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Canakinumab in patients with COVID-19 and type 2 diabetes — A multicentre, randomised, double-blind, placebo-controlled trial

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Summary

Background Patients with type 2 diabetes and obesity have chronic activation of the innate immune system possibly contributing to the higher risk of hyperinflammatory response to SARS-CoV2 and severe COVID-19 observed in this population. We tested whether interleukin-1β (IL-1β) blockade using canakinumab improves clinical outcome.

Methods CanCovDia was a multicenter, randomised, double-blind, placebo-controlled trial to assess the efficacy of canakinumab plus standard-of-care compared with placebo plus standard-of-care in patients with type 2 diabetes and a BMI > 25 kg/m² hospitalised with SARS-CoV2 infection in seven tertiary-hospitals in Switzerland. Patients were randomly assigned 1:1 to a single intravenous dose of canakinumab (body weight adapted dose of 450-750 mg) or placebo. Canakinumab and placebo were compared based on an unmatched win-ratio approach based on length of survival, ventilation, ICU stay and hospitalization at day 29. This study is registered with ClinicalTrials.gov, NCT04510493.

Findings Between October 17, 2020, and May 12, 2021, 116 patients were randomly assigned with 58 in each group. One participant dropped out in each group for the primary analysis. At the time of randomization, 85 patients (74·6 %) were treated with dexamethasone. The win-ratio of canakinumab vs placebo was 1·08 (95 % CI 0·69-1·69; p = 0·72). During four weeks, in the canakinumab vs placebo group 4 (7·0%) vs 7 (12·3%) participants died, 11 (20·0 %) vs 16 (28·1%) patients were on ICU, 12 (23·5 %) vs 11 (21·6%) were hospitalised for more than 3 weeks, respectively. Median ventilation time at four weeks in the canakinumab vs placebo group was 10 [IQR 6.0, 16.5] and 16 days [IQR 14.0, 23.0], respectively. There was no statistically significant difference in HbA1c after four weeks despite a lower number of anti-diabetes drug administered in patients treated with canakinumab. Finally, high-sensitive CRP and IL-6 was lowered by canakinumab. Serious adverse events were reported in 13 patients (11·4%) in each group.

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Interpretation In patients with type 2 diabetes who were hospitalised with COVID-19, treatment with canakinumab in addition to standard-of-care did not result in a statistically significant improvement of the primary composite outcome. Patients treated with canakinumab required significantly less anti-diabetes drugs to achieve similar glycaemic control. Canakinumab was associated with a prolonged reduction of systemic inflammation.

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Keywords: COVID-19; Diabetes; Obesitiy; IL-1beta; Inflammasome

Research in context

Evidence before this study

We searched PubMed 1 June 2020 for studies about COVID19 and IL1 antagonism. Search terms included "COVID19"[All Fields] OR "Sars-CoV2"[All Fields]) AND "anakinra"[All Fields]) OR "canakinumab"[All Fields] OR "IL1 antagonist"[All Fields]).

Several prospective studies have shown beneficial cardiovascular effects of IL1 antagonism in patients with and without diabetes and cardiovascular diseases. A meta-analysis found improvements of glycemic parameters using IL1 antagonists. However, no clinical data using IL1 antagonists in patients with COVID19 were published so far.

Added value of this study

The study did not show an improvement on the clinical course with canakinumab in addition of standard of care of patients with type 2 diabetes and overweight who were hospitalized with COVID19, but the study gives rise to beneficial effects of canakinumab on glucose control despite usage of dexamethasone reflected by a lower need for diabetes-medication including insulin.

Implications of all the available evidence

Future studies should further evaluate the effects of IL-1 antagonism on glucose control and complications of type 2 diabetes.

Introduction

Patients with type 2 diabetes and obesity infected with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV2) have a significantly increased risk for a severe clinical course and increased mortality.[1–5] Conversely, infection with SARS-CoV2 is associated with new onset or worsening of diabetes.[6,7] These associations may be due to the ability of both, metabolic stress and SARS-CoV2 to activate common signalling pathways including IL-1 driven inflammation.

Obesity associated type 2 diabetes is characterized by a low-grade chronic inflammation. Indeed, metabolic stress due to increased concentrations of glucose, fatty acids, cholesterol and uric acid activate the innate immune system. This is partly due to an inflammasome-mediated over-activation of the IL-1 system.[8–12] This over-activity impairs insulin secretion and sensitivity,[12–16] contributing to cardiovascular diseases[17] and heart failure.[18] Accordingly, IL-1 antagonism has been demonstrated to improve glycaemia,[19–25] cardiovascular complications,[17,26] and to reduce hospitalization for heart failure and heart failure-related mortality.[27–31] The latter is of potential importance in the context of corona virus disease 2019 (COVID-19), because patients with type 2 diabetes per se are at high risk to develop heart failure with a high mortality rate.[32]

IL-1 has also been suggested to contribute to the complications of SARS-CoV2. Several studies have shown that the corona virus activates the NLRP3 inflammasome leading to a severe inflammatory response driven by the IL-1β pathway.[33,34] Clinical studies of IL-1 antagonism have generated mixed results, but overall showed a beneficial effect.[35–42] Thus, the IL-1 receptor antagonist anakinra was recently authorized by the European Medicine Agency for the treatment of COVID-19,[43] while the indication for canakinumab remains limited to rare diseases.[44]

Based on the available information, we hypothesized that blockade of IL-1β using canakinumab may have beneficial effects on both, COVID-19 morbidity and diabetes.

Methods

Study Design

CanCovDia was a multicentre, 1:1 randomised, double-blind, placebo-controlled trial to evaluate the effects of treatment with canakinumab plus standard-of-care

29 days after randomization in overweight patients with type 2 diabetes hospitalised with COVID-19.

Patients were recruited in seven hospitals across Switzerland. CanCovDia was an investigator-initiated trial and was performed in accordance with the protocol, which was approved by the local ethics committees at each site (EKNZ 2020-02008), and the statistical plan (both available in appendix). There was a slight deviation from the protocol: blood samples could not always be drawn after eight hours of overnight fast at day 2.

Patients

Eligible patients were at least 18 years of age, overweight (body mass index (BMI) > 25 kg/m^2), hospitalised with laboratory confirmed SARS-CoV2 infection since at most six days, and had a known diagnosis of type 2 diabetes. Key exclusion criteria were suspected or known untreated active bacterial, fungal, viral, or parasitic infection and treatment with immunomodulators. Of note, corticosteroids (any route of administration) such as dexamethasone as well as anti-viral treatment such as remdesivir were permitted as part of the standard-of-care for COVID-19 according to national recommendations, which were regularly adapted during the study period. In addition, patients were allowed to be randomised in the WHO Solidarity trial[45] at the same time.

Randomisation and masking

Individuals who met the eligibility criteria were randomly assigned within two days after enrolment to either placebo or canakinumab in a 1:1 manner. The randomization list was prepared by an independent scientist at the University Hospital Basel who was not part of the study conduct. The randomization was performed in blocks sizes of two and four with simple sequential allocation without stratifying factors. Investigators used an electronic online trial database for randomization of each participant and informed the local pharmacy about the unique patient randomization number and weight for adjusting the dose of canakinumab. On-site study personnel were unaware of the treatment assignments.

Procedures

Patients were treated either with placebo (250 ml of 5% glucose) or with canakinumab in a single 250 ml of 5% glucose intravenous infusion over two hours. The canakinumab dose was adapted to the body weight of each patient: 450 mg for body weight of 40–59 kg, 600 mg for 60–79 kg, or 750 mg for >80 kg. At day 29, data for primary outcome, clinical/functional status, vital signs, concomitant medication, adverse events, and blood samples, were collected. Patients were followed for an additional observational period of 60 days during which functional status, vital signs, concomitant medication, adverse events, and blood samples were collected.

Outcomes

Primary outcome was the unmatched win-ratio determined by the ordered components: 1) longer survival time, 2) longer ventilation-free time, 3) longer intensive care unit (ICU)-free time, 4) shorter hospitalization time within 29 days after treatment with canakinumab as compared to placebo.

First secondary outcome was time to clinical improvement up to four weeks, defined as the time from randomization to either discharge from the hospital or an improvement of two points on a seven-category ordinal scale, whichever came first. The ordinal scale consisted of the following categories[46]: 1, not hospitalised with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6, hospitalized, requiring extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, or both; and 7, death.

Further predefined exploratory outcomes were death rate, admission to ICU, and secondary worsening of disease (i.e., development of acute respiratory distress syndrome, increase of oxygen demand after 72h of treatment) within 29 days after randomization, as well as prolonged hospital stay for more than three weeks. Ratio to baseline was evaluated for glycated haemoglobin A1c (HbA1c), C-reactive protein (CRP), natriuretic peptide (NTproBNP), and estimated glomerular filtration rate (eGFR) at day 29 and three months as well as for fasting glucose, fasting insulin, D-Dimer, IL-6, IL-18, and ferritin at day 29 for both groups.

In addition, type and number of anti-diabetes treatments as well as subjective function was measured by functional scale (5 levels of limitations in daily life activities, from "no" to "severe limitations") as published elsewhere[47] at day 29 and three months and compared between placebo and canakinumab.

Safety outcomes included adverse events of common terminology criteria for adverse events category (CTCAE) Grade 3 and higher during study drug administration and throughout the study period and were reported during drug administration, at day 29 and three months after randomization.

Statistical analysis

All analyses were conducted with the statistical software package R (R Core Team, 2021; http://www.r-project.org/index.html), using "two-sided" statistical tests and confidence intervals with standard significance and

confidence levels $\alpha = 5\%$ and $(100\% - \alpha) = 95\%$, respectively. The p-values and confidence intervals of the secondary and subgroup analyses must be interpreted with particular care, since no correction for multiple testing was applied. Categorical data are presented as absolute and relative frequencies, while numerical variables are presented as median and interquartile range.

Canakinumab and placebo were compared on the basis of the unmatched win-ratio approach.[48] First, every patient in the canakinumab arm was compared with every patient in the placebo arm. For each comparison of two patients, the winner was determined by the first component of the primary endpoint in which the two patients were known to differ (up to four weeks after study treatment): 1. longer survival time, 2. shorter ventilation time, 3. shorter ICU time, 4. shorter hospitalisation time. The win-ratio (WR) was estimated by dividing the number of patients in which canakinumab won with the number of patients in which placebo won. Confidence intervals and p-values were obtained from the normal approximation of the log-win-ratio, as described elsewhere.[48] Missing data were handled by considering the components of the primary endpoint as non-informatively censored on the last observation date.

Time to clinical improvement was compared between the two study arms by univariable Cox regression, while the binary (or ordinal) and the other continuous secondary endpoints by univariable (ordinal) logistic regressions and univariable log-linear regressions, respectively, with missing values handled by available-case analyses. Results are presented as hazard ratios (HR), odds ratios (OR), and geometric mean ratios (GMR), respectively, with the corresponding 95% confidence intervals (95%CI). The primary analysis was repeated in several subgroups and subgroup-treatment interaction tests were performed as tests for the variance of the log-win-ratio. All statistical analyses were performed on the full analysis set according to the intention-to-treat principle (i.e. all patients were analysed on the basis of the intervention to which they were randomly allocated), except for a supplementary analysis of the primary endpoint performed on the per protocol set to assess the robustness of the results with regard to protocol violations.

Sample size was estimated with the aim of showing the superiority (as regards to the win-ratio primary outcome) of treatment with canakinumab vs. placebo at a significance level 5%, on the basis of the following assumptions (based on preliminary observational data collected during the first months of the pandemic): within four weeks after randomization, of the patients in the placebo group: 20–% die, 10% do not die, but need ventilation, 10% neither die nor need ventilation, but are admitted to ICU, 10% neither die, need ventilation nor are admitted to ICU, but are hospitalized the whole time, the relative treatment effect is the same on each of the above four proportions, times are exponentially distributed. Disregarding potential dropouts, a total of $n = 112$ patients was estimated to need to be recruited (56 in each study group) in order to reach a power of 80% when the relative treatment effect is = 0.5 (i.e. when each of the above four proportions is halved in the treatment group).

Role of the funding source

The Swiss National Science Foundation and the University of Basel provided financial support. Novartis provided the study drug (canakinumab). The funding sources were not involved in the trial design, conduct or the analysis of the study. All co-authors had access to the dataset. The decision to submit the manuscript for publication was made jointly by all co-authors.

Results

From October 17, 2020, through May 12, 2021, 452 patients were screened, and 116 patients were randomly assigned in a 1:1 ratio to treatments (Figure 1). The full analysis set consists of the 114 patients (57 in each group) who were randomized, gave written informed consent, and started the treatment. Two patients in the canakinumab group withdrew consent after the infusion, so that at day 29 (primary endpoint) the placebo and canakinumab group had 57 and 55 patients, respectively. In the follow-up period three patients in the placebo group withdrew consent or were lost to follow-up. For the per protocol analysis, one patient in each group was removed due to erroneous tocilizumab infusions and another patient received only half a dose of placebo as the patient suddenly decided to interrupt the treatment.

Baseline characteristics (described in Table 1) were balanced between groups including age, BMI, diabetes duration, complications, baseline diabetes medication, COVID-19-related symptoms and steroid treatment except for a lower kidney function, increased levels of ferritin and soluble urokinase plasminogen activator receptor (suPAR) in the canakinumab compared to the placebo group (Table 1). Median age was 71 (IQR 62-78) years, and 36 patients (31·6 %) were female. Median diabetes duration was 9 (IQR 3-16) years and median HbA1c 7·6 % (IQR 6·7-8·8). In 56 patients (49·1 %) diabetes-related complications were known with diabetic nephropathy and coronary heart disease being the most common complications in 25 (21·9 %) patients, respectively. Median BMI was 30·8 (IQR 28-35) kg/m^2. Median time interval between diagnosis of COVID-19 and hospitalisation was 4 (IQR 2-8) days. Seventy-five patients (65·8 %) required nasal or high-flow oxygen and 11 patients (9·6 %) were mechanically ventilated. At the time of randomization, 85 patients (74·6 %) were

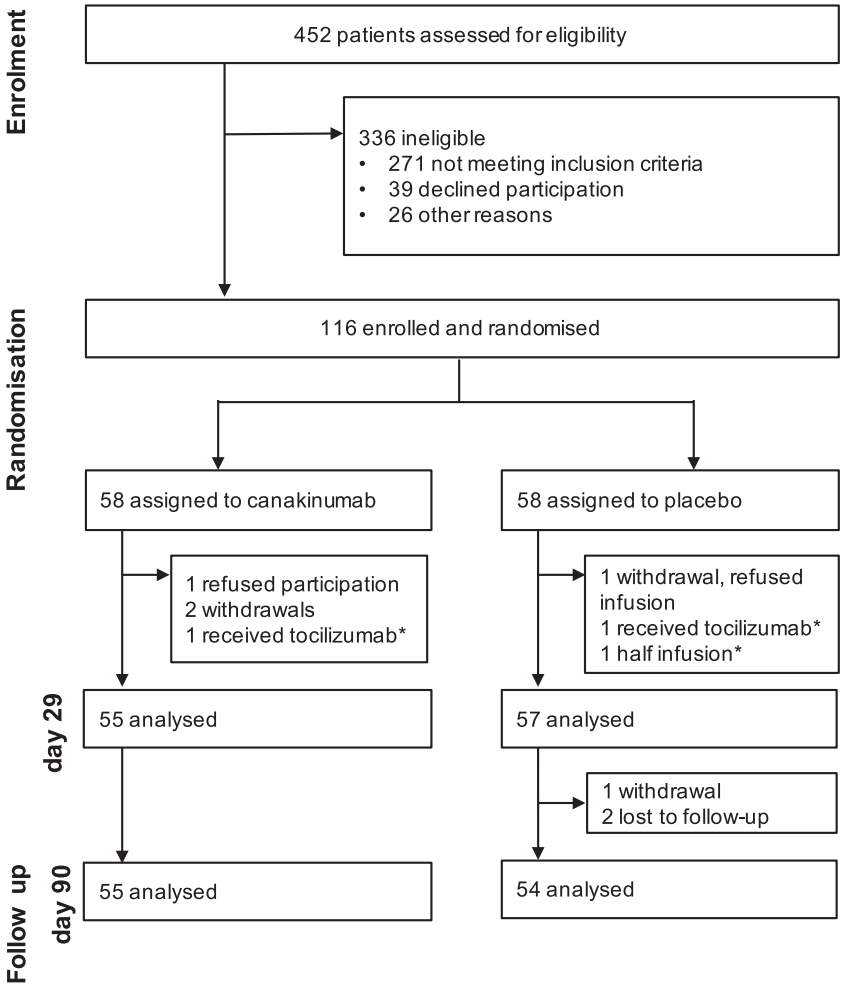

Figure 1. Trial profile. Patients included in the full analysis data set. Asterisk indicates patients that were excluded from the per protocol analysis.

	Overall	Missing	Canakinumab	Placebo
n	114	%	57	57
Sex = female	36 (31·6)	0	19 (33·3)	17 (29·8)
Age (years)	71·00 [62·00, 78·00]	0	72·00 [63·00, 79·00]	69·00 [61·00, 76·00]
Time since diabetes diagnosis (years)	9·00 [3·00, 16·00]	5·3	10·00 [4·00, 18·00]	7·50 [2·75, 13·00]
Diabetes-related complications	56 (49·1)	0	32 (56·1)	24 (42·1)
Retinopathy	10 (8·8)	0	8 (14·0)	2 (3·5)
Nephropathy	25 (21·9)	0	12 (21·1)	13 (22·8)
Neuropathy	16 (14·0)	0	10 (17·5)	6 (10·5)
Stroke	5 (4·4)	0	3 (5·3)	2 (3·5)
Coronary heart disease	25 (21·9)	0	14 (24·6)	11 (19·3)
Peripheral arterial disease	4 (3·5)	0	3 (5·3)	1 (1·8)
Other	5 (4·4)	0	3 (5·3)	2 (3·5)
Time since COVID-19 diagnosis (days)	4·00 [2·00, 8·00]	0	3·00 [2·00, 8·00]	4·00 [2·00, 7·00]
Smoker		0		
Never smoked	56 (49·1)		27 (47·4)	29 (50·9)
Ex-smoker	51 (44·7)		27 (47·4)	24 (42·1)
Active smoker	7 (6·1)		3 (5·3)	4 (7·0)

Table 1 *(Continued)*

	Overall	Missing	Canakinumab	Placebo
Weight (kg)	90·90 [80·58, 101·40]	0	88·00 [80·10, 101·40]	93·00 [82·00, 101·40]
BMI (kg/m^2)	30·80 [28·00, 35·10]	0	31·20 [27·70, 34·70]	30·70 [28·80, 35·90]
Respiratory support		0		
No	28 (24·6)		11 (19·3)	17 (29·8)
Yes, oxygen	75 (65·8)		40 (70·2)	35 (61·4)
Yes, invasive ventilation	11 (9·6)		6 (10·5)	5 (8·8)
•Oxygen (l/min)	4·00 [2·00, 6·00]	36	3·00 [2·00, 5·25]	4·00 [2·00, 6·00]
•FiO2 (%)	55·00 [35·00, 62·50]	90·4	40·00 [35·00, 60·00]	55·00 [55·00, 60·00]
Systolic blood pressure (mmHg)	126·00 [115·00, 142·75]	0	127·00 [115·00, 140·00]	125·00 [113·00, 146·00]
Diastolic blood pressure (mmHg)	73·00 [66·25, 81·00]	0	73·00 [68·00, 78·00]	72·00 [65·00, 83·00]
Heart rate (beats/min)	77·00 [68·25, 87·00]	0	76·00 [70·00, 85·00]	77·00 [67·00, 88·00]
Biguanide (metformin)	61 (53·5)	0	25 (43·9)	36 (63·2)
DPP-4-Inhibitor	25 (21·9)	0	13 (22·8)	12 (21·1)
SGLT2-Inhibitor	20 (17·5)	0	9 (15·8)	11 (19·3)
GLP-1-Analoga	11 (9·6)	0	5 (8·8)	6 (10·5)
Sulfonylurea	13 (11·4)	0	5 (8·8)	8 (14·0)
Glitazon	1 (0·9)	0	0 (0·0)	1 (1·8)
None	37 (32·5)	0	22 (38·6)	15 (26·3)
Basal insulin	48 (42·1)	0	26 (45·6)	22 (38·6)
•Dose last 24h (international units)	23·00 [12·00, 50·00]	57·9	30·00 [16·00, 49·75]	20·00 [12·00, 47·50]
Prandial insulin	74 (64·9)	0	36 (63·2)	38 (66·7)
•Cumulative dose last 24h (international units)	16·00 [8·00, 29·50]	35·1	15·00 [8·00, 27·00]	17·50 [8·00, 30·62]
Antihypertensive	76 (66·7)	0	38 (66·7)	38 (66·7)
Analgesic	62 (54·4)	0	27 (47·4)	35 (61·4)
Antibiotic	38 (33·3)	0	21 (36·8)	17 (29·8)
Antiviral	25 (21·9)	0	13 (22·8)	12 (21·1)
Antimycotic	2 (1·8)	0	1 (1·8)	1 (1·8)
Anticoagulant	44 (38·6)	0	25 (43·9)	19 (33·3)
Thrombosis prophylaxis	79 (69·3)	0	37 (64·9)	42 (73·7)
Antiepileptic	7 (6·1)	0	4 (7·0)	3 (5·3)
Psychiatric drug	24 (21·1)	0	11 (19·3)	13 (22·8)
Sedative	23 (20·2)	0	9 (15·8)	14 (24·6)
Catecholamine	10 (8·8)	0	7 (12·3)	3 (5·3)
Corticosteroids	85 (74·6)	0	41 (71·9)	44 (77·2)
HbA1c (%)	7·60 [6·70, 8·80]	0·9	7·60 [6·70, 8·83]	7·70 [6·70, 8·70]
Glucose (mmol/L)	8·10 [6·60, 10·90]	0·9	8·10 [6·55, 10·40]	8·30 [6·80, 11·40]
Insulin (pmol/L)	61·18 [37·07, 163·49]	0·9	56·74 [28·86, 162·11]	63·34 [41·59, 180·28]
Creatinine (µmol/l)	82·50 [70·25, 120·00]	0	95·00 [74·00, 135·00]	79·00 [66·00, 95·00]
Estimated GFR (CKD-EPI, ml/min/1·73m^2)	71·00 [48·00, 91·00]	0	60·00 [42·00, 82·00]	82·00 [61·00, 96·00]
NT-proBNP (ng/L)	466·00 [158·25, 1292·00]	0	569·00 [168·00, 1289·00]	339·00 [128·00, 1304·00]
Ferritin (µg/L)	786·00 [448·75, 1325·00]	1·8	611·00 [413·00, 1157·00]	1089·00 [543·00, 1450·00]
D-Dimer (mg/l)	0·90 [0·58, 1·44]	1·8	1·03 [0·64, 1·59]	0·81 [0·58, 1·37]
CRP (mg/l)	59·20 [30·10, 110·60]	0	67·00 [33·00, 117·00]	57·70 [26·50, 85·20]
IL-18 (pg/ml)	629·00 [369·00, 893·00]	0·9	645·50 [393·75, 918·50]	611·00 [327·00, 877·00]
IL-6 (pg/ml)	8·08 [2·96, 23·66]	0·9	9·96 [3·59, 33·48]	7·27 [2·72, 18·56]
IL-1Ra (pg/ml)	938·00 [510·00, 1603·00]	0·9	1078·00 [613·25, 1684·50]	680·00 [423·00, 1318·00]
suPAR (ng/ml)	7·44 [5·23, 10·40]	1·8	8·19 [5·92, 11·97]	7·07 [4·86, 9·42]

***Table 1*: Baseline characteristics of the patients in the full analysis set by study arm.** Categorical data are given as absolute frequencies (%), numerical variables as median with [interquartile range]. Missing values are ignored, but the proportion of missing values is reported for each variable. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin A1c; GFR, glomerular filtration rate; ICU, intensive care unit; NT-proBNP, N-terminal pro-B-type *natriuretic* peptide; SGLT2, sodium-glucose like transporter 2.

treated with dexamethasone [canakinumab 41 (71 9%), placebo 44 (77 2%)] and 25 patients (21·9 %) received antiviral treatment with remdesivir [canakinumab 13 (22 8 %), placebo 12 (21 1 %)] as part of the standard-of-care.

The primary endpoint, the win-ratio of canakinumab vs. placebo using the full analysis set was 1.08 (95% CI 0·69, 1·69, p = 0·722) (Figure 2A). This result was similar using the per protocol set (win-ratio 1.08, 95% CI 0·68, 1·69, p = 0·752, s. appendix).

After 29 days, four people had died (7·0 %) at age between 58-90 years in the canakinumab vs. seven (12·3 %) at age between 65-86 years in the placebo group. In the canakinumab study arm, there were ten patients with ventilation (median 10 days, IQR [6, 16.5]), whereas in the placebo group, there were 13 patients

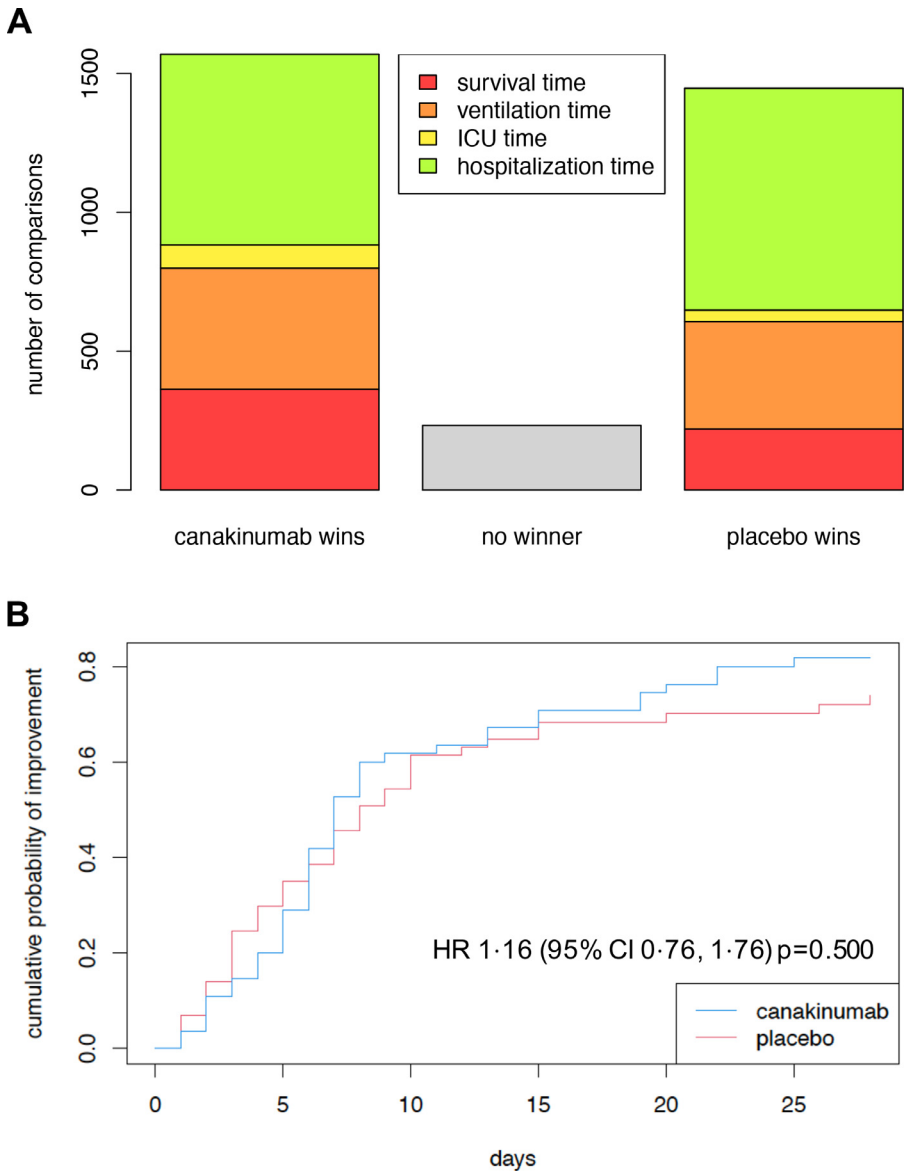

Figure 2. A) Primary outcome. Results of all comparisons between canakinumab and placebo patients in the full analysis set (only the comparisons without winner with respect to a component of the primary endpoint are considered further with respect to the next component of the primary endpoint). Canakinumab wins 1569 vs. placebo wins 1447 and no winner 233. Thus, win-ratio of canakinumab vs placebo with regard to the primary endpoint is 1·08, with 95% CI (0·69, 1·69). **B)** Kaplan-Meier plot for cumulative probability of clinical improvement until day 29.

with ventilation (median 16 days IQR [14, 23]. Of note, in the placebo group there were three patients ventilated for more than 28 days. In the canakinumab group 11 patients were in the ICU (20·0%) after 29 days vs 16 patients (28·1%) in the placebo group. After canakinumab treatment, 12 patients were hospitalized for more than three weeks (23·5%) vs. 11 (21·6%) in the placebo group.

Cox regression analysis of the cumulative probability of clinical improvement until day 29 according to the seven-category ordinal scale did not show a statistically significant difference between canakinumab or placebo (HR 1.16 (95%CI 0.76, 1.76), p = 0.500, Figure 2B). Clinical improvement of patients did not differ in patients treated with canakinumab compared to placebo after 29 days (OR 0·94 (0·45, 1·96), p = 0·873) and three

	Canakinumab	Placebo	Treatment effect (95%CI) (*p*-value)
Seven-category ordinal scale at 4 weeks			0·94 (0·45, 1·96) (*p*=0·873)
not hospitalized, normal activities	33 (60·0)	35 (61·4)	
not hospitalized, no normal activities	9 (16·4)	7 (12·3)	
hospitalized, no oxygen	4 (7·3)	2 (3·5)	
hospitalized, oxygen	2 (3·6)	2 (3·5)	
hospitalized, noninvasive ventilation	1 (1·8)	1 (1·8)	
hospitalized, invasive ventilation	2 (3·6)	3 (5·3)	
dead	4 (7·3)	7 (12·3)	
Seven-category ordinal scale at 3 months			0·80 (0·36, 1·75) (*p*=0·576)
not hospitalized, normal activities	38 (69·1)	35 (64·8)	
not hospitalized, no normal activities	10 (18·2)	10 (18·5)	
hospitalized, no oxygen	2 (3·6)	1 (1·9)	
hospitalized, oxygen	0 (0·0)	1 (1·9)	
hospitalized, noninvasive ventilation	0 (0·0)	0 (0·0)	
hospitalized, invasive ventilation	0 (0·0)	0 (0·0)	
dead	5 (9·1)	7 (13·0)	
Subjective function at 4 weeks			1·30 (0·64, 2·65) (*p*=0·473)
no limitations	7 (14·0)	13 (26·0)	
negligible limitations	22 (44·0)	17 (34·0)	
occasional limitations	6 (12·0)	6 (12·0)	
important limitations	6 (12·0)	4 (8·0)	
severe limitations	9 (18·0)	10 (20·0)	
Subjective function at 3 months			0·97 (0·47, 2·02) (*p*=0·940)
no limitations	21 (42·0)	20 (41·7)	
negligible limitations	17 (34·0)	16 (33·3)	
occasional limitations	6 (12·0)	6 (12·5)	
important limitations	4 (8·0)	4 (8·3)	
severe limitations	2 (4·0)	2 (4·2)	
death at 4 weeks	4 (7·0)	7 (12·3)	0·54 (0·13, 1·90) (*p*=0·347)
ICU during first 4 weeks	11 (20·0)	16 (28·1)	0·64 (0·26, 1·53) (*p*=0·320)
More than 3 weeks in hospital	12 (23·5)	11 (21·6)	1·12 (0·44, 2·87) (*p*=0·813)
Loss of taste or smell at 4 weeks	7 (14·9)	7 (15·2)	0·98 (0·31, 3·10) (*p*=0·965)
Number of anti-diabetes treatments at 4 weeks			0·48 (0·23, 0·98) (*p*=0·046)
0	17 (33·3)	11 (21·6)	
1	19 (37·3)	16 (31·4)	
2	12 (23·5)	16 (31·4)	
3	3 (5·9)	8 (15·7)	
Number of anti-diabetes treatments at 3 months			0·54 (0·26, 1·11) (*p*=0·094)
0	11 (21·6)	9 (18·8)	
1	24 (47·1)	15 (31·2)	
2	12 (23·5)	15 (31·2)	
3	4 (7·8)	9 (18·8)	
			0·47 (0·23, 0·95) (*p*=0·037)

Table 2 *(Continued)*

	Canakinumab	Placebo	Treatment effect (95%CI) (*p*-value)
Number of anti-diabetes treatments including basal and prandial insulin at 4 weeks			
0	8 (15·7)	4 (8·0)	
1	18 (35·3)	14 (28·0)	
2	15 (29·4)	12 (24·0)	
3	7 (13·7)	15 (30·0)	
4	3 (5·9)	5 (10·0)	
Number of anti-diabetes treatments including basal and prandial insulin at 3 months			0·70 (0·34, 1·43) (*p*=0·327)
0	5 (10·0)	7 (14·6)	
1	16 (32·0)	11 (22·9)	
2	17 (34·0)	11 (22·9)	
3	9 (18·0)	12 (25·0)	
4	2 (4·0)	6 (12·5)	
5	1 (2·0)	1 (2·1)	
Biguanide (metformin) at 4 weeks	22 (40·0)	34 (59·6)	0·45 (0·21, 0·95) (*p*=0·039)
Biguanide (metformin) at 3 months	25 (48·1)	34 (65·4)	0·49 (0·22, 1·07) (*p*=0·077)
DPP-4-Inhibitor at 4 weeks	12 (21·8)	10 (17·5)	1·31 (0·51, 3·40) (*p*=0·570)
DPP-4-Inhibitor at 3 months	13 (25·0)	10 (19·2)	1·40 (0·55, 3·63) (*p*=0·479)
SGLT2-Inhibitor at 4 weeks	12 (21·8)	16 (28·1)	0·72 (0·30, 1·69) (*p*=0·446)
SGLT2-Inhibitor at 3 months	13 (25·0)	16 (30·8)	0·75 (0·31, 1·77) (*p*=0·512)
GLP-1-Analoga at 4 weeks	5 (9·1)	8 (14·0)	0·61 (0·17, 1·97) (*p*=0·417)
GLP-1-Analoga at 3 months	8 (15·4)	7 (13·5)	1·17 (0·39, 3·60) (*p*=0·780)
Sulfonylurea at 4 weeks	1 (1·8)	4 (7·0)	0·25 (0·01, 1·73) (*p*=0·216)
Sulfonylurea at 3 months	1 (1·9)	5 (9·6)	0·18 (0·01, 1·20) (*p*=0·129)
Ratio to baseline of HbA1c (%) at 4 weeks	0·93 (0·85, 1·00)	0·96 (0·88, 1·03)	0·98 (0·93, 1·03) (*p*=0·431)
Ratio to baseline of HbA1c (%) at 3 months	0·91 (0·84, 0·96)	0·91 (0·83, 0·97)	1·00 (0·94, 1·06) (*p*=0·926)
Ratio to baseline of Glucose (mmol/L) at 4 weeks	0·90 (0·63, 1·10)	0·93 (0·74, 1·28)	0·88 (0·74, 1·06) (*p*=0·170)
Ratio to baseline of Insulin (pmol/L) at 4 weeks	0·94 (0·59, 1·66)	0·64 (0·29, 1·44)	2·21 (1·09, 4·48) (*p*=0·029)
Ratio to baseline of CRP (mg/l) at 4 weeks	0·05 (0·02, 0·14)	0·10 (0·03, 0·30)	0·47 (0·27, 0·82) (*p*=0·009)
Ratio to baseline of CRP (mg/l) at 3 months	0·03 (0·01, 0·09)	0·05 (0·02, 0·15)	0·50 (0·27, 0·92) (*p*=0·027)
Ratio to baseline of D-Dimer (µg/mL) at 4 weeks	0·87 (0·55, 1·58)	0·93 (0·62, 1·45)	0·94 (0·55, 1·62) (*p*=0·821)
Ratio to baseline of NT-proBNP (ng/L) at 4 weeks	0·45 (0·20, 0·90)	0·48 (0·23, 0·96)	1·00 (0·66, 1·52) (*p*=0·990)
Ratio to baseline of NT-proBNP (ng/L) at 3 months	0·41 (0·17, 0·77)	0·35 (0·22, 0·66)	0·99 (0·68, 1·42) (*p*=0·935)
Ratio to baseline of Estimated GFR (CDK-EPI, ml/min/1·73m^2) at 4 weeks	1·00 (0·91, 1·16)	1·00 (0·94, 1·08)	0·95 (0·82, 1·09) (*p*=0·450)
Ratio to baseline of Estimated GFR (CDK-EPI, ml/min/1·73m^2) at 3 months	0·96 (0·88, 1·11)	0·99 (0·92, 1·15)	0·87 (0·74, 1·02) (*p*=0·076)
Ratio to baseline of IL-6 (pg/ml) at 4 weeks	0·35 (0·06, 0·87)	0·77 (0·30, 2·61)	0·28 (0·11, 0·68) (*p*=0·005)
Ratio to baseline of IL-18 (pg/ml) at 4 weeks	0·66 (0·50, 0·74)	0·61 (0·51, 0·90)	1·00 (0·83, 1·20) (*p*=0·979)
Ratio to baseline of Ferritin (µg/L) at 4 weeks	0·32 (0·18, 0·49)	0·30 (0·17, 0·42)	1·27 (0·90, 1·78) (*p*=0·167)

***Table 2*: Secondary outcomes. Categorical data are reported as absolute frequencies (%), numerical variables as median [interquartile range]. The treatment effect is described as odds ratio for the ordinal logistic regressions (odds of worse category) and logistic regressions (odds of negative event): that is, an odds ratio less than 1 corresponds to an advantage of canakinumab over placebo. For the log-linear regressions, the treatment effect is multiplicative: that is, an effect less than 1 means that the ratio to baseline is lower for canakinumab than placebo.**

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin A1c; GFR, glomerular filtration rate; ICU, intensive care unit; NT-proBNP, N-terminal pro-B-type *natriuretic* peptide; SGLT2, sodium-glucose like transporter 2.

months (OR 0·80 (0·36, 1·75), p = 0·576). Subjective function of patients did not differ in patients treated with canakinumab compared to placebo after 29 days (OR 1.30 (0.64, 2.65), p = 0·473) and three months (OR 0·97 (0·47, 2·02), p = 0·940) (Table 2).

Win-ratio analysis was also performed for several subgroups as outlined in Figure 3. Patients with an eGFR (CKD-EPI ml/min/1.73m^2) rate below the median 71 at baseline showed almost significant benefit from the canakinumab treatment compared to placebo (WR

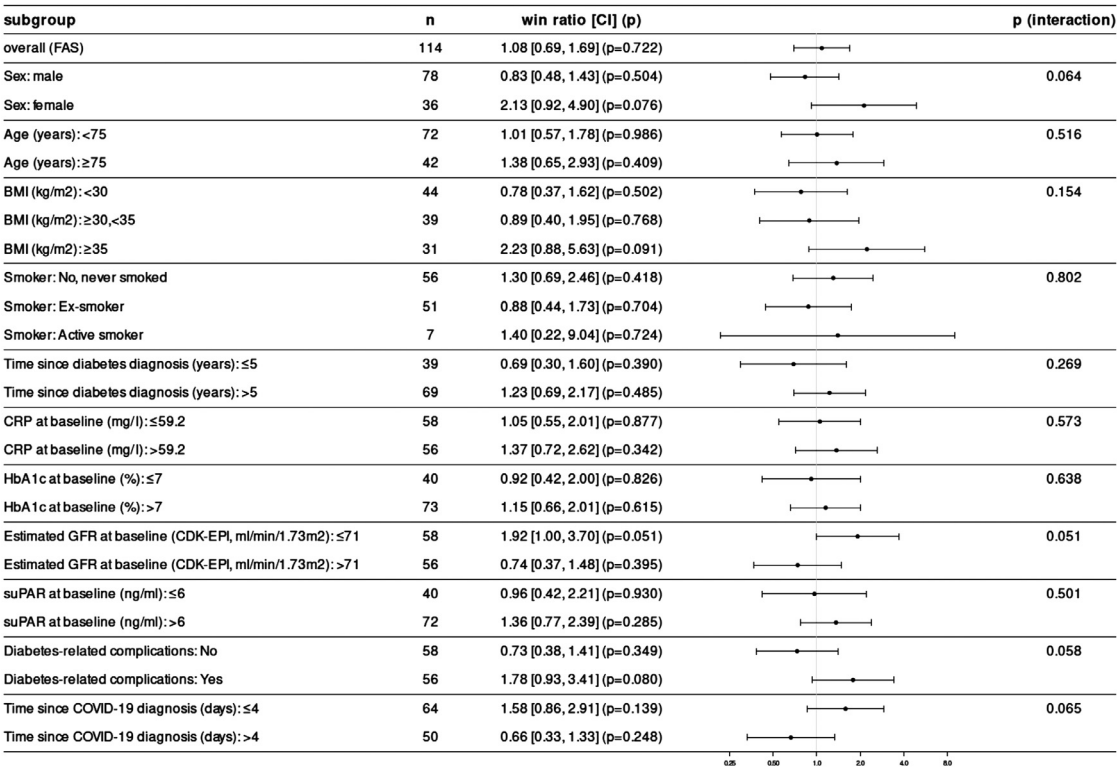

Figure 3. Forest plots for the win-ratios of canakinumab vs placebo. Presented are for each subgroup the win-ratio with its 95% confidence interval and the p-value for the null hypothesis of no difference between canakinumab and placebo. The last column gives the p-values for the interaction tests. GFR glomerular filtration rate, CKD-EPI Chronic Kidney Disease Epidemiology Collaboration.

1·92 (1·00, 3·70), p = 0·051) vs patients with an eGFR above 71 (WR 0·74 (0·37, 1·48), p = 0·395). No significant difference was seen in patients with diabetes-related complications (WR 1·78 (0·93, 3·41), p = 0·080) vs those without diabetic complications (WR 0·73 (0·38, 1·41), p = 0·349). Patients with a BMI of 35 kg/m^2 and higher treated with canakinumab compared to placebo had a WR of 2.23 (0·88, 5·63; p = 0·091) whereas patients with a BMI of 30 kg/m^2 and lower had a WR of 0·78 (0·37, 1·62; p = 0·502). Females treated with canakinumab compared to placebo had a WR of 2.13 (0·92, 4·90; p = 0·076) whereas males had a WR of 0·83 (0·48, 1·43; p = 0·504).

Median ratio to baseline CRP and IL-6 was lower at 29 days in the canakinumab group vs placebo (GMR 0·47 (0·27, 0·82), p = 0·01, and GMR 0·28 (0·11-0·68), p = 0·005), respectively (Table 2). Lower CRP levels were also observed after three months in patients treated with canakinumab compared to placebo (GMR 0·50 (0.27, 0.92), p = 0·027).

Number of anti-diabetes treatments at 29 days was lower in patients treated with canakinumab compared to placebo (OR 0·47 (0·23,0·95), p = 0.037) despite similar median HBA1c (canakinumab 7·40 % (6·65, 8·30), placebo 7·50 % (6·68, 8·33), p = 0·955) (Table 2).

Median ratio to baseline of serum insulin (pmol/L) was significantly higher 29 days after randomization in patients treated with canakinumab 0·94 (IQR 0·59, 1·66) compared to placebo 0·64 (IQR 0·29, 1·44), corresponding to an GMR of 2·21 (1·09, 4·48; p = 0·029), (Table 2). Twenty-nine days after randomization, there were no statistically significant differences in D-Dimer, IL-18, Ferritin, and NT-proBNP levels between the two groups (Table 2).

Adverse events at the final follow-up period of three months occurred in 34 patients (29·8 %) of which 15 (13·6 %) were observed in patients treated with canakinumab and in 19 patients (16·6 %) in the placebo group. Table 3 outlines all observed adverse events. Serious adverse events occurred in 26 patients (22 %), 13 in each group. There were more infections in the canakinumab group compared to placebo. However, patients treated with placebo hat more respiratory deterioration compared to canakinumab. In total, five patients (9·1 %) in the canakinumab group died vs 7 (13 %) in the placebo group. All adverse events were considered unrelated to the study drug.

	Canakinumab	Placebo
Any adverse event	31 (55·3%)	34 (62·9%)
Infections	12 (21·4%)	15 (27·7%)
respiratory	8 (14·3%)	6 (11·1%)
urogenital	2 (3·5%)	2 (3·7%)
other	2 (3·5%)	7 (12·9%)
Respiratory	8 (14·3%)	9 (16·6%)
Cardiovascular	2 (3·5%)	1 (1·8%)
Gastrointestinal	2 (3·5%)	3 (5·5%)
Hematologic	3 (5·3%)	0
Neurologic	3 (5·3%)	5 (9·2%)
Other	1 (1·8%)	1 (1·8%)
Any serious adverse event	18 (32·1%)	17 (31·5%)
Respiratory deterioration	9 (16·0%)	14 (25·9%)
Infections	5 (8·9%)	0
Myocardial infarction	2 (3·5%)	0
Other	2 (3·5%)	3 (5·5%)
Death	5 (8·9%)	7 (12·9%)

***Table 3*: Safety outcomes in the safety population until final follow-up period of three months.** Given are absolute numbers and percentage.

Discussion

In patients with type 2 diabetes hospitalised with COVID-19, IL-1β inhibition with canakinumab did not result in a significant improvement of survival time, ventilation time, ICU stay and length of hospitalization. However, there was a numerical lower number of deaths, and shorter ICU and ventilation time in the canakinumab group. Interestingly, patients at highest risk for severe COVID-19 due to a lower eGFR, diabetes-related complications and BMI higher than 35 kg/m^2 appeared more likely to benefit from the treatment with canakinumab. Furthermore, patients treated with canakinumab required significantly fewer anti-diabetes drugs to achieve similar glycaemic control and had higher serum insulin levels. Finally, markers of systemic inflammation were lower following canakinumab treatment.

There are multiple possible explanations, why the composite primary endpoint was not reached. An insufficient sample size is the most likely and supported by the fact that most endpoints were numerically favoring the use of canakinumab. Improved standard of care, especially the use of treatments with anti-inflammatory effects such as dexamethasone, will have reduced IL-1β signalling in patients receiving placebo as well. Despite this, based on our study results it must be concluded that the use of canakinumab for the treatment of COVID-19 in overweight type 2 diabetic patients cannot be recommended.

However, canakinumab had a beneficial effect on metabolism resulting in a lower need for anti-diabetes medication. While the beneficial effect of IL-1 antagonism in diabetes is well documented,[9] it was not previously shown in the context of a viral infection treated with dexamethasone. Both, viral infections, and corticosteroids worsen glucose metabolism. The underlying mechanism of this effect needs to be investigated but may be due to protection of β-cells. Indeed, SARS-CoV2 seems to directly damage β-cells possibly via activation of IL-1β.[49] Conversely, IL-1 antagonism preserves insulin secretion in patients with type 2 diabetes.[23] In support of this hypothesis, serum insulin was higher following treatment with canakinumab. However, to definitively prove an optimized insulin secretion it would have been necessary to perform dynamic testing.

CRP and IL-6 are well-established biomarkers indicating an increased risk for cardiovascular diseases and risk for diabetes.[50–53] IL-1 antagonism decreases both biomarkers, improves diabetes control and prevents cardiovascular diseases.[17,23] Although we observed a decrease of both parameters, with a sustained effect on CRP for three months, it is unlikely that the single injection of canakinumab will have long-term beneficial effects in the patients included in this study.

Taken together, the secondary outcomes related to diabetes control and complications consistently improved. However, no correction for multiple testing was performed.

This study has limitations. Patients received the study medication within six days after admission to the hospital but not within a specific period after symptoms onset, which may have been already too late to strongly influence the inflammatory course of COVID-19. The concomitant use of dexamethasone in most patients as part of the local standard-of-care may have reduced IL-1β release limiting the additional effect of canakinumab. In fact, only 16 patients in the canakinumab group and 13 patients in the placebo group did not receive glucocorticoids.

In conclusion, canakinumab treatment is a promising approach to optimize diabetes control including during viral infections and concomitant corticosteroid application, while its benefit on the clinical course of COVID-19 remains to be demonstrated.

Contributors

The study was designed by MYD, PH, PS, MH, JMM. MB, JMM, CG, FRJ, SC, AW, PAB, JDC, SF, TB, CCW, DLB, HFG, FB, AC, EW, EI, SZ, GB, YA, LD, BM, PH, PS, MC and MYD contributed to the interpretation of the results. Statistical analyses were done by MC and reviewed by an independent statistician. The first draft of the manuscript was prepared by MH and JMM who had unrestricted access to the data. The Article was reviewed and approved by MB, JMM, CG, FRJ, SC, AW, PAB, JDC, SF, TB, CCW, DLB, HFG, FB, AC, EW, EI, SZ, GB, YA, LD, BM, PH, PS,

MC and MYD made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. MB, JMM, CG, FRJ, SC, AW, PAB, JDC, SF, TB, CCW, DLB, HFG, FB, AC, EW, EI, SZ, GB, YA, LD, BM, PH, PS, MC and MYD accessed all the data reported in the study.

Data sharing statement

Data for this article are available upon request to the authors.

Declaration of interests

MYD is listed as the inventor on a patent filed in 2003 for the use of an IL-1 receptor antagonist for the treatment of or prophylaxis for type 2 diabetes. JMM owns stocks of Novartis AG. DLB received consulting fees from Gilead, MSD and ViiiV, and honoraria from Abbvie, Gilead, MSD and ViiV. HFG received payments for participation to advisory boards from Merck, Gilead Sciences, Novartis, Jansen, ViiV and GSK.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101649.

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