Risk of superinfection in critically ill COVID-19 patients receiving tocilizumab plus dexamethasone

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Abstract

To assess the risk of superinfection in patients with severe COVID-19 in an ICU receiving dexamethasone with or without tocilizumab, we performed an observational cohort study. Of 246 patients, 59 developed superinfections (mainly respiratory) leading to poorer prognoses. Adding tocilizumab to dexamethasone was not associated with an increased risk of superinfection in these patients.

Background

Early studies reported low rates of bacterial and fungal superinfections in hospitalized COVID-19 patients, reaching 8% in the largest series to date.[1–4] However, the management of patients with severe COVID-19 has changed significantly since then. Beginning in July 2020, most patients admitted to an intensive care unit (ICU) have been given dexamethasone, while some have also received tocilizumab in line with recent guidelines.[5–10] Data on the risk of superinfection following implementation of these new therapeutic strategies remain scarce, especially in ICUs, and it is not clear if there is an increased risk of superinfection in patients treated with two anti-inflammatory drugs, *i.e.*, tocilizumab plus dexamethasone. [7, 10]

Objectives

This real-life cohort study assessed the risk of superinfection in severe COVID-19 cases, and the role of tocilizumab in this risk.

Patients And Methods

We conducted a retrospective cohort study to investigate bacterial and fungal superinfections associated with COVID-19 in ICU patients. The study included all patients diagnosed with COVID-19 by RT-PCR on nasopharyngeal swabs admitted to an ICU in Bordeaux University Hospital, between March 2020 and August 2021, for respiratory failure requiring oxygen > 6L/min and given dexamethasone with (group 1) or without (group 2) tocilizumab. Demographic data, comorbidities [hypertension, obesity (body mass index > 30kg/m²), diabetes, and immunodeficiency], and clinical, microbiological, and radiological parameters were recorded. Immunocompromised patients included patients with malignancy or non-malignant immunodeficiency [HIV infection, systemic disease treated with long-term steroids (> 30 days) or any immunosuppressive drug, or solidorgan transplantation]. Clinical respiratory status was evaluated using the 6-point World Health Organization (WHO) clinical scale, which has been described in detail elsewhere.[11] On admission, viral and bacterial coinfections were systematically screened using pharyngeal multiplex PCR, urinary antigen tests, blood cultures, and sputum cultures (where possible). When the clinical signs suggested superinfection or healthcare/ventilator-associated pneumonia (H/VAP) during hospitalization, blood cultures, urine cultures, and tracheal aspiration or bronchoalveolar lavage were performed. Fungal superinfections were systematically screened by serum galactomannan and *Aspergillus* spp. PCR every week. On admission, all patients were given ceftriaxone (2g/day) for 5 days

and dexamethasone (6mg/day) for 10 days. Those with a fever associated with increased inflammatory parameters (C-reactive protein > 75mg/L) were also given tocilizumab (8mg/kg) within the first 24 h according to local guidelines. Continuous variables are described as the median and interquartile range (IQR), while categorical variables are expressed as frequencies (%). Group comparisons of continuous variables were performed using Student's *t*-test. Categorical data were compared using the χ^2 test for count data. To analyze the risk of superinfection, survival analysis was performed using a multivariate Cox model. According to French law and the French Data Protection Authority, the handling of these data for retrospective research purposes was declared to the Data Protection Officer of the University Hospital of Bordeaux, who acknowledged the use of anonymized data. Patients were notified about the use of their anonymized healthcare data via a departmental booklet.

Results

During the study period, 246 patients with severe COVID-19 were admitted to an ICU, of whom 150 received dexamethasone and tocilizumab (group 1) and 96 received dexamethasone without tocilizumab (group 2) (Table 1). The median period from symptom onset to ICU admission was 8 days, with no difference in that period seen between the two groups. Of the patients, 26% had malignant or non-malignant immunodeficiency (22% vs. 32%, $p = 0.07$) and 23% had no chronic comorbidity (26% vs. 19%, $p = 0.19$). The median SAPS-II and SOFA scores were 23 and 3, respectively, with no difference between the two groups. Acute respiratory distress syndrome (ARDS, $\text{PaO}_2/\text{FiO}_2 \leq 300\text{mmHg}$) was present on admission in 226 patients. Severe ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 100\text{mmHg}$) was diagnosed in 35% of the patients in group 1 and 16% of those in group 2 ($p < 0.01$). Fifty-six patients required mechanical ventilation (MV): 25% of those in group 1 and 20% of those in group 2 ($p = 0.23$). Ninety-nine patients needed non-invasive ventilation (45% of those in group 1 and 22% of those in group 2, $p < 0.001$). High-flow nasal oxygen was used in 177 patients (79% of those in group 1 and 61% of those in group 2, $p < 0.01$). The median clinical status score on the WHO scale was 4 in both groups ($p = 0.93$). On admission, 33 patients had a bacterial respiratory coinfection, with no difference between the groups. During the study, 59 patients developed 66 superinfections (23% of those in group 1 and 26% of those in group 2, $p = 0.32$). The superinfection was H/VAP in 39 patients, with Gram-negative bacillus documented in 19 cases (45%). These superinfections occurred a median of 10 days after admission. There were 11 cases of COVID-associated pulmonary aspergillosis (CAPA) a median of 9 days after admission. Eight patients had bacteremia (including three with catheter-related bacteremias), and six had urinary tract infections. One patient developed *Pneumocystis jirovecii* pneumonia and one had a *Clostridioides difficile* infection. The median ICU stay was 19 days in the case of superinfection versus 5 days in patients without superinfection ($p < 0.01$). The 28-day mortality rate of patients with superinfection was 36% (21/59), compared with 7% in the others (14/187) ($p < 0.01$). The 28-day mortality was 13% in group 1 and 17% in group 2 ($p = 0.38$). In multivariate analysis, factors associated with a higher risk of superinfection included hemopathy [odds ratio (OR), 2.47; 95% confidence interval (CI), 1.11–5.47], invasive MV (OR, 3.74; 95% CI, 1.92–7.26; $p = 0.0001$), and the SAPS-II score on admission (OR, 1.03; 95% CI, 1.01–1.06; $p = 0.006$) (Table 2). The use

of tocilizumab in addition to dexamethasone was not associated with an increased risk of superinfection (OR, 0.61; 95% CI, 0.33–1.06; $p = 0.11$).

Table 1

Comparison of ICU-hospitalized COVID-19 patients according to immunodulatory treatment on admission

Variable		All patients n = 246	Dexamethasone with Tocilizumab (Group 1) n = 150	Dexamethasone alone (Group 2) n = 96	P value
Male sex, n (%)		178 (72)	118 (79)	60 (62)	0.005
Age, years, median (IQR)		61 (50–71)	60 (49–70)	62 (53–72)	0.20
Age > 65 years, n (%)		101 (41)	56 (37)	45 (47)	0.09
SAPS-II on admission, median (IQR)		27 (22–36)	27 (22–36)	27 (22–36)	0.40
SOFA score on admission, median (IQR)		3 (3–4)	3 (3–4)	3 (2–4)	0.08
Charlson Comorbidity Index, median (IQR)		3 (1–5)	2 (1–4)	3 (1–5)	0.05
Concomitant bacterial infection, n (%)		33 (13)	19 (13)	14 (15)	0.40
Coexisting comorbidities, n (%)	Body Mass Index > 30 kg/m ²	86 (35)	53 (35)	33 (34)	0.49
	Solid cancer	24 (10)	13 (9)	11 (11)	0.31
	Hematologic malignancy	21 (8)	11 (7)	10 (10)	0.27
	Diabetes mellitus	49 (20)	30 (20)	19 (20)	0.55
	Arterial hypertension	88 (36)	55 (37)	33 (34)	0.41
	Non-malignant immunodeficiency	24 (10)	11 (7)	13 (13)	0.08
Admission WHO-scale, median (IQR)		4 (4–4)	4 (4–4)	4 (4–4)	0.93
ARDS (PaO ₂ /FiO ₂ < 300 mmHg), n (%)		226 (92)	141 (94)	85 (89)	0.13
CRP on admission, mg/L, median (IQR)		140 (84–219)	166 (102–233)	103 (60–154)	< 0.001
Ferritin on admission, ng/mL, median (IQR)		1,536 (649–2,624)	1,797 (1,114–2,907)	845 (453–2,043)	< 0.001

P values in bold are statistically significant (P < 0.05)

Variable	All patients n = 246	Dexamethasone with Tocilizumab (Group 1) n = 150	Dexamethasone alone (Group 2) n = 96	P value
Invasive mechanical ventilation, n (%)	56 (23)	37 (25)	19 (20)	0.23
Non-invasive ventilation, n (%)	76 (31)	53 (35)	23 (24)	0.06
High-flow oxygen, n (%)	177 (72)	118 (79)	59 (61)	0.003
Length of mechanical ventilation, days, median (IQR)	14 (9–28)	14 (9–28)	15 (7–27)	0.89
Prone position, n (%)	23 (9)	20 (13)	3 (3)	0.007
Vasopressor support, n (%)	19 (8)	11 (7)	8 (8)	0.77
Renal replacement therapy, n (%)	5 (2)	4 (3)	1 (1)	0.68
Superinfection, n (%)	59 (24)	34 (23)	25 (26)	0.32
COVID-associated pulmonary aspergillosis, n (%)	11 (4)	6 (4)	5 (5)	0.44
Length of ICU stay, days, median (IQR)	6 (3–14)	7 (4–17)	4 (2–8)	< 0.001
14-day WHO-scale, median (IQR)	2 (1–4)	3 (1–4)	1 (1–3)	0.30
28-day WHO-scale, median (IQR)	1 (1–2)	1 (1–2)	1 (1–1)	0.86
28-day mortality, n (%)	22 (9)	10 (7)	12 (12)	0.09
60-day mortality, n (%)	33 (13)	17 (11)	16 (17)	0.16
P values in bold are statistically significant (P < 0.05)				

Table 2
Univariate and Multivariate analysis of predictors independently associated with superinfection episodes in hospitalized patients with COVID-19

Predictor	Univariate analysis		Multivariate analysis	
	OR	Pvalue	OR (95% CI)	Pvalue
Male sex	1.16	0.69		
Age > 65 years	2.02	0.02	1.73 (0.94–3.17)	0.08
Body Mass Index > 30 kg/m ²	0.62	0.15	1.08 (0.53–2.20)	0.84
Solid cancer	1.29	0.56		
Hematologic malignancy	2.74	0.01	2.47 (1.11–5.47)	0.03
Diabete mellitus	1.27	0.47		
Arterial hypertension	0.99	0.98		
Non-malignant immunodeficiency	1.31	0.61		
Invasive mechanical ventilation	4.31	10 ⁻⁴	3.74 (1.92–7.26)	0.0001
Concomitant bacterial infection	2.04	0.05	1.35 (0.59–3.14)	0.48
Tocilizumab	0.47	0.01	0.61 (0.33–1.13)	0.11
SAPS II on admission	1.07	10 ⁻⁴	1.03 (1.01–1.06)	0.006
CRP on admission	1.00	0.45		
Ferritin on admission	1.00	0.63		
Admission WHO-scale	2.77	10 ⁻⁴	0.81 (0.36–1.79)	0.60

Discussion

In this large observational study, 24% of the patients admitted to the ICU for severe COVID-19 who received dexamethasone developed a superinfection. Adjunct tocilizumab was not associated with an increased risk of superinfection. The main factors associated with the risk of superinfection were invasive MV, the SAPS-II score on admission, and hematological malignancy. Early studies of COVID-19 patients reported low rates of bacterial and fungal superinfection.[1–3] At that time, most patients with severe COVID-19 received empirical broad-spectrum antimicrobials, which probably contributed to the low superinfection rates. Empirical antimicrobial therapy is no longer used systematically to avoid antibiotic-resistant superinfections.[7] More recently, IL-6 receptor blockers have been recommended for severe COVID-19 when there is uncertainty about serious adverse infections, especially in the ICU.[7, 12] In a recent meta-analysis, 21.9% of patients randomized to receive IL-6 antagonists developed a superinfection *versus* 17.6% of those randomized to receive usual care or placebo (OR, 0.99; 95% CI,

0.85–1.16). However, the patients were not all ICU patients and the reliability of the results was classified as moderate due to the risk of bias.[10]

Our results are in line with those of a recent French study reporting a 27% superinfection rate during the course of COVID-19 in ICUs.[13] In that study, the superinfection rates of immunocompromised and non-immunocompromised patients (34% vs. 26%) and SAPS-II score at admission (26% vs. 27%) were similar, but only 5% (5/100) of the patients received tocilizumab, compared to 61% in our study.[13] The proportion of patients requiring MV was 54% in the study of Saade, versus 23% in our study. Bacterial H/VAP was the main cause of superinfection, affecting 24% of the patients. Blonz reported a VAP rate of 49% in a population of patients on invasive MV for more than 48 h, while Dudoignon reported a 30% VAP rate in a population of MV patients.[14, 15] In our study, the lower respiratory superinfection rate could be explained by the reduced use of MV, which is the main contributor to superinfection. During our study, 4% of the patients developed CAPA, a rate in accordance with other studies.[16] The non-respiratory superinfection rate did not differ between the two groups, in accordance with the literature.[2]

Our results contrast other published data. In early 2020, Falcone reported a 21.9% superinfection rate among patients admitted to hospital (including only 27% in ICUs), and that the use of immunomodulatory agents (tocilizumab/baricitinib) was associated with an increased risk of superinfection (OR, 5.09; 95% CI, 2.2–11.8; $p < 0.001$).[17] Gangneux *et al.* showed that the combination of anti-IL6 and dexamethasone was associated with a significantly increased risk of CAPA (OR, 2.71) in patients on MV.[18]

Our results suggest that, in patients admitted to an ICU and treated with dexamethasone, superinfection is mainly associated with MV, the SAPS-II score, and hematological malignancy, rather than adjunct tocilizumab. Recent studies have already demonstrated the harmful effects of dexamethasone.[13] Our results can be explained by multiple factors. The ICU was in a non-inundated area of France with a low prevalence of extended-spectrum beta-lactamase. Systematic screening of coinfections and superinfections was protocolized with a multidisciplinary approach, and the experience from other centers prompted us to delay MV when possible. The retrospective single-center design was the main limitation of this study, and must be kept in mind when interpreting the results.

Conclusions

Factors associated with superinfection in the ICU during COVID-19 infection include hematological malignancy, MV, and the SAPS-II score. Tocilizumab in combination with dexamethasone is not associated with an increased risk of superinfection in these patients.

Declarations

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see:

<http://www.textcheck.com/certificate/ez5vQL>

Ethics approval and consent to participate

Patients were informed of the anonymous use of their medical data for clinical research in accordance with French legal standards (CNIL n°2009055).

Consent for publication

All authors agreed to the publication of the current version of the article.

Availability of data and materials

The data sets used during the study are available from the corresponding author on reasonable request.

Competing interests

None.

Funding

No financial support.

Authors' contributions

FC and NI designed the study. FC, and NI collected demographic, clinical and paraclinical data. FC, NI, GM, FB and OG regularly treated COVID-19 patients in ICU. SP and AM checked all the prescriptions of tocilizumab. FC and MH performed the statistical analysis. FC and NI wrote the article. All authors reviewed and approved the article.

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