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A comparison of the effectiveness of different doses of tocilizumab and sarilumab in the treatment of severe COVID-19: a natural experiment due to drug shortages☆

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ABSTRACT

Objectives: Interleukin (IL)-6 inhibitors are administered to treat patients hospitalized with COVID-19. In 2021, due to shortages, different dosing regimens of tocilizumab, and a switch to sarilumab, were consecutively implemented. Using real-world data, we compare the effectiveness of these IL-6 inhibitors.
Methods: Hospitalized patients with COVID-19, treated with IL-6 inhibitors, were included in this natural experiment study. Sixty-day survival, hospital- and intensive care unit (ICU) length of stay, and progression to ICU or death were compared between 8 mg/kg tocilizumab, fixed-dose tocilizumab, low-dose tocilizumab, and fixed-dose sarilumab treatment groups.
Results: A total of 5485 patients from 49 hospitals were included. After correction for confounding, increased hazard ratios (HRs) for 60-day mortality were observed for fixed-dose tocilizumab (HR 1.20, 95% confidence interval [CI] 1.04-1.39), low-dose tocilizumab (HR 1.12, 95% CI 0.97-1.31), and sarilumab (HR 1.24, 95% CI 1.08-1.42), all relative to 8 mg/kg. The 8 mg/kg dosing regimen had lower odds of progression to ICU or death. Both hospital- and ICU length of stay were shorter for low-dose tocilizumab than for the 8 mg/kg group.
Conclusion: We found differences in the probability of 60-day survival and the incidence of the combined outcome of mortality or ICU admission, mostly favoring 8 mg/kg tocilizumab. Because of potential time-associated residual confounding, further clinical studies are warranted.

Introduction

The efficacy of dexamethasone in patients with COVID-19 who need supplemental oxygen supports the notion that in severely ill patients, pulmonary damage is caused by an uncontrolled systemic inflammatory response [1,2]. Subsequently, interleukin(IL)-6 –a proinflammatory cytokine–was found to be associated with

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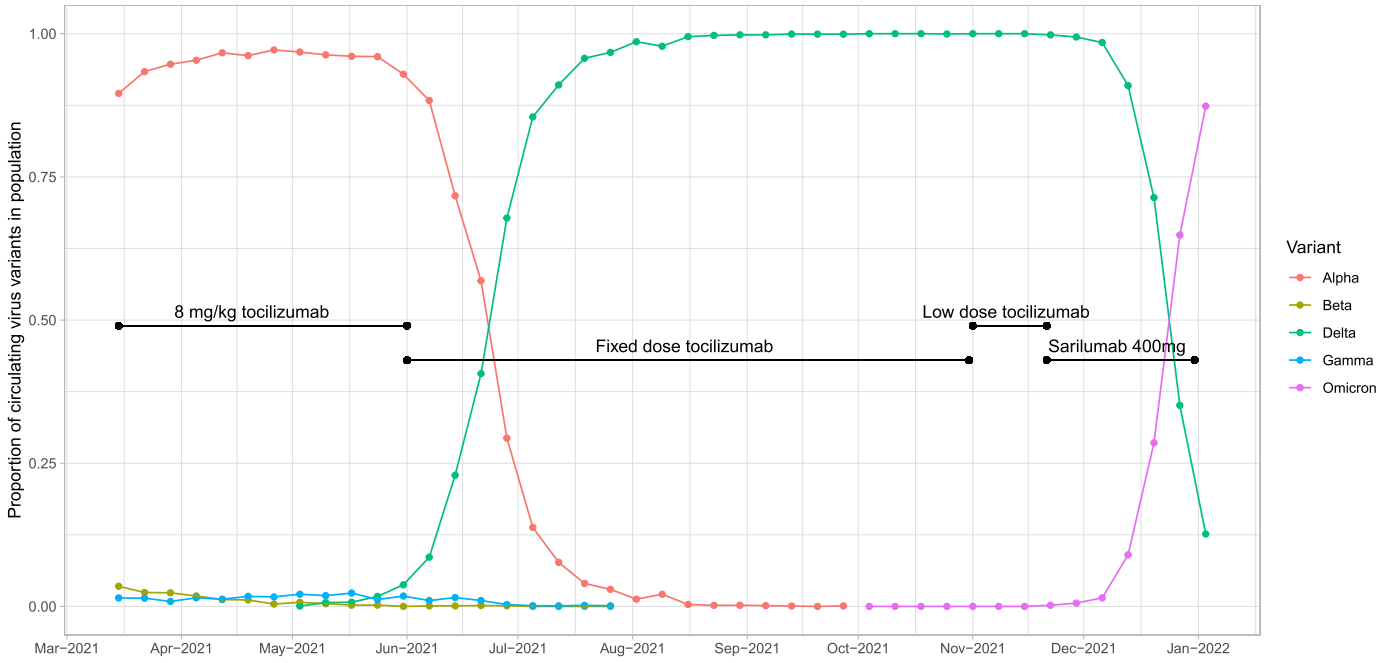

Figure 1. Proportion of different SARS-CoV-2 variants and the recommended interleukin-6 inhibitor during the study period in The Netherlands, using publicly available data from the National Institute for Public Health and the Environment [19]. The different interleukin-6 inhibitor treatment periods were added to this information.

worse outcomes in hospitalized patients [2–4]. Shortly thereafter, several large randomized controlled trials (RCTs) showed that addition of an IL-6 inhibitor reduced in-hospital mortality and the need for invasive mechanical ventilation in severely ill patients [2,3,5]. From the beginning of 2021 onwards, Dutch national guidelines recommended that patients hospitalized with COVID-19 are to be treated with 8 mg/kg tocilizumab if they need ≥6 liters/minute of supplemental oxygen and have a serum C-reactive protein value of ≥75 mg/l (7.5 mg/dl) [6].

Before global implementation of IL-6 inhibition as additional medical treatment for severe COVID-19, no dose-finding studies were performed.

Due to the increased use caused by the ongoing pandemic, many countries had to deal with shortages of IL-6 inhibitors [4,7]. Due to these shortages, the recommended treatment in the Netherlands was altered several times. These adaptations involved the switch from an 8 mg/kg-based to a weight-based or fixed-dose recommendation, then to tocilizumab 400 mg, and finally to sarilumab 400 mg (see Figure 1) [5,8–11]. A comparison of survival between patients treated with the different IL-6 inhibitor regimens has not yet been performed.

Natural experiments (sometimes called quasi-randomized trials) are an efficient way to study real-world data and can provide information on causal relationships, with effect sizes similar to those found in RCTs [12]. In natural experiments, the treatment is not allocated by the researcher and ideally unrelated to confounding factors, under the assumption of the absence of secular trends in patients or pathogen characteristics [12]. Concealment of treatment allocation, preventing physicians' preferences when deciding on treatments, is one of the purposes of randomization. Since treatment with either 8 mg/kg doses tocilizumab, fixed-dose tocilizumab, low-dose tocilizumab or sarilumab was determined only by the moment of hospitalization, this approximates randomization of the different treatment groups.

Using real-world data, we aimed to compare outcomes between patients hospitalized with COVID-19 who were treated with different IL-6 inhibitors and different dosing regimens driven by drug shortages in The Netherlands.

Methods

Study population

Patients aged ≥18 years, who were hospitalized for COVID-19 and received intravenous treatment with tocilizumab or sarilumab between March 15, 2021, up to and including December 31, 2021, were eligible for inclusion. Patients who received treatment with an IL-6 inhibitor for a disease other than COVID-19 were excluded from the analyses.

Outcome measures

The primary outcome measure was survival time. Secondary outcome measures were survival time in the intensive care unit (ICU) admitted subpopulation, reaching a combined outcome of ICU admission or mortality, and duration of ICU and hospital admission.

Data

Data were retrieved by LOGEX (LOGEX BV, Amsterdam, The Netherlands), a Dutch healthcare data company, in collaboration with LCG (National Medicines Coordination Centre). Administrative healthcare data, containing information on a set of baseline characteristics, diagnosis, treatment, and other care activities are routinely submitted to LOGEX and these data were re-used for the present analysis. For this study, pseudonymized data from patients with a diagnosis of COVID-19 who were hospitalized between March 2021 up to and including December 2021 were collected. Data from 49 of 71 Dutch hospitals were available and subsequently included. Details on the calculation of hospital- and ICU length of stay (LOS) can be found in the Supplementary information. The datasets analyzed are not publicly available.

Summary variables

A modified Charlson Comorbidity Index (CCI) was used to summarize comorbidities [13]. Only the comorbidities were included

that were registered in the hospital for which a patient was admitted for COVID-19 and that were registered in the past 3 years. Therefore, the CCI serves as a proxy parameter for the comorbidity of patients in this study. With the available data the immune status was determined as follows. A patient was considered to be immunocompromised if any of the following conditions were met: organ transplant, bone marrow or stem cell transplantation (autologous or allogeneic), recent (<6 months) treatment for malignant hematologic disease, including chemotherapy and chimeric antigen receptor T-cell therapy; cancer therapy for all solid tumors in the last 3 months, including chemotherapy and immune checkpoint inhibitors, and patients treated with immunosuppressive drugs, including B-cell depleting drugs or lymphopenia-inducing medication. No data on chronic corticosteroid use (before hospitalization) were available.

Allocation of treatment

The treatment groups were formed based on the guideline recommendations that were applicable at the time, see Figure 1. The first regimen, from March 15th, 2021 to May 31st, 2021, was 8 mg/kg tocilizumab, max 800 mg (group called "8 mg/kg"). The second regimen, from June 2021 to November 2021, was weight-based dosing [5], or a fixed dose of 600 mg. Weight-based dosing in the second regimen consisted of four groups: 800 mg tocilizumab if weight was >90kg, 600 mg tocilizumab if weight was >65 and ≤90 kg, 400 mg tocilizumab if weight was >40 and ≤65 kg and 8 mg/kg tocilizumab if weight was <40 kg (group called "Fixed-dose tocilizumab"). The third regimen, low-dose tocilizumab consisted of a 400mg fixed-dose of tocilizumab and starting November 2021 (group called "Low-dose tocilizumab"). After 3 weeks, due to persisting shortages, sarilumab 400 mg was advised, and formed the final group in our analysis (group called "Sarilumab 400 mg"), see Figure 1. To account for variation, a 100 mg range was used for all fixed doses. Patients who received a dose that did not fit one of these groups were excluded from the analysis. Bodyweight was not available for any of the patients in our database. Only the first dose of IL-6 inhibitors was studied.

Statistical analyses

Medians and interquartile ranges were used to describe continuous variables. Categorical variables were summarized as frequency and percentage. 95% confidence intervals were calculated. We corrected for relevant differences in baseline characteristics [14]. First, to compare survival, several analyses were performed. A Kaplan–Meier survival analysis was done to compare the unadjusted survival between the treatment groups using a log-rank test. Next, a multivariable Cox proportional hazards analysis was performed, determining the difference in survival between the different treatment groups when correcting for age, sex, immunocompromised status and CCI. A sensitivity analysis including only ICU-admitted patients was performed. Second, a Cox proportional hazard analysis was performed to determine the effect of the allocation to different treatment groups on the combined outcome of mortality or ICU admission. Events were counted from at least 24 hours after the IL-6 inhibitor was administered and the HR was corrected for age, sex, immunocompromised status, and CCI. Finally, a linear regression analysis was done to analyze the effect of different treatment groups on the ICU- and hospital LOS, after correction for age, sex, CCI, and immunocompromised status.

To avoid informative censoring, patients who were known to have survived and still had any activity (e.g., hospital visit) registered after hospital discharge were assumed to have survived until the end of follow-up at day 60. If patients did not die during hospital admission but had no activities registered after admission either, their outcome was set to missing. Finally, a linear regression analysis was done to analyze the effect of the different treatment groups on the ICU LOS and hospital LOS, after correction for age, sex, and CCI.

An extreme cases analysis was performed for the people with missing outcomes. In the all-died setting, all patients with missing outcomes were assumed to have died on the day of hospital discharge. In the all-alive setting, all patients with missing outcomes were assumed to have survived until the end of follow-up. Information on patients who had two separate COVID-19 hospital admission can be found in the Supplementary material.

Given the competing outcomes for ICU and hospital LOS—patients who die may have a shorter stay than patients who survive—a sensitivity analysis was done only including patients who survived. To account for missing outcome data, a second sensitivity analysis for the Cox proportional hazards analysis was performed in which missing outcome and survival time data were imputed using multivariate imputation by chained equations (mice). Outcome was imputed using logistic regression and survival time was imputed using predictive mean matching. A total of 10 multiple imputation rounds were performed, and the pooled results were used to repeat the Cox proportional hazard analysis using the same predictor variables as in the main analysis.

HRs from the Cox proportional hazard model and unadjusted survival probabilities were used to calculate the time specific number needed to treat (NNT), which is the number of patients that need to be treated to have one additional patient survive at a specific time point [15]. The mg/kg group was used as the reference group for these calculations.

All statistical analyses were performed using R Statistical Software (version 3.6.1).

Ethics

This study was approved by the Institutional Review Board of the Leiden University Medical Center for observational COVID-19 studies and performed according to Dutch legislation on studies with clinical data.

Results

During the study period, 5485 patients met the inclusion criteria. A total of 168 (3.0%) patients received a dose that did not fit within our prespecified groups and were excluded. Data were complete for most variables. No outcome was registered in 10.1% of patients. A total of 19.2% had an incomplete registration of hospital and/or ICU LOS. Out of hospital (after discharge) all-cause mortality was 1.4%.

Demographics

Patients in the 8 mg/kg and fixed-dose group were slightly younger than the low-dose tocilizumab and sarilumab groups (Table 1). Most deaths occurred in the sarilumab and low-dose tocilizumab group. From the patients who died, the 8 mg/kg group had the ICU as location of death more often than the other groups. Total in-hospital mortality was 26.7%.

Survival analyses

The Kaplan–Meier survival curves per dosing group can be found in the Supplementary file (Supplementary Figure 1). After adjustment for confounders, the 8 mg/kg group showed a better survival than fixed-dose tocilizumab and sarilumab groups, but not than the low-dose tocilizumab (Table 2 and Supplementary Figure

Table 1
Characteristics and outcomes of patients treated with IL-6 inhibitors.

Dosing group		8 mg/kg (n = 2212)	Fixed-dose tocilizumab (n = 1196)	Low-dose tocilizumab 400 mg (n = 843)	Sarilumab 400 mg (n = 1234)
Patient characteristics					
Sex (%)	Men	1394 (63.0)	741 (62.0)	552 (65.5)	812 (65.8)
	Women	818 (37.0)	455 (38.0)	291 (34.5)	422 (34.2)
Age group, years (%)	18-29	18 (0.81)	25 (2.1)	7 (0.8)	12 (1.0)
	30-39	61 (2.76)	79 (6.6)	31 (3.7)	51 (4.1)
	40-49	172 (7.8)	152 (12.7)	56 (6.6)	81 (6.6)
	50-59	524 (23.7)	238 (19.9)	126 (15.0)	206 (16.7)
	60-69	653 (29.49)	261 (21.8)	198 (23.5)	294 (23.8)
	70-79	628 (28.36)	273 (22.8)	277 (32.9)	363 (29.4)
	80+	156 (7.05)	168 (14.1)	148 (17.6)	227 (18.4)
Charlson Comorbidity Index, median (IQR)		0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)	0.0 (0.0 to 2.0)	0.0 (0.0 to 2.0)
Immunocompromised (%)		60 (2.7)	43 (3.6)	32 (3.8)	45 (3.7)
Outcomes					
ICU admission (%)		1272 (57.5)	619 (51.8)	337 (40.0)	548 (44.4)
ICU length of stay, median (IQR)		8.0 (4.0 to 17.0)	7.0 (4.0 to 15.0)	8.0 (3.0 to 14.0)	8.0 (4.0 to 15.0)
Hospital length of stay, median (IQR)		13.0 (8.0 to 22.0)	12.0 (8.0 to 20.0)	11.0 (6.0 to 18.0)	11.0 (7.0 to 18.0)
Location of death (%)	Ward	305 (60.2)	233 (75.2)	197 (77.3)	308 (78.8)
	ICU	202 (39.8)	77 (24.8)	58 (22.8)	83 (21.2)
Outcome (%)	Death	507 (22.9)	310 (25.9)	255 (30.3)	391 (31.7)
	Alive	1563 (70.6)	722 (60.4)	478 (56.7)	705 (57.1)
	Missing	142 (6.4)	164 (13.7)	110 (13.1)	138 (11.2)

ICU, intensive care unit; IQR, interquartile range. For definition of dosing groups: see methods section.

Table 2
Multivariable Cox proportional hazards regression analysis with 60-day mortality as endpoint, correcting for age, sex, immunocompromised status, and Charlson Comorbidity Index, including all patients with a known outcome.

Group	Hazard ratio (95% confidence interval)
8 mg/kg	1
Fixed-dose tocilizumab	1.20 (1.04 to 1.39)
Low-dose tocilizumab	1.12 (0.97 to 1.31)
Sarilumab 400 mg	1.24 (1.08 to 1.42)

Table 3
Multivariable Cox proportional hazards regression analysis with 60-day mortality as endpoint, correcting for age, sex, immunocompromised status, and the Charlson Comorbidity Index, with imputed data.

Group	Hazard ratio (95% confidence interval)
8 mg/kg	1
Fixed-dose tocilizumab	1.28 (1.14 to 1.44)
Low-dose tocilizumab	1.18 (1.03 to 1.34)
Sarilumab 400 mg	1.25 (1.11 to 1.39)

2). In a second Cox proportional hazards analysis including imputed outcome and survival time values for patients with missing data, the 8 mg/kg group has improved survival when compared with the other three groups (Table 3).

The first extreme cases sensitivity analysis, in which all patients with an unknown outcome were assumed to have survived until the end of follow-up at day 60, showed no differences in survival between the 8 mg/kg group and the fixed-dose and low-dose group, but survival was slightly improved for the 8 mg/kg group compared to the sarilumab group (Supplementary Table 1). In the extreme case analysis in which all patients with an unknown outcome were assumed to have died on the day of discharge, survival was worse for all three groups than for the 8 mg/kg group (Supplementary Table 2).

When only patients who were admitted to the ICU during their hospital admission were included in the analysis, a difference in the unadjusted analysis was found between the different treatment groups: the 8 mg/kg and fixed-dose groups had a better survival than the low-dose and sarilumab groups (Supplementary Figure 3). After correction for confounding, the 8 mg/kg group showed better survival at day 60 than the sarilumab group, but no difference was found with the other two groups (Supplementary Table 3). With imputed data for missing outcome and survival time variables, similar results were found (Supplementary Table 4).

Table 4
Cox proportional hazard analysis with admission to the intensive care unit or mortality as the outcome variable, correcting for age, sex, immunocompromised status, and the Charlson Comorbidity Index.

Group	Hazard ratio (95% confidence interval)
8 mg/kg	1
Fixed-dose tocilizumab	1.24 (1.09 to 1.42)
Low-dose tocilizumab	1.41 (1.22 to 1.63)
Sarilumab 400 mg	1.43 (1.26 to 1.63)

NNT

The unadjusted survival probability for the 8 mg/kg group at day 60 was 0.75. Combined with the HRs from Table 2, the NNT was calculated (for calculations, see Supplementary file). When comparing 8 mg/kg to the fixed-dose tocilizumab group, the NNT was 24, meaning that treating 24 patients with an 8 mg/kg dosing regimen instead of the fixed-dose group would prevent one death at day 60. i.e., when treating 1000 patients with the 8 mg/kg instead of a fixed dose, an additional 42 patients would be saved. When comparing 8 mg/kg to low-dose tocilizumab, the NNT was 39, and 20 when comparing the 8 mg/kg group to the sarilumab group.

Combined outcome

We compared progression to the combined outcome of ICU admission or mortality between the different treatment groups. After correcting for confounders, the hazards for reaching the combined outcome were significantly higher for patients who received fixed-dose tocilizumab, low-dose tocilizumab or sarilumab compared with tocilizumab in an 8 mg/kg dosing regimen (Table 4).

Length of hospital stay

The total hospital stay was shorter in low-dose tocilizumab and sarilumab than the 8 mg/kg group, after correction for confounding (Supplementary Table 5). This effect remained when the analysis was restricted to patients who survived (Supplementary Table 6) or those with a complete hospital LOS (Supplementary Methods and Supplementary Table 7). As a post hoc analysis, we plotted the median hospital LOS and the number of admissions over time (Supplementary Figure 4). A total of 90 patients had two separate COVID-19-related hospital admissions, with less than 90 days between the two admissions. For the main analysis, the period in between hospitalization was included in the hospital LOS, assuming they were transferred to another hospital. Given that this might not be the case for everyone, we randomly sampled 25%, 50%, and 75% of these 90 patients and only used the duration of their first hospital admission as the LOS. The results were similar, with a shorter hospital admission for patients receiving low-dose tocilizumab and sarilumab compared with the 8 mg/kg group (Supplementary Tables 8, 9, and 10). After correction for confounding, ICU LOS was shorter for the low-dose tocilizumab group compared with the 8 mg/kg group (Supplementary Table 11). When restricting to patients who survived (Supplementary Table 12) or those with complete LOS data (Supplementary Table 13), no differences were found.

Discussion

We found that in hospitalized patients with COVID-19, those treated with tocilizumab with an 8 mg/kg dosing regimen had a survival benefit if compared to fixed-dose tocilizumab and sarilumab. While there is no significant difference between 8 mg/kg and low-dose tocilizumab, the hazard rate estimate was similar to the hazard rate estimate for fixed-dose and sarilumab. In a subset of ICU-admitted patients, the 8 mg/kg group also had an improved survival at 60 days compared with the sarilumab group, but not to the other tocilizumab dosing groups. Those receiving 8 mg/kg tocilizumab had a lower risk of progressing to the combined outcome of ICU admission or death than the other three treatment groups. ICU LOS was shorter for low-dose tocilizumab than for the 8 mg/kg group. Hospital LOS was longest in the 8 mg/kg and fixed-dose groups.

At present, comparisons between the different doses of tocilizumab and/ or sarilumab in patients with COVID-19 have mostly been made between separate studies. A 2021 meta-analysis, including over 3000 patients and 6500 controls from 33 different trials compared different doses of tocilizumab between studies. This study found a lower mortality in the 8 mg/kg tocilizumab group compared with controls, but not in the 400 mg, 400-800 mg, or <400 mg tocilizumab groups or sarilumab [16]. In addition, a phase-II RCT comparing 4 mg/kg and 8 mg/kg tocilizumab found a trend toward higher mortality at day 28 in the 4 mg/kg group, although no formal analysis was performed given the small sample size [17]. Several studies have focused on ICU-admitted patients. The REMAP-CAP trial compared 8 mg/kg tocilizumab with 400 mg sarilumab and standard of care, and both IL-6 inhibitors were found to improve survival compared with standard of care [2]. No direct comparison of sarilumab and tocilizumab was performed.

Study strengths and limitations

The study has several strengths. First, real-world data based on health insurance claims reflect the heterogeneity of patients and make our findings generalizable. Second, the large number of patients in our study meant that all treatment groups had a sufficient number of patients to make meaningful comparisons with other groups and perform sensitivity analyses. Even though the change in recommended dosing was driven by drug shortages, there are no known cases where patients did not receive any treatment with IL-6 inhibitors because of these shortages. Finally, while important, setting up an RCT to compare these different treatments would be expensive and time consuming, and a natural experiment is an efficient way to determine the effect of different treatments and doses of IL-6 inhibitors in patients with COVID-19.

Our study has several weaknesses, mostly related to the use of real-world data. Even though the point in time of COVID-19 infection is mostly random, there are several factors that might have an influence, like sex, age, and social economic status. While we were able to correct some of them, we did not have data on all potential confounders that could have influenced the timing of SARS-CoV-2 infection. Second, it was not possible to differentiate between weight-based dosing and 600 mg fixed-dose tocilizumab in our data, hence we combined those two groups, even though, ideally, we would combine 8 mg/kg and weight-based dosing (which are almost identical) and compare with 600mg fixed-dose tocilizumab. For patients who weigh 75 kg or more, a fixed-dose of 600 mg tocilizumab would lead to <8 mg/kg, which could explain the differences between the 8 mg/kg and fixed-dose groups.

We found no evidence for a dose-response relationship, as the hazard rates for mortality did not increase with decreasing doses. This may have been influenced by other factors that influence our outcome measures and changed during the course of our study, like the case-mix, the vaccination coverage and the dominant strain. While the case-mix may have changed during the pandemic, we were able to adjust for some potential differences. No data on vaccination status was available, and this could lead to an underestimation of our results, as the increased vaccination coverage during the course of 2021 will have protected against mortality. Patients were not systematically tested for specific virus strains, but the Alpha strain is thought to lead to increased ICU admission and in-hospital mortality compared to the delta strain, both in vaccinated and unvaccinated patients [18]. Similar to the increased vaccination coverage, the decreased mortality of the Delta variant compared to Alpha could lead to underestimation of our results.

NNT considerations

Because we cannot estimate a NNT comparing 8 mg/kg tocilizumab to placebo from our data, we use data from the RECOVERY trial [5], with a NNT of 25. This means that if 1000 patients are treated with tocilizumab 8 mg/kg instead of placebo, approximately 40 additional lives would be saved. In times of drug shortages, there are different options. If 500 treatments are available for a population of 1000 people, and 500 of them are given the 8 mg/kg dose, an additional 20 lives would be saved. Between 1.5 and twice as many patients could likely be treated with a low-dose tocilizumab compared with 8 mg/kg, meaning that those 500 treatments can be used to treat 750-1000 patients with low-dose tocilizumab. However, on average an additional 1 in 39 would die by choosing a low-dose instead of 8 mg/kg, leading to 11-14 lives saved in this population (30 to 40 by giving them 8 mg/kg tocilizumab instead of placebo, minus 19 to 26 because of the low-dose), as opposed to the 20 lives saved when 500 people are treated with 8 mg/kg. However, there may be other (ethical) considerations, such as equal distribution of medication

We found that in the complete hospital population, sarilumab, low-dose tocilizumab, and fixed-dose tocilizumab led to worse survival compared to the 8 mg/kg group. The 8 mg/kg would therefore be the first-choice treatment option. In case of ongoing drug shortages using fixed-dose or low-dose tocilizumab to treat more patients should be considered with caution. Defining protocols for

additional patient selection criteria to reduce the number of patients who receive tocilizumab could be an alternative approach when anticipating shortages.

Declaration of competing interest

LMvdT is chair of the working group COVID-19 treatment for the Dutch Federation of Medical Specialists (FMS). MGJdB is chair of the Dutch Working Party on Antibiotic Policy and chair of the COVID-19 treatment guideline committee in the Netherlands. All other authors declare no conflicts of interest.

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Ethical approval

This study was approved by the Institutional Review Board of the Leiden University Medical Center for observational COVID-19 studies and performed according to Dutch legislation on studies with clinical data.

Author contributions

MCS, RJM, DH, NH, GHG and MGJdB conceived the study. FK, WEMB and RdV prepared the data. MCS did the analyses and wrote the first draft of the manuscript. All authors contributed to interpretation of the results and provided feedback on the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.01.041.

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