.1 [1.1, 1.2]	$p = 0.78$	>0.99/>0.99/>0.99
D-dimer, ug/L (<500)	1079 [631, 2159]	843 [598, 1412]	1045 [774, 2382]	$p = 0.50$	>0.99/>0.99/0.72
Liver & kidney function, median [IQR]					
Albumin, g/L (34-50)	26 [25, 29]	27 [25, 30]	36.5 [22, 31.8]	$p = 0.75$	>0.99/>0.99/>0.99
AST, U/L (10-38)	67 [40, 94]	65 [44, 87]	46 [35, 67]	$p = 0.039$	>0.99/0.15/0.051
ALT, U/L (10-55)	45 [31, 105]	44 [31, 75]	57 [39, 87]	$p = 0.42$	>0.99/>0.99/0.6.0
Bilirubin, μmol/L (<20)	10 [7, 11]	8 [6.5, 11]	7 [6, 11]	$p = 0.092$	>0.99/0.092/0.48
LDH, U/L (90-240)	430 [343, 543]	534 [394, 665]	397 [320, 504]	$p = 0.0002$	0.027/0.60/0.0002
Creatinine, μmol/L (60-115/40-95)	87 [68, 114]	75 [62, 102]	87 [68, 112]	$p = 0.24$	0.59/>0.99/0.39
Inflammation, median [IQR]					
CRP, mg/L (<3.1)	101 [46.3, 140]	98.1 [64.7, 147]	77.5 [32.0, 114]	$p = 0.032$	>0.99/0.17/0.043
Ferritin, ug/L (15-370/15-225)	845 [436, 2215]	1315 [636, 2801]	1065 [500, 1648]	$p = 0.12$	0.41/>0.99/0.16

***Table 2*: Clinical laboratory measures and pulmonary function for COVID-19 patients either in the 24 h prior to tocilizumab administration or upon admission to the ICU (dexamethasone controls).**

[a] Continuous variables were compared using a Kruskal Wallis Test.

[b] pair wise comparison of 8 mg/kg vs 400 mg toci / dex vs 8 mg/kg/ dex vs 400 mg/. Categorical variables were analyzed using Fisher's Exact test; continuous variables were analyzed using Dunn's Multiple Comparison test that followed the group wise Kruskal Wallis Test.

There was also a significant difference in the response of PaO_2/FiO_2 between groups ($p = 0.013$); post-tests demonstrated that the improvement of PaO_2/FiO_2 was significantly greater in the 8 mg/kg tocilizumab versus dexamethasone group (30 vs -8, $p = 0.045$), and 400 mg tocilizumab group versus dexamethasone alone (61 vs -8, $p = 0.018$). There were no significant differences in the response of ferritin or lymphocyte cell count.

Last, we compared the frequency of ICU interventions and outcome (Table 4). While the frequency of mechanical ventilation was higher in the dexamethasone group (60%) compared to the tocilizumab groups (48% and 49%), this difference was not statistically significant. There was also no significant difference in the length of mechanical ventilation (median 6-8.5 days), ICU stay (median 6.5–7 days), or hospital stay (16-18 days). A total of 2 patients (5%) died within 28 days of tocilizumab in the 8 mg/kg group, 5 patients (8%) died in the 400 mg group, and 7 (13%) in the dexamethasone only group. All-cause in hospital mortality was 4 (10%) vs. 9 (15%) vs. 9 (17%) (Pair-wise comparison *p*-values 0.55/0.38/>0.99). None of the differences in mortality was statistically significant, likely due in large part to the small sample size and low event frequency. Comparison of the odds ratios for 28-day mortality between the groups were as follows: OR=2.89, (95% CI 0.57-14.3) for dexamethasone only vs. tocilizumab 8 mg/kg; OR=1.64, (95% CI 0.52-4.92) for dexamethasone only vs. tocilizumab 400 mg; OR=0.57, (95% CI 0.11-2.91) for tocilizumab 8 mg/kg vs 400 mg. For total mortality, the odds ratios were as follows: OR 1.84, (95% CI 0.50-5.73) for dexamethasone only vs. tocilizumab 8 mg/kg; OR 1.14, (95% CI 0.43-3.00) for dexamethasone only vs. tocilizumab 400 mg; OR 0.62, (95% 0.20-2.25) for tocilizumab 8 mg/kg vs. 400 mg. There were 27 (68%) and 39 (64%) survivors given 8 mg/kg and 400mg of tocilizumab, respectively, who were discharged from the hospital within 28 days of drug treatment, thus it is possible, however not probable, that patients may have died within the 28-day window but were lost to follow-up.

Cost-effectiveness of fixed dose tocilizumab

In the base case scenario and at an assumed willingness-to-pay (WTP) threshold of $50,000 Canadian (CAD) per life-year and assuming a limited supply of tocilizumab, 8 mg/kg per patient of tocilizumab for half the patients

Group	Day 0	Day 5	Median of differences[a]	Kruskal Wallis test[b]	Dunn's multiple comparison post-test	
CRP (mg/L), median [IQR]						
Tocilizumab 8 mg/kg (n=32)	103 [57.1, 143]	5.2 [2.8, 14.3]	-98	$p = 0.0005$	Toci. 8 mg/kg vs 400 mg	$p>0.99$
Tocilizumab 400 mg (n=40)	96.4 [64.4, 147]	6.8 [2.3, 29.1]	-84		Toci. 8 mg/kg vs Dex.	$p = 0.0014$
Dexamethasone control (n=35)	81.3 [56.9, 135]	48.0 [14.5, 85.1]	-22		Toci. 400 mg vs Dex.	$p = 0.0040$
Ferritin (ug/L), median [IQR]						
Tocilizumab 8 mg/kg (n=32)	919 [431, 2414]	700 [234, 1515]	-334	$p = 0.75$	Toci. 8 mg/kg vs 400 mg	$p>0.99$
Tocilizumab 400 mg (n=48)	1298 [649, 2701]	953 [542, 1887]	-265		Toci. 8 mg/kg vs Dex.	$p>0.99$
Dexamethasone control (n=35)	1126 [262, 1718]	760 [418, 1310]	-271		Toci. 400 mg vs Dex.	$p>0.99$
Lymphocyte count ($x10^9$/L), median [IQR]						
Tocilizumab 8 mg/kg (n=36)	0.8 [0.6, 1.0]	1.5 [0.8, 1.9]	0.4	$p = 0.11$	Toci. 8 mg/kg vs 400 mg	$p = 0.12$
Tocilizumab 400 mg (n=53)	0.7 [0.5, 1.0]	1.1 [0.7, 1.5]	0.2		Toci. 8 mg/kg vs Dex.	$p = 0.41$
Dexamethasone control (n=35)	0.8 [0.6, 1.2]	1.0 [0.7, 1.8]	0.3		Toci. 400 mg vs Dex.	$p>0.99$
PaO2/FiO2, median [IQR]						
Tocilizumab 8 mg/kg (n=32)	114 [79, 156]	141 [125, 218]	30	$p = 0.013$	Toci. 8 mg/kg vs 400 mg	$p>0.99$
Tocilizumab 400 mg (n=48)	105 [77, 149]	167 [127, 197]	61		Toci. 8 mg/kg vs Dex.	$p = 0.045$
Dexamethasone control (n=35)	142 [118, 200]	172 [114, 209]	-8		Toci. 400 mg vs Dex.	$p = 0.018$

***Table 3*: Comparison of paired CRP, ferritin, lymphocyte cell count, and the ratio of PaO_2:FiO_2 taken 5 days apart in critically ill COVID-19 patients given tocilizumab 8 mg/kg (maximum 800 mg), 400 mg, or dexamethasone alone.**

[a] Day 5 − Day 0 difference was calculated per participant per analyte; group median displayed.

[b] Median of differences was compared between the 3 groups using a Kruskal Wallis Test with a Dunn's Multiple Comparison test comparing each group to another.

Abbreviations: Dex., dexamethasone; toci, tocilizumab.

with the other half receiving no tocilizumab, as compared to 400 mg for all patients, has an incremental cost-effectiveness ratio of $53,263 CAD per life-year (Table 5). In a probabilistic sensitivity analysis at the same willingness-to-pay, 400 mg per patient of tocilizumab is cost-effective in 51.6% of 10,000 Monte Carlo simulations (Figure 2). The net monetary benefit with a 95% credible interval for the 400 mg and 8 mg/kg per patient strategies are $456,019 [392,785-517,183] and $454,873 [388,413-517,663], respectively (Table 5).

Discussion

Inhibition of IL-6, combined with corticosteroids, is one of the few interventions that reduces mortality in critically ill patients with COVID-19.[17] However, scarcity of tocilizumab is a chronic problem in many jurisdictions. This study adds to the evidence that lower dose tocilizumab may provide a sufficient therapeutic effect and nearly double the number of patients able to benefit from the intervention, and is the first study to examine cost-effectiveness in a Canadian setting. Following the publication of the REMAP-CAP trial in January 2021,[6] use of tocilizumab at our center rose dramatically, from 820 mg/month in Dec 2020, to a peak of 47,800 mg in the first week of April 2021. From April 9 and June 24, 2021 approximately 250,000 mg of tocilizumab were given to 624 patients with COVID-19 in the VGH ICU. Had the 8 mg/kg dosing been continued, the same amount of tocilizumab would have only treated 395 patients.

There was no significant difference in clinical outcomes such as 28-day mortality, all-cause in-hospital mortality, ICU or hospital length of stays based on the dose of tocilizumab used. Although there were numerically more patients who died by day 28 in the 400 mg cohort than the 8 mg/kg cohort (8% vs 5%), the sample size is small and the difference can be true or may have occurred by chance. The improvement in surrogate markers is reassuring. Both doses of tocilizumab caused a dramatic reduction in CRP of over 90% from baseline within 5 days of administration, as well as improvements in hyperferritinemia and lymphopenia. CRP fell by more than 90% in both tocilizumab groups but only by 41% in the dexamethasone alone group, illustrating the potent anti-inflammatory effect of IL-6 blockade. Similar differences between IL-6 blockade and corticosteroids on inflammatory markers have been observed by others,[18] and the dramatic decline in inflammatory markers occurs both with standard and lower dose tocilizumab.[10,19] Elevated IL-6 is an important biomarker of respiratory failure, ARDS, and mortality in COVID-19.[2,20] The present study provides solid evidence that IL-6 inhibition with 400 mg tocilizumab is associated with improvement in lung function, as measured by PaO_2/FIO_2 ratio, a finding that reinforces our early experience in the spring of 2020 as well as findings from other studies.[21]

IL-6 is unique among cytokines in having two signaling pathways − classic and trans.[22] Classic signaling occurs through membrane bound IL-6 receptor which is only found on immune cells (lymphocytes, macrophages, dendritic cells), liver and gut epithelium.[23] Other tissues, including those most affected by COVID-19 (lungs, heart, brain), rely on the trans signaling via

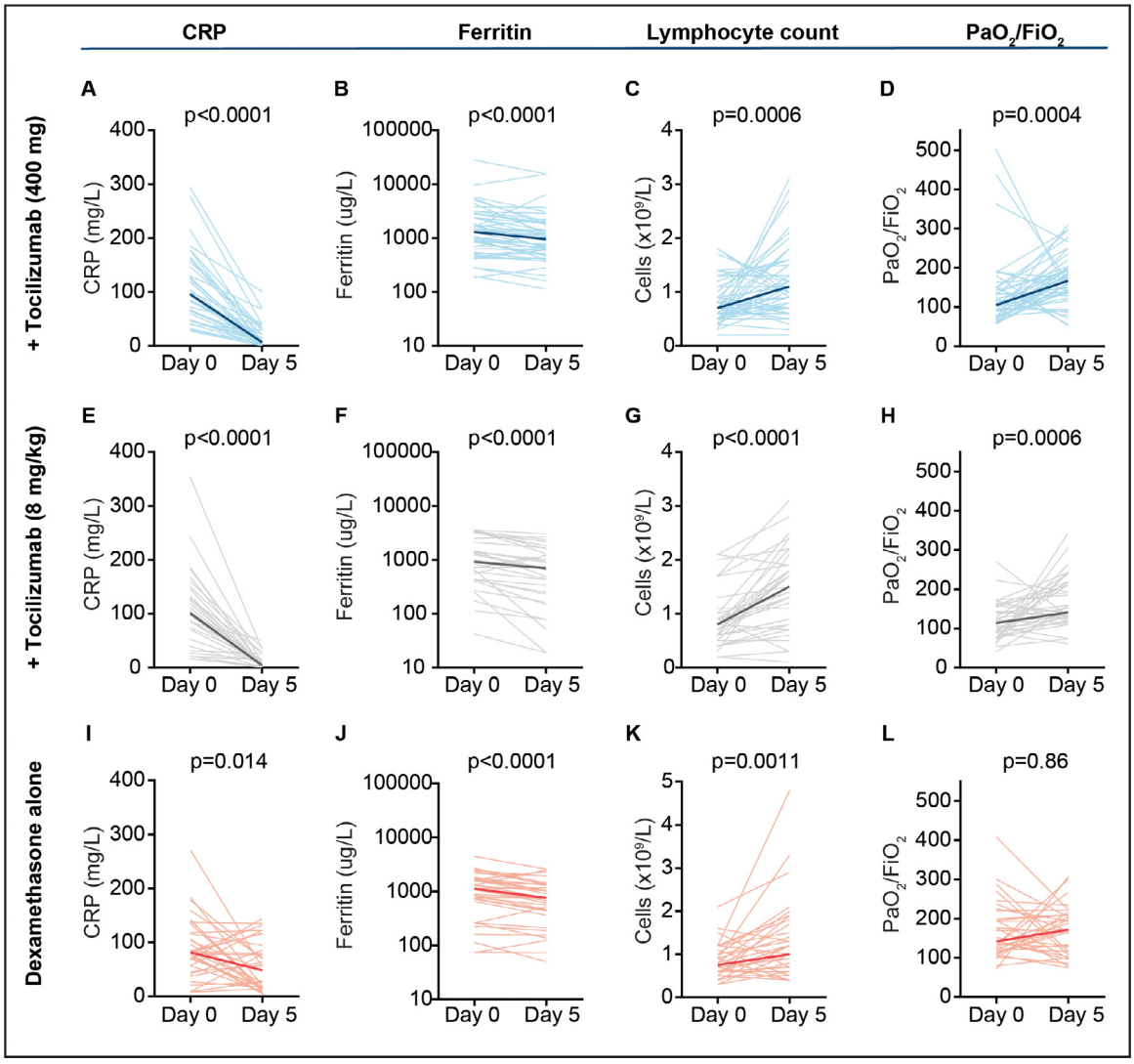

Figure 1. Longitudinal change in CRP, ferritin, lymphocyte cell count, and the ratio of PaO2:FiO2 in COVID-19 patients given dexamethasone alone or in conjunction with tocilizumab. Paired data was collected in the 6–24 h prior to tocilizumab administration (day 0) and then again a median of 5 days later (day 5) in COVID-19 patients given dexamethasone in combination with A–D) 400 mg IV fixed dose or E–H) 8 mg/kg (maximum 800 mg) of tocilizumab. I–L) Paired data taken upon admission to the ICU (day 0) and 5 days later (day 5) in patients given dexamethasone alone. Paired data was plotted and analyzed using a Wilcoxon signed rank test. Dark, thicker line in each panel represents group median values.

the soluble IL-6 receptor (sIL-6R) and its buffer, soluble glycoprotein 130 (sgp130).[22] Thus, the "bottleneck" for IL-6 signaling in COVID-19 is not IL-6 itself, but rather the sIL-6R and sgp130 buffer system. The concentration of IL-6 in the serum of patients with COVID-19 is typically modestly elevated, in the 20-200 pg/mL range, but this biomarker can be quite dynamic, often rising well over 1000 pg/mL.[3,21] Less data are available on sIL-6R in COVID-19, but some studies demonstrate a concentration of 40-60 ng/mL with a much more restricted range than IL-6.[24]

Pharmacological modelling studies have also argued that fixed dosing or lower doses than the 8 mg/kg dose may be reasonable. We based our initial decision to reduce the dose based on the high Cmax levels achieved by 400 mg. Previous studies in RA found that a free tocilizumab level of 1 μg/mL or higher is associated with binding and inactivation of more than 95% of sIL-6R molecules and perhaps more importantly, normalization of CRP.[25] This 1 μg/mL threshold may represent a desirable minimum concentration (Cmin) for serum tocilizumab levels in COVID-19 as well. This demonstrates that fixed dosing offers comparable anti-inflammatory effects to weight based dosing. Moreover, there are data that weight-based dosing of tocilizumab may risk over-exposure in patients with higher body mass.

	Tocilizumab 8 mg/kg (*n*=40)	Tocilizumab 400 mg (*n*=59)	Dexamethasone control (*n*=53)	Kruskal Wallis test[b]	*P*-values pair-wise comparisons[c]
ICU interventions and outcomes					
ICU interventions, n (%)					
Ventilated	19 (48)	29 (49)	32 (60)	–	>0.99/0.29/0.26
VV-ECMO[a]	2 (5)	4 (7)	0 (0)	–	>0.99/0.18/0.12
ARDS	18 (45)	28 (47)	23 (43)	–	0.84/>0.99/0.71
Shock	7 (18)	9 (15)	14 (26)	–	0.79/0.33/0.17
CRRT	3 (8)	2 (3)	5 (9)	–	0.39/>0.99/0.25
Prone	16 (40)	21 (36)	19 (36)	–	0.68/0.83/>0.99
iNO	9 (23)	13 (22)	7 (13)	–	>0.99/0.28/0.32
Paralysis	3 (8)	12 (20)	7 (13)	–	0.094/0.51/0.45
Outcomes					
Length of ventilation, days, median [IQR]	8 [4, 12]	6 [4, 17]	8.5 [4, 17]	$p = 0.94$	>0.99/>0.99/>0.99
Length of ICU stay, days, median [IQR]	6.5 [3, 14]	7 [3, 15]	7 [4, 14]	$p = 0.97$	>0.99/>0.99/>0.99
Hospital stay,days, median [IQR]	16 [10, 30]	17 [11, 29]	18 [11, 28]	$p = 0.99$	>0.99/>0.99/>0.99
28-day mortality, n (%)	2 (5)	5 (8)	7 (13)	–	0.70/0.29/0.54
Total mortality, n (%)	4 (10)	9 (15)	9 (17)	–	0.55/0.38/>0.99

***Table 4*: Comparison of ICU interventions and outcomes for COVID-19 patients given tocilizumab 8 mg/kg (maximum 800 mg), 400 mg tocilizumab or dexamethasone alone.**

[a] increasing use of ECMO over time in our institution was due largely to development of increased capacity rather than patient-specific factors.

[b] Continuous variables were compared using a Kruskal Wallis Test.

[c] pair wise comparison of 8mg/kg vs 400 mg toci / dex vs 8 mg/kg/ dex vs 400mg/. Categorical variables were analyzed using Fisher's Exact test; continuous variables were analyzed using Dunn's Multiple Comparison test that followed the group wise Kruskal Wallis Test.

Abbreviations: VV-ECMO, veno-venous extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; iNO, inhaled nitric oxide.

Clearance of tocilizumab does not correlate well with body weight as it is saturated at higher body weights due to non-linear elimination kinetics.[26] With 8 mg/kg dosing, there is a disproportionate increase in drug exposure in heavier patients based on area under the curve (AUC) measurements.[27] Compared to weight-based dosing, fixed dosing exhibits less variability in AUC measurements in patients weighing between 40 kg to 120 kg, even with the maximum dose of 800 mg.[27] However, it remains to be seen whether 400 mg fixed dosing is too low for patients with higher body mass; a recent pharmacokinetic modeling study found that the day 14 Cmin may be below 1 ug/mL in patients over 90 kg.[28]

In an American context, the standard 8 mg/kg dose of tocilizumab with dexamethasone, as compared dexamethasone alone, is cost-effective, with an incremental cost-effectiveness ratio (ICER) of US $26, 840 (95% credible interval $14,800-$101,030), well below one commonly accepted US willingness-to-pay threshold of US $100,000.[29] Examining the Canadian context where a limited tocilizumab supply is a reality, the use of 400 mg of tocilizumab for all patients produces similar net monetary benefits as that produced by treating half the patients with the 8 mg/kg dose of tocilizumab and the other half with no tocilizumab. The former strategy is also cost-effective, assuming a conservative Canadian willingness-to-pay of $50,000 CAD/life-year in just over 50% of simulations. Further, while the objective of traditional cost-effectiveness analysis is to maximize population health, it does not take into account the distribution of health inequalities that can be inherent to treatment strategy comparisons.[30] We believe the relative cost-effectiveness parity seen between the two treatment strategies, in addition to the crucial equitable consideration of being able to treat nearly twice the number of patients with some tocilizumab in the context of a compelling pharmacokinetic

Treatment strategy	Cost ($ CAD)	Life-years	ICER ($ CAD per life-year)	Net Monetary Benefit [95% Credible Interval] ($ CAD)
Tocilizumab 400 mg	226,265	13.65	–	456,019 [392,785-517,183]
Tocilizumab 8 mg/kg	244,907	14	53,263	454,872 [388,413-517,663]

***Table 5*: Baseline cost-effectiveness and probabilistic sensitivity analysis. Treatment strategies examined are 400 mg fixed dose tocilizumab (all patients) versus 8mg/kg tocilizumab (half the patients) in the context of limited tocilizumab supply.**

Abbreviations: CAD, Canadian dollar; ICER, incremental cost-effectiveness ratio.

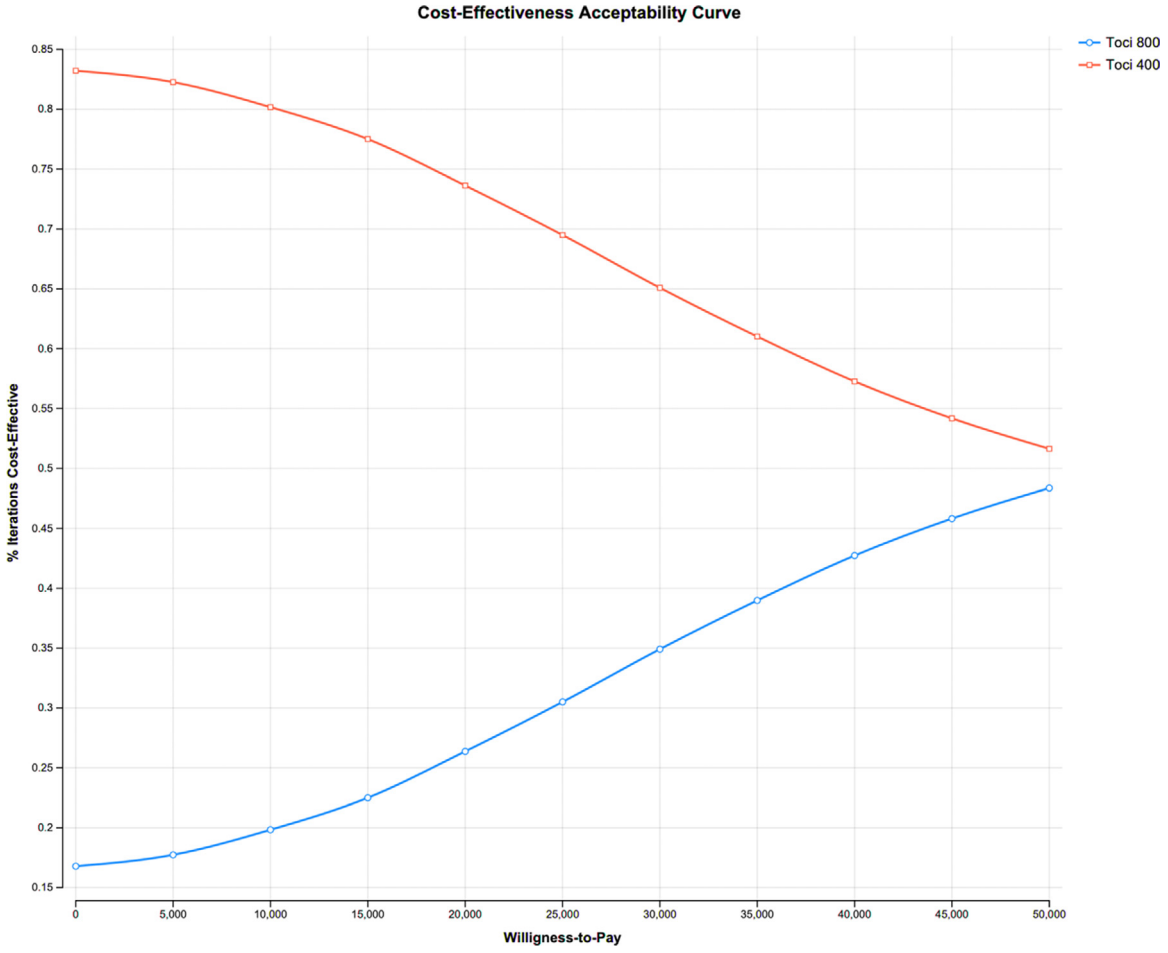

Figure 2. Cost-effectiveness acceptability curve. At a willingness-to-pay of $50,000 CAD, tocilizumab 400 mg per patient is favored in 51.6% of 10,000 Monte Carlo simulations.

mechanism, are of particular importance as repeat surges continue in this pandemic.

This study has a number of limitations. Although most baseline characteristics were similar between the two groups and standard of care remained similar in the two time periods studied, other confounders such as COVID-19 variants and other treatments or supportive care practices may have impacted outcomes in this small, non-randomized study. The 8 mg/kg tocilizumab group did have a higher LDH at baseline than the 400 mg group and elevated LDH is an adverse prognostic marker. We did not have a defined or standardized post-drug period and laboratory testing was done primarily for clinical care rather than for research purposes. However, we used objective outcomes and included consecutive patients. Despite these limitations, this study provides an important insight into immunomodulatory therapy in severe COVID-19. In an unprecedented pandemic that is rapidly evolving, observational data are contributing 'real time' understanding of the optimal dose of IL-6 inhibition.

Conclusion

In the context of ongoing shortages, 400 mg fixed dose tocilizumab represents a possible means to extending the supply of life-saving medication for severe COVID-19 and providing benefit to a larger number of patients.

Contributors

Sophie Stukas and Luke Chen conceptualized the study. Sophie Stukas and Rebecca Grey curated the data and performed initial data analysis. Mypinder Sekhon, Cheryl Wellington and Luke Chen acquired funding and provided study materials. George Goshua conducted the pharmacoeconomic analysis. All authors were involved in data collection and writing the original draft. All authors reviewed, edited and approved the final version of the manuscript.

Data sharing statement

De-identified clinical and laboratory data are available upon request.

Declaration of interests

None.

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Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100228.

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