Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: a multicentre cohort study (SAM-COVID-19)

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ABSTRACT

Objectives: The objective of this study was to estimate the association between tocilizumab or corticosteroids and the risk of intubation or death in patients with coronavirus disease 19 (COVID-19) with a hyperinflammatory state according to clinical and laboratory parameters.
Methods: A cohort study was performed in 60 Spanish hospitals including 778 patients with COVID-19 and clinical and laboratory data indicative of a hyperinflammatory state. Treatment was mainly with tocilizumab, an intermediate-high dose of corticosteroids (IHDC), a pulse dose of corticosteroids (PDC), combination therapy, or no treatment. Primary outcome was intubation or death; follow-up was 21 days. Propensity score-adjusted estimations using Cox regression (logistic regression if needed) were calculated. Propensity scores were used as confounders, matching variables and for the inverse probability of treatment weights (IPTWs).
Results: In all, 88, 117, 78 and 151 patients treated with tocilizumab, IHDC, PDC, and combination therapy, respectively, were compared with 344 untreated patients. The primary endpoint occurred in 10 (11.4%), 27 (23.1%), 12 (15.4%), 40 (25.6%) and 69 (21.1%), respectively. The IPTW-based hazard ratios (odds ratio for combination therapy) for the primary endpoint were 0.32 (95%CI 0.22–0.47; $p < 0.001$) for tocilizumab, 0.82 (0.71–1.30; p 0.82) for IHDC, 0.61 (0.43–0.86; p 0.006) for PDC, and 1.17 (0.86–1.58; p 0.30) for combination therapy. Other applications of the propensity score provided similar results, but were not significant for PDC. Tocilizumab was also associated with lower hazard of death alone in IPTW analysis (0.07; 0.02–0.17; $p < 0.001$).

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Conclusions: Tocilizumab might be useful in COVID-19 patients with a hyperinflammatory state and should be prioritized for randomized trials in this situation. **Jesús Rodríguez-Baño, Clin Microbiol Infect 2021;27:244**

Introduction

The clinical spectrum of coronavirus disease 2019 (COVID-19) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) varies from asymptomatic disease to severe pneumonia and death [1,2]. Increased serum concentrations of inflammatory and coagulation markers (including C-reactive protein (CRP), ferritin, and D-dimer) and proinflammatory cytokines (such as IL-2R, IL-6, IL-10, and TNF-α) have been associated with disease severity in COVID-19 [3,4]. These findings indicate that a hyperinflammatory state may play a crucial role in severe cases of COVID-19, as in other coronaviruses [5].

Regarding treatment of COVID-19, so far remdesivir is the only antiviral that has shown some efficacy [6]. Because of the dysregulated immune response characteristic of severe COVID-19, it is conceivable that immunosuppressant drugs may have some effect in selected patients. Despite the fact that some guidelines have recommended against the use of corticosteroids [7,8], dexamethasone (6 mg/day) in the RECOVERY trial reduced mortality among those receiving either invasive mechanical ventilation or oxygen alone [9]. Other host response modifiers under investigation include tocilizumab, a recombinant humanized anti-human IL-6 receptor [10], for which some comparative observational studies have been reported [11–14].

Observational studies may help in the design of randomized trials of immunomodulatory agents for the treatment of severe COVID-19 by providing an estimation of their potential effects and identifying potential candidates for these therapies. The objective of this study was to provide an observational estimation of the association between tocilizumab/corticosteroids and outcome in non-intubated patients, specifically in those with data suggestive of a hyperinflammatory state, within a large nationwide clinical cohort of patients with COVID-19 to test the hypothesis that these drugs might be associated with a reduced risk of intubation or death.

Methods

Design, patients and procedures

The SAM-COVID study is a retrospective cohort study nested in the COVID19@Spain cohort (NCT04355871), in which consecutive patients admitted to Spanish hospitals because of COVID-19 (confirmed by PCR in nasopharyngeal swab or lower respiratory tract sample) from February 2nd to March 31st 2020 were included [15]. SAM-COVID was also registered (NCT04382781) before the analysis started.

Adult patients from the COVID19@Spain cohort were eligible for SAM-COVID if presenting on a specific date (day 0) with at least one clinical criterion and one laboratory criterion suggestive of a hyperinflammatory state. Clinical criteria were (a) temperature ≥38°C and (b) increase in oxygen support required to achieve O_2 saturation >92%. Laboratory criteria were (a) ferritin >2000 ng/mL or increase >1000 ng/mL since admission, (b) D-dimers >1500 μg/mL (or doubled in 24 h), and (c) IL6 >50 pg/mL. Investigators from the COVID@Spain cohort sites were asked to further review the charts of patients by assessing daily clinical and laboratory data, and to provide additional information. Exclusion criteria were (a) being under mechanical ventilation at day 0, (b) occurrence of the primary endpoint in ≤2 day after day 0 (in order to avoid immortal time bias), (c) written decision to avoid any escalation in medical treatment before day 0, (d) previous use of systemic corticosteroids, tocilizumab, other immunomodulatory drugs or immunoglobulins, and (e) treatment with immunomodulatory drugs other than corticosteroids or tocilizumab, or with immunoglobulins during the first 48 h after day 0. In addition, day 0 must have been before March 31 to assure 21 days of follow-up when the database was locked. Sixty hospitals participated in this study. The database was monitored for missing data and inconsistencies.

Variables

The main endpoint was intubation or death, whichever happened first; follow-up was 21 days. Patients were censored on the last day of contact if discharged before day 21. Secondary outcomes were death, rates of secondary bacterial infection, digestive tract bleeding, and proportion of patients with a score of ≤3 in a seven-point ordinal scale at day 21 (1, not hospitalized; 2, hospitalized without supplemental oxygen; 3, hospitalized with supplemental oxygen; 4, hospitalized and requiring supplemental oxygen with a high nasal flow cannula or non-invasive ventilation; 5, hospitalized and requiring mechanical ventilation; 6, hospitalized and requiring extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation with amine support; and 7, death).

The main treatments after day 0 were with tocilizumab, intermediate-high dose corticosteroids (IHDC), pulse dose corticosteroids (PDC), combination therapy with tocilizumab and corticosteroids, or no treatment. In order to try to mimic the exposure as in a randomized trial and intention-to-treat analysis, we classified exposure to treatment arms in the primary analysis as follows: patients were assigned to tocilizumab, IHDC or PDC if administered in ≤2 days after day 0; patients receiving both tocilizumab and corticosteroids in the first 2 days were assigned to the combination treatment group, while patients not receiving any of these drugs were assigned to the non-treatment arm. Patients who started treatment with the above drugs in days 3 and 4 were excluded from the primary analysis, as it would be debatable to which arm they should be assigned, and to avoid immortal time bias; however, these patients were included in a sensitivity analysis in which treatments were considered as time-dependent variables. Corticosteroid treatment was classified as PDC if ≥ 250 mg of methylprednisolone or equivalent per day were administered, or as IHDC otherwise. Other variables collected are included in Table 1. The data were obtained from the patients' charts. An electronic case report was built using REDCap electronic data capture tools [16]. Missing values were classified as a separate category in the analyses.

The study was approved by the University hospitals Virgen Macarena and Virgen del Rocío ethic committee which waived the

Table 1
Demographic and clinical data of patients. Data are number (proportion) of patients with known exposure to the variable except where specified

	No treatment ($n = 344$)	Tocilizumab ($n = 88$)	p value[a]	Corticosteroids, intermediate–high dose ($n = 117$)	p value[b]	Corticosteroids, pulse dose ($n = 78$)	p value[c]	Combination therapy ($n = 151$)	P value[d]
Age, median years (IQR)	69 (59–76)	66 (56–72)	0.10	71 (62–76)	0.05	71 (60–76)	0.24	65 (58–74)	0.01
Female gender	106/343 (30.9)	24/64 (27.3)	0.50	33/116 (28.4)	0.61	21/78 (26.9)	0.48	42/149 (28.1)	0.54
Caucasian ethnicity	316/338 (93.5)	80/87 (92.0)	0.61	110/113 (97.3)	0.12	75/78 (96.2)	0.37	132/147 (89.8)	0.15
Comorbidities:									
Cardiac disease	62/344 (18.0)	11/88 (12.5)	0.21	21/117 (17.9)	0.98	11/78 (14.1)	0.40	17/150 (11.3)	0.06
Hypertension	175/344 (50.9)	30/88 (34.1)	0.005	61/117 (52.1)	0.81	42/78 (53.8)	0.63	73/151 (48.3)	0.60
Chronic pulmonary disease	37 (10.8)	6/88 (6.8)	0.27	18/117 (15.4)	0.18	9/78 (11.5)	0.84	17/151 (11.3)	0.86
Severe chronic renal insufficiency	13 (3.8)	0/87 (0)	0.08	3/116 (2.6)	0.77	5/78 (6.4)	0.34	1/151 (0.7)	0.07
Liver cirrhosis	5/337 (1.5)	1/87 (1.1)	1.0	1/117 (0.9)	1.0	1/78 (1.3)	1.0	0/151 (0)	0.33
Malignancy	15/344 (4.4)	1/88 (1.1)	0.09	4/117 (3.4)	0.39	4/78 (5.1)	0.89	2/151 (1.3)	0.07
HIV infection	0/344 (0)	1/88 (1.1)	0.20	0/117 (0)	—	0/78 (0)	—	0/151 (0)	—
Obesity	39/309 (11.4)	12/78 (14.3)	0.54	19/111 (17.1)	0.16	5/68 (7.4)	0.22	23/134 (17.2)	0.20
Diabetes mellitus	72/344 (20.9)	15/88 (17.0)	0.41	29/117 (24.8)	0.38	12/78 (15.4)	0.26	26/151 (17.2)	0.34
Dementia	14/344 (4.1)	1/88 (1.1)	0.18	4/117 (2.4)	0.75	0	0.08	0/151 (0)	0.01
Admission data:									
Percentage oxygen saturation with room air, mean (SD)	92.6 (6.0)	92.1 (6.4)	0.51	91.0 (5.1)	0.1	90.0 (5.6)	0.001	91.8 (5.2)	0.19
Bilateral infiltrates in thorax radiography	235/288 (81.6)	67/78 (85.9)	0.37	91/102 (89.2)	0.07	52/69 (82.6)	0.84	132/131 (87.0)	0.16
Lymphocytes/μL, mean (SD)	1069 (1049)	989 (814)	0.67	1313 (1952)	0.09	1244 (1753)	0.25	948 (520)	0.17
LDH in U/L, mean (SD)	388 (158)	392 (143)	0.39	388 (152)	0.20	385 (119)	0.39	408 (166)	0.73
C-reactive protein in mg/L, mean (SD)	112 (101)	118 (100)	0.64	124 (107)	0.28	118 (99)	0.63	112 (99)	0.96
Antiviral treatment before day 0:									
Lopinavir/ritonavir	242/335 (72.2)	71/87 (81.6)	0.07	86/117 (73.5)	0.79	59/78 (75.6)	0.49	111/151 (73.5)	0.77
Hydroxychloroquine	319/335 (94.4)	86/88 (97.7)	0.27	104/117 (88.9)	0.04	73/78 (93.6)	0.84	144/151 (95.4)	0.65
Remdesivir	3/334 (0.9)	0/88 (0)	1.0	0/117 (0)	0.52	0/78 (0)	1.0	0/151 (0)	0.55
Azithromycin	223/337 (66.2)	65/88 (73.9)	0.16	79/117 (67.5)	0.79	48/78 (61.5)	0.58	116/147 (78.9)	0.005
Interferon β	71/332 (21.4)	24/86 (27.9)	0.19	25/116 (21.6)	0.97	12/78 (15.4)	0.84	27/151 (17.9)	0.85
Data on day 0:									
Median days of symptoms (IQR)	8 (6–11)	10 (8–13)	0.02	10 (7–12)	0.05	6 (9–12)	0.22	11 (8–13)	<0.001
Median days from admission to day 0 (IQR)	1 (0–4)	3 (1–5)	0.001	2 (1–4)	0.08	2 (1–5)	0.21	3 (1–5)	0.001
Fever	202/344 (58.7)	42/88 (47.7)	0.06	65/117 (55.6)	0.54	38/78 (48.7)	0.10	77/151 (51.0)	0.11
Worsening in oxygen requirements	230/344 (66.9)	81/88 (92.0)	<0.001	87/117 (74.4)	0.13	70/78 (89.7)	<0.001	136/151 (90.1)	<0.001
Ferritin >2000 ng/mL	95/194 (49.0)	19/59 (32.2)	0.02	34/78 (43.6)	0.42	29/62 (46.8)	0.76	51/100 (51.0)	0.74
D-dimers >1500 μg/mL	192/311 (61.7)	43/82 (52.4)	0.12	55/112 (49.1)	0.02	40/73 (54.8)	0.27	78/140 (55.7)	0.24
IL6 >50 pg/mL	100/132 (75.8)	57/59 (96.6)	<0.001	47/53 (88.7)	0.04	26/37 (70.3)	0.49	81/95 (85.3)	0.07
Oxygen support at day −1:			0.001		0.001		0.001		<0.001
Nasal cannula or mask	282/340 (82.9)	57/88 (63.6)		82/117 (70.1)		51/78 (65.3)		71/149 (48.3)	
Mask with reservoir bag	46/340 (13.5)	26/88 (29.2)		30/117 (25.6)		25/78 (32.1)		65/149 (43.0)	
High-flow nasal cannula	10/340 (2.9)	3/88 (3.4)		1/117 (0.9)		1/78 (1.3)		5/149 (3.3)	
Non-invasive mechanical ventilation	2/340 (0.6)	2/88 (3.4)		4/117 (3.4)		1/78 (1.3)		8/149 (5.3)	
Low-molecular-weight heparin:									
Prophylactic dose	244/340 (71.8)	69/88 (80.2)	0.22	93/117 (79.5)	0.11	57/78 (73.1)	0.88	115/150 (76.7)	0.27
Anticoagulant dose	36/340 (10.6)	12/88 (14.0)	0.44	17/117 (14.5)	0.23	16/78 (20.5)	0.01	26/150 (17.3)	0.03
Immunomodulatory drugs after day 4:									
Corticosteroids, low dose	39/344 (11.3)	11/88 (12.5)	0.71	—	—	35/78 (44.9)	<0.001	—	—
Corticosteroids, high dose	26/344 (7.5)	6/88 (6.8)	1.0	0/117 (0)	<0.001	—	—	—	—
Tocilizumab	22/344 (6.5)	—	—	7/117 (5.9)	0.87	10/78 (12.8)	0.08	—	—

IQR: interquartile range.
[a] For tocilizumab versus no treatment.
[b] For corticosteroids, high-intermediate dose versus no treatment.
[c] For corticosteroids, pulse dose versus no treatment.
[d] For combination versus no treatment.

need to obtain written informed consent due to the observational nature of the study. The study is reported according to STROBE recommendations (Supplementary Material Table S1).

Statistical analysis

Patients classified as receiving no treatment were compared to those treated with tocilizumab, IHDC, PDC, or combination treatment for baseline variables at admission and day 0 using Student t-test or Mann–Whitney U test for continuous variables and χ^2 or Fisher test for categorical variables, as appropriate. The association of treatment with time-related endpoints was analysed using Kaplan–Meier curves and Cox regression analysis. The sites were included as a random effect variable in the models. Propensity scores for receiving early treatment with tocilizumab, IHDC, PDC or combination therapy instead of no treatment were calculated by performing non-parsimonious multivariate logistic regression models by including all measured potential predictors for treatment. The ability of the propensity scores to predict the observed data was calculated by the area under the receiver operating characteristic curve (AUROC) with 95% confidence intervals (95% CIs). The propensity scores were used to calculate the inverse probability of treatment weight (IPTW) in Cox analysis, as a confounder and as a matching variable (treated/not treated, 1:2 ratio), using the nearest neighbour method with a tolerance <5%. When the proportional hazards assumptions were not fulfilled for performing Cox regression, logistic regression (conditional if matched analyses) was used. Multivariate models with forward addition of different variables to the model adjusted by the propensity score were also performed, after excluding collinearity. Sensitivity analyses were performed by including patients who started treatments on days 3 and 4, and considering exposure to study drugs as time-dependent variables, counting the days until the first dose of the drug was administered from day 0. All analyses were performed using IBM SPSS Statistics v26 and R.

Results

Overall, 1014 eligible patients were identified; 778 were included in the primary analysis (Fig. 1), including 344 in the no-treatment arm, 88 treated with tocilizumab, 117 with IHDC, 78 with PDC, and 151 with combination treatment (all received tocilizumab, 77 received IHDC and 74 PDC).

The features of the patients are shown in Table 1. Overall, patients in the treatment arms needed a higher level of oxygen support at day 0 than those in the no-treatment arm. The proportion of patients with measured and elevated levels of IL-6 was higher in the tocilizumab and IHDC arms; it was the only laboratory criterion for inclusion in 24.4% of the patients. By contrast, ferritin and D-dimers were less frequently elevated in the tocilizumab and IHDC arms, respectively. Details regarding the drugs dosing are shown in the Supplementary Material Table S2.

The crude outcomes of patients according to treatment arm are shown in Table 2, and crude Kaplan–Meier curves for the primary endpoint are shown in Fig. 2. The proportional hazard assumption was not fulfilled in the comparison of IHDC and combination versus no treatment, and logistic regression was used for these comparisons. The propensity score-adjusted associations of treatments for the primary endpoint are shown in Table 3, which also includes the variables used for the propensity score calculation. The comparison of features of the propensity score-matched patients are shown in the Supplementary Material Table S3. The IPTW-adjusted Kaplan–Meier curves for tocilizumab and PDC are shown in the Supplementary Material Fig. S1. Overall, tocilizumab was associated with lower hazard for the primary endpoint in all adjusted analyses; the estimations for PDC were all on the protective side but were significant only in the IPTW model. IHDC and combination therapy were not associated with significant risk differences. Addition of other variables to the models and sensitivity analyses considering treatments as time-dependent variables provided no significant changes in the estimations.

Regarding the secondary outcomes, the crude estimations are shown in Table 2. The proportion of patients with a score $\leq$3 on the 7-point scale at day 21 was higher in the tocilizumab arm. No differences were seen in the rates of secondary bacterial infection or gastrointestinal bleeding. Regarding mortality, the Kaplan–Meier curves (crude data) are shown in the Supplementary Material Fig. S2. The adjusted analyses are shown in Table 3, and the IPTW-adjusted Kaplan–Meier curves are in the Supplementary Material Fig. S3. Tocilizumab was associated with a lower hazard of death in all adjusted models. PDC was nearly associated with a lower risk of death only in the IPTW model; neither IHDC nor combination therapy could demonstrate a significant association with mortality (Table 3).

Discussion

In this observational, multicentre, propensity score-adjusted study, tocilizumab was associated with lower hazards of intubation or death in patients with COVID-19 presenting with clinical and laboratory data suggestive of a hyperinflammatory state. The association with PDC was also significant in the analysis with the IPWT but not with other adjustments, although the estimations are

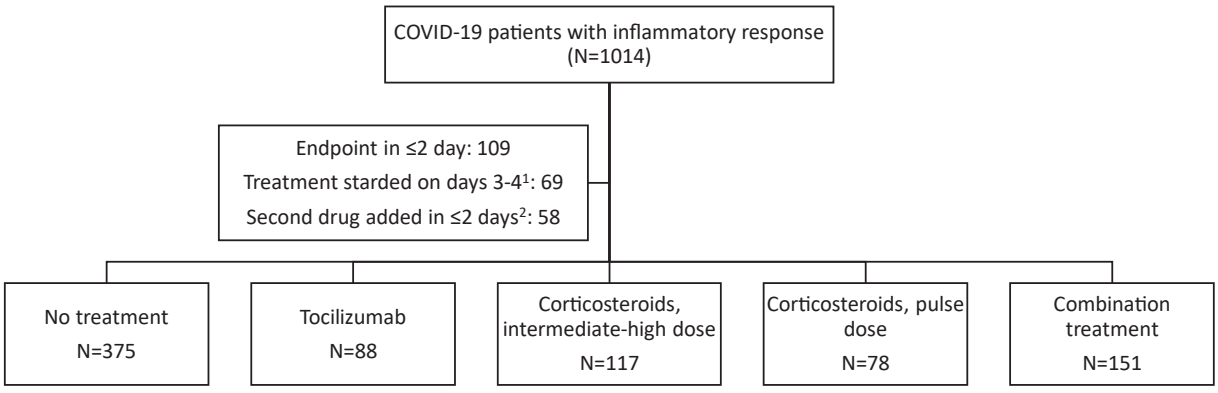

Fig. 1. Flowchart of patients included in the primary analysis.

Table 2
Crude outcomes of patients in the different treatment arms. Data are number (proportion) of patients with known exposure to the variable except where specified

	No treatment ($n = 344$)	Tocilizumab ($n = 88$)	p value[a]	Corticosteroids, intermediate–high dose ($n = 117$)	p value[b]	Corticosteroids, pulse dose ($n = 78$)	p value[c]	Combination ($n = 151$)	p value[d]
Primary outcome[e]	69/344 (20.1)	10/88 (11.4)	0.05	27/117 (23.1)	0.57	12/78 (15.4)	0.28	40/151 (26.5)	0.13
Median follow-up without the endpoint, days (IQR)	20 (13–21)	21 (16–21)	0.01	21 (16–21)	0.56	21 (12.21)	0.55	20 (11–21)	0.87
Scale at day 21	$n = 344$	$n = 88$	—	$n = 117$	—	$n = 78$	—	$n = 151$	—
1	253 (73.5)	70 (79.5)		80 (68.4)		55 (70.5)		100 (66.2)	
2	10 (2.9)	2 (2.3)		4 (3.4)		2 (2.6)		8 (5.3)	
3	16 (4.7)	8 (9.1)		8 (6.8)		8 (10.3)		14 (9.3)	
4	4 (1.2)	0		0		1 (1.3)		1 (0.7)	
5	19 (5.5)	6 (6.8)		2 (1.7)		4 (5.1)		9 (6.0)	
6	1 (0.3)	0		1 (0.9)		0		19 (6.0)	
7 (death)	41 (11.9)	2 (2.3)	0.004	22 (18.8)	0.08	8 (10.3)	0.84	19 (12.6)	0.88
Scale ≤3	279 (81.1)	80 (90.9)	0.02	92 (78.6)	0.56	65 (83.3)	0.64	122 (80.8)	0.93
Digestive tract bleeding	2/341 (0.6)	1/88 (1.1)	0.49	1/115 (1.4)	1.0	1/74 (1.4)	0.44	3/150 (2.0)	0.16
Secondary bacterial infection	36/339 (10.3)	11/88 (12.5)	0.57	10/115 (8.7)	0.72	8/75 (10.7)	1.0	18/150 (12.0)	0.64

IQR, interquartile range.
[a] For tocilizumab versus no treatment.
[b] For corticosteroids, intermediate-high dose versus no treatment.
[c] For corticosteroids, pulse dose versus no treatment.
[d] For combination versus no treatment.
[e] P values obtained by univariate Cox regression except for combination therapy, for which logistic-regression was used.

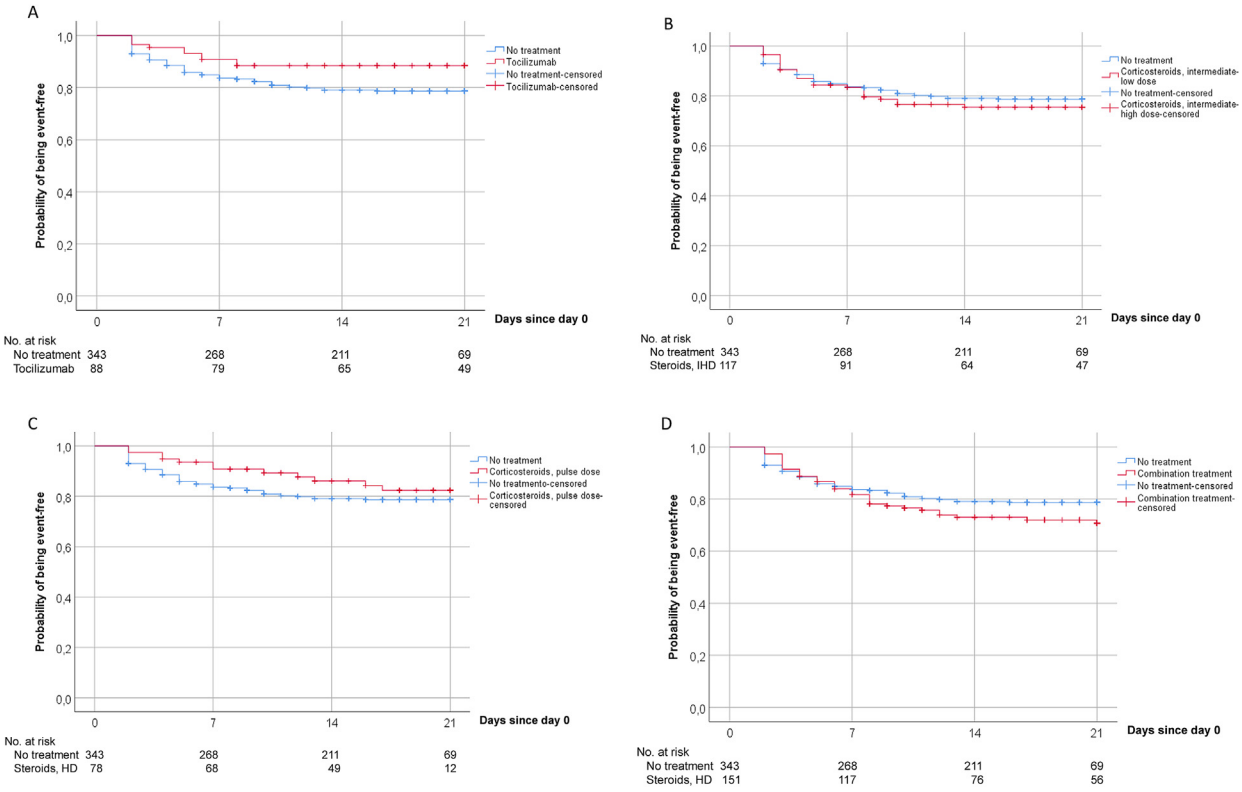

Fig. 2. Probability of remaining event-free (intubation or death) according to the different treatments used, in comparison with no treatment (crude analyses). (A) Tocilizumab. (B) Corticosteroids, intermediate-high dose. (C) Corticosteroids, pulse dose. (D) Combination therapy.

informative. On the other hand, we could not find a significant association between IHDC or combination therapy and outcomes.

One of the problems in observational studies is the assignment of patients to treatment arms. In this study we mimicked exposure and intention-to-treat analysis in randomized trials, in which treatments are typically started in ≤2 days, and we excluded patients for whom the endpoint was reached in such a period or patients starting treatment in days 3 and 4, in order to avoid immortal time bias. In fact, sensitivity analysis which included patients treated on days 3–4 and considered exposure to drugs as time-dependent variables did not show different results, suggesting that immortal time bias was not affecting the estimations.

We used a 'hard' composite primary outcome including intubation or death because some patients may be candidates for additional medical treatment but not for intubation due to their previous conditions. Anyhow, the results were similar when only mortality or the proportions of patients with a score of ≥3 in the 7-point scale were considered. Our data were not specific for adverse

Table 3
Estimation of the association of treatments with the primary endpoint (time until intubation or death) and with mortality in the different models. Adjusted models used specific propensity scores[a] for receiving each drug

Intubation or death		
Tocilizumab versus no treatment	**HR (95%CI)**	**p**
Crude	0.52 (0.27–1.01)	0.05
With propensity score	0.32 (0.15–0.67)	0.003
Inverse probability of treatment weights	0.32 (0.22–0.47)	<0.001
Matched cases	0.42 (0.19–0.92)	0.03
Time-dependent variable with propensity score	0.36 (0.17–0.75)	0.007
Corticosteroids, intermediate-high dose versus no treatment	**OR (95%CI)**	**p**
Crude	1.17 (0.71–1.95)	0.52
With propensity score	0.83 (0.48–1.45)	0.53
Inverse probability of treatment weights	1.00 (0.72–1.41)	0.96
Matched cases	0.80 (0.42–1.41)	0.50
Time-dependent variable with propensity score	0.95 (0.59–1.53)	0.84
Corticosteroids, pulse dose versus no treatment	**HR (95%CI)**	**p**
Crude	0.71 (0.38–1.32)	0.28
With propensity score	0.71 (0.36–1.38)	0.31
Inverse probability of treatment weights	0.61 (0.43–0.86)	0.006
Matched cases	0.69 (0.32–1.51)	0.36
Time-dependent variable with propensity score	0.79 (0.41–1.53)	0.50
Combination therapy versus no treatment	**OR (95%CI)**	**p**
Crude	1.41 (0.90–2.21)	0.13
With propensity score	1.20 (0.71–2.01)	0.48
Inverse probability of treatment weights	1.17 (0.86–1.58)	0.30
Matched cases	1.71 (0.88–3.31)	0.10
Time-dependent variable with propensity score	1.17 (0.74–1.84)	0.48
DEATH		
Tocilizumab versus no treatment	**HR (95%CI)**	**p**
Crude	0.17 (0.04–0.70)	0.01
With propensity score	0.12 (0.02–0.56)	0.007
Inverse probability of treatment weights	0.07 (0.02–0.17)	<0.001
Matched cases	0.22 (0.05–0.96)	0.04
Corticosteroids, intermediate-high dose versus no treatment	**HR (95%CI)**	**p**
Crude	1.66 (0.99–2.79)	0.05
With propensity score	1.16 (0.66–2.03)	0.59
Inverse probability of treatment weights	1.21 (0.62–2.35)	0.56
Matched cases	1.02 (0.66–1.58)	0.90
Corticosteroids, pulse dose versus no treatment	**OR (95%CI)**	**p**
Crude	0.80 (0.35–1.81)	0.59
With propensity score	0.74 (0.31–1.77)	0.51
Inverse probability of treatment weights	0.64 (0.24–1.04)	0.06
Matched cases	0.67 (0.24–1.84)	0.43
Combination therapy versus no treatment	**OR (95%CI)**	**p**
Crude	1.03 (0.57–1.85)	0.90
With propensity score	1.31 (0.67–2.54)	0.42
Inverse probability of treatment weights	1.17 (0.75–1.64)	0.57
Matched cases	1.36 (0.58–3.21)	0.47

[a] Propensity scores were calculated including age, gender, ethnicity, comorbidities (cardiac disease, hypertension, chronic pulmonary disease, chronic renal disease, liver cirrhosis, malignancy, diabetes mellitus, obesity, HIV infection), laboratory data (lymphocytes, lactate dehydrogenase, alanine aminotransferase, ferritin, D-dimers, IL-6), previous treatments, radiographic findings, 7-point scale and type of oxygen requirement. Their predictive ability for observed data are 0.79 (95%CI: 0.74–0.85) for tocilizumab, 0.72 (0.68–0.77) for corticosteroids, intermediate-high dose, 0.77 (0.71–0.82) for corticosteroids, pulse dose, and 0.81 (0.77–0.85) for combination therapy.

events, and this is a crucial aspect that should be considered in more detail in future studies.

Regarding confounders, we used propensity scores in different ways in order to control for the indication bias. Because the IPTW provides a higher weight to patients treated with the drug of interest when having a lower probability of receiving that drug, the confidence intervals are reduced, while in the case of tocilizumab all models showed a significant association with improved outcomes; it was only with this analysis that PDC showed a significant association. We hypothesize that the lack of significant association with other analysis for PDC might be due to insufficient statistical power.

We found four observational comparative studies with tocilizumab in non-intubated patients with severe COVID-19 pneumonia. In one of them, 32 patients treated with tocilizumab were compared to 33 controls; patients treated with tocilizumab showed numerically lower mortality but the differences were not significant [11]. In another, treatment with tocilizumab (62 patients) was associated with better adjusted survival and a favourable clinical course in comparison with standard treatment (23 patients) [12]. A third study compared 179 patients treated with tocilizumab (88 intravenously) with 365 receiving standard of care in three Italian centres; tocilizumab was associated with a lower adjusted risk of invasive mechanical ventilation or death [13]. Finally, a fourth study found lower mortality in non-intubated patients, but adjusted analyses were not performed [14]. Several randomized trials with tocilizumab are ongoing; a press release by the promoter of the COVACTA trial reported that it did not show superiority over placebo in the primary endpoint (data not published) [17]. However, inclusion criteria in this trial did not consider data suggestive of a hyperinflammatory state [18].

Regarding corticosteroids, recent meta-analyses showed contradictory results [19,20]. In these reviews, the dosing of corticosteroids was not specified. The results from a quasi-experimental study suggested that early administration of 0.5–1 mg/kg of methylprednisolone for 3 days is associated with a protective effect

for a composite outcome including admission to ICU, mechanical ventilation or death [21], while a cohort study including 35 propensity score-matched couples of patients with and without corticosteroids (methylprednisolone, 40–50 mg/day) found no significant differences in outcomes [22]. A preliminary report of data from the RECOVERY randomized trial found that dexamethasone 6 mg/day (equivalent to methylprednisolone 30 mg) resulted in lower mortality among patients requiring oxygen or mechanical ventilation; the effect was more prominent in patients under mechanical ventilation [9]. It should be noted that corticosteroids in our study were used at higher doses in most patients, and were started only once the patients had developed a hyperinflammatory state based on clinical and laboratory data. We found no studies with pulse dose corticosteroids. While our results in this group are less clear, we think they support the development of a randomized trial in this clinical situation. We did not find any studies investigating the combination of tocilizumab and corticosteroids; the negative results in our study should be taken with caution since this was a heterogeneous group including different timing and dosing of both drugs. We could not perform more detailed analysis in this group since the numbers of patients in the subgroups were too low.

This study has several limitations. First, control for confounders in any observational study may be incomplete despite all efforts. Second, even though we registered the study design before performing any analysis, the criteria for assignment to study arms were not specified; however, they were decided before the analyses were performed. Third, a wide range of dosing regimens were used in the corticosteroid arms. Fourth, the investigators were not blinded for the exposure; however, we used hard outcomes and included consecutive cases. Fifth, the assessment of adverse events was not complete. And sixth, the study was performed during the first month of the pandemic in Spain; management may have changed afterwards.

The study also has some strengths, including the multicentre participation, the use of specific exposure definitions and advanced analyses for observational studies, and representativeness of real-life patients.

In conclusion, these findings suggest that testing tocilizumab should be prioritized for being tested in randomized trials targeting patients with data suggestive of a hyperinflammatory state, and that pending further evidence, it should be considered with caution in the treatment of this condition if participation in randomized trials is not possible. Additional data are needed for tocilizumab in patients who previously received corticosteroids, which might be the standard of care now. The results for PDC were less consistent but are also encouraging.

Transparency Declaration

IJ has received honoraria for participating in an advisory board from Gilead Sciences, and for educational activities from ViiV. JB has received research grants from AbbVie, Gilead Sciences, Merck, and ViiV, and honoraria for being a speaker or advisory board participation from AbbVie, Gilead Sciences, Janssen, Merck, and ViiV. JRA received fees for participating in an advisory board, being a speaker, and research grant support from Viiv, Janssen, Gilead, MSD, Teva, Alexa and Serono. PR is involved as speaker or advisory board participant for Gilead Sciences, AbbVie and ViiV. JR-B, JP, JC and MY have no conflicts of interest to declare. SAM-COVID was funded by Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III (COV20/01031) co-funded by European Union (ERDF/ESF, "Investing in your future") and Fundación SEIMC/GeSIDA. In addition, Juan Berenguer, Jesús Rodríguez-Baño, Inmaculada Jarrín, Jordi Carratalá, Jerónimo Pachón, and José R Arribas received funding for research from Plan Nacional de I+D+i 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Ciencia, Innovación y Universidades – co- financed by European Development Regional Fund "A way to achieve Europe", Operative program Intelligent Growth 2014–2020 through the networks: Spanish AIDS Research Network (RIS) [RD16/0025/0017 (JB), RD16/0025/0018 (JRA), RD16/0025/00XX (IJ)] and Spanish Network for Research in Infectious Diseases (REIPI)[RD16/0016/0001 (JRB), RD16/0016/0005 (JC), and RD16/0016/0009 (JP).

Appendix

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Appendix A. Supplementary data

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