Viral Clearance After Early Corticosteroid Treatment In Patients With Moderate Or Severe Covid-19

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Abstract

The aim of this study was to evaluate the impact of early treatment with corticosteroids on SARS-CoV-2 clearance in hospitalized COVID-19 patients.

Retrospective analysis on patients admitted to the San Raffaele Hospital (Milan, Italy) with moderate/severe COVID-19 and availability of at least two nasopharyngeal swabs.

The primary outcome was the time to nasopharyngeal swab negativization.

A multivariable Cox model was fitted to determine factors associated with nasopharyngeal swab negativization.

Of 280 patients included, 59 (21.1%) patients were treated with steroids.

Differences observed between steroid users and non-users included the proportion of patients with a baseline PaO_2/FiO_2 ≤200 mmHg (45.8% vs 34.4% in steroids and non-steroids users, respectively; p=0.023) or ≤100 mmHg (16.9% vs 12.7%; p=0.027), and length of hospitalization (20 vs 14 days; p<0.001).

Time to negativization of nasopharyngeal swabs was similar in steroid and non-steroid users (p=0.985).

According to multivariate analysis, SARS-CoV-2 clearance was associated with age ≤70 years, a shorter duration of symptoms at admission, a baseline PaO_2/FiO_2 >200 mmHg, and a lymphocyte count at admission >$1.0*10^9$/L. SARS-CoV-2 clearance was not associated with corticosteroid use.

Our study shows that delayed SARS-CoV-2 clearance in moderate/severe COVID-19 is associated with older age and a more severe disease, but not with early use of corticosteroids

Introduction

As of July 08 2020, the ongoing pandemic of severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV-2) has caused more than 11 million cases of Coronavirus disease-19 (COVID-19), resulting in more than 580,000 deaths [1]. Severe forms of COVID-19 are typically characterized by bilateral interstitial pneumonia and hyperactivation of the inflammatory cascade [2]. Considering the current lack of proven antiviral therapy, several different immunosuppressive agents have been evaluated with the aim of reducing the hyperinflammatory status associated with COVID-19 and improving the patients' prognosis [3].

Corticosteroids are inexpensive and readily available agents that are widely used for their anti-inflammatory effects in patients with respiratory infections. Earlier studies indicated that the use of corticosteroids in patients with SARS and MERS was associated with delayed viral clearance, and no clear benefits in term of survival, length of hospitalization, or use of mechanical ventilation [4]. In

contrast, a recent study demonstrated a possible survival benefit in patients with moderate to severe COVID-19 associated with early corticosteroid use [5]. In addition, preliminary results from the RECOVERY trial [6] confirmed the clear survival benefit of steroid therapy amongst patients requiring respiratory support.

However, very little data on SARS-CoV-2 viral clearance after steroid treatment is currently available [7,8]. The aim of this study was to evaluate the impact of an early treatment with corticosteroids on SARS-CoV-2 viral clearance in hospitalized COVID-19 patients.

Results

Two-hundred and eighty patients were included in this study. The median age was 63.5 (53.5 – 74.0) years, 34% of patients were >70 years, 78% were males, 92% Caucasian, 3% were active smokers, 74% were overweight, and 66% had at least one comorbidity (including diabetes (18%), hypertension (45%), and any cardiovascular (29%), neoplastic (15%), respiratory (9%), neurological (7%), renal (4%), liver (2%), and rheumatic (2%) disease). At hospital admission, COVID-19 associated symptoms had been present for 7 days (4 – 10), while 36.8% and 13.6% of patients had a $PaO_2/FiO_2 \leq 200$ mmHg or ≤ 100 mmHg, respectively. Serum levels of C-reactive Protein (CRP), lactate dehydrogenase (LDH) and ferritin were 70.9 (28.2 – 121.6) mg/L, 340 (275 – 449) U/L, and 1068 (561 – 1876) ng/mL, respectively; plasma D-dimer levels were 1.01 (0.59 – 2.05) µg/mL, total lymphocytes were 1.0 (0.8 – 1.3) 10^9/L, and the neutrophils/lymphocytes ratio was 5.0 (3.1 – 8.6).

During hospitalization, 12 (4.3%) patients died, 24 (8.6%) were admitted to the intensive care unit (ICU), and 95 (34%) required mechanical ventilation (invasive or non-invasive). Antiretrovirals, hydroxychloroquine, and biological agents were administered to 222 (79%), 261 (93%), and 97 (35%) patients, respectively.

Fifty-nine (21.1%) patients were treated with steroids, after a median of 1 day (0 – 2) since admission, and for a total of 9 (7 – 16) days. Initially, intravenous methylprednisolone was used in 55 (93.2%) cases, oral prednisone in 3 (5.1%) cases, and intravenous dexamethasone in 1 (1.7%) case of steroid use. Initial steroid methylprednisolone-equivalent dosage was 0.87 (0-51 – 1.0) mg/Kg.

At steroid discontinuation, 44 (74.6%) steroid users were treated with intravenous methylprednisolone, 10 (6.9%) with oral prednisone, and 5 (8.5%) with intravenous dexamethasone; methylprednisolone-equivalent dosage was 0.38 (0.21 – 0.53) mg/Kg.

Differences between steroid users and non-users were observed with regard to the proportion of patients with a baseline $PaO_2/FiO_2 \leq 200$ mmHg (45.8% vs 34.4% in steroids and non-steroids users, respectively; p=0.023) and ≤100 mmHg (16.9% vs 12.7%, p=0.027), and with regard to the length of hospitalization (20 vs 14 days; p<0.001). Although steroid users had a higher proportion of severe respiratory impairment at admission than non-users, no significant differences between the two groups were found with regard to mortality (6.8% vs 3.6%; p=0.29), use of mechanical ventilation (36% vs 34%; p=0.76), and risk of

subsequent infections (10.4% in both groups; p=0.87). Among 47/59 steroid users without a previous diabetes mellitus diagnosis, 2 (4.3%) steroid users developed new-onset diabetes during hospitalization.

During follow-up, each patient underwent 4 (3 – 5) consecutive nasopharyngeal swabs. The distribution of follow-up nasopharyngeal swabs, and the proportion of negative samples according to days since first positive swab and use of steroids are reported in Figure 1. Time to negativization of nasopharyngeal swabs according to the use of steroids, biological agents, and baseline lymphocyte cell count is also shown in Figure 1.

Using multivariate analysis (Table 1), SARS-CoV-2 clearance was associated with age ≤70 years (aHR=1.52, CI 1.08 – 2.14; p=0.017), shorter symptoms duration at hospital admission (aHR=0.82 (0.70-0.96) per 5-days longer; p=0.015), baseline PaO_2/FiO_2 > 200 mmHg (aHR=1.44, CI 1.03 – 2.01; p=0.03), and a lymphocyte count at admission > $1.0*10^9$/L (aHR=1.63, CI 1.16 – 2.28; p=0.005). Use of corticosteroids did not impact on viral clearance (aHR= 1.06, CI 0.73 – 1.55; p=0.755).

Table 1. Multivariable analysis: factors associated with the risk of negativization of nasopharyngeal swab.

Covariates	Category	Adjusted hazard ratio (95% confidence interval)	p-value
Age, years	≤70 vs >70	1.517 (1.077-2.136)	0.017
Gender	Female vs Male	1.234 (0.847-1.800)	0.274
Days from symptoms to hospital admission	Per 5-days longer	0.821 (0.700-0.963)	0.015
Comorbidities*	≥1 vs none	1.070 (0.766-1.496)	0.691
PaO_2/FiO_2	>200 vs ≤200	1.440 (1.034-2.005)	0.031
Use of immunomodulatory drugs	Yes vs No	0.865 (0.624-1.199)	0.383
Use of antiviral drugs or hydroxychloroquine	Yes vs No	0.751 (0.296-1.904)	0.546
Use of steroid	Yes vs No	1.062 (0.728-1.548)	0.755
Lactate dehydrogenase, U/L	≤330 vs >330	0.915 (0.652-1.285)	0.608
C-reactive protein, mg/L	≤68.7 vs >68.7	0.888 (0.639-1.234)	0.478
Total lymphocytes, per 10^9/L	>1 vs ≤1	1.625 (1.156-2.284)	0.005

All covariates were measured at baseline.

*The following comorbidities were considered: malignancies, diabetes, cardiovascular disease, hypertension, asthma, chronic obstructive pulmonary disease, moderate or severe liver disease, moderate or severe renal disease, neurological disease (chronic neurological disorder, dementia), rheumatic diseases.

Discussion

A concern against the use of corticosteroids in COVID-19 is the potential negative impact of steroids on the control of SARS-CoV-2 viral replication and the consequent delayed viral clearance, as reported in other viral pneumonia [4]. Our study shows that steroid treatment has no impact on viral clearance in patients with moderate or severe COVID-19. Our results are similar to those reported in two other studies on smaller cohorts of patients [7,8].

In our study, we also observed an association between delayed viral clearance and older age. The characteristic age-related immune decline observed in elderly patients [9] may impair their ability to control SARS-CoV-2 infection, potentially explaining the higher risk of viral persistence observed in subjects ≥ 70 years. A delayed viral clearance was also related with a longer duration of symptoms before hospitalization and with respiratory impairment and lymphopenia at admission. All these different factors may reflect a more severe disease and consequently a higher probable viral load in the respiratory tract [10].

Our study has several limitations. First, we cannot exclude a potential selection bias, given that the included patients need to have at least two nasopharyngeal swabs. This criterion excluded patients showing a more aggressive course who unfortunately died within a few days of hospital admission (leading also to an underestimation of the number of observed deaths). Second, treatment with steroids was not standardized, and the decision to administer this drug and the timing of administration was at the discretion of the different physicians. This approach might be associated with a potential indication bias.

In conclusion, our study showed that delayed SARS-CoV-2 clearance in moderate/severe COVID-19 was associated with older age and a more severe disease, but not with an early use of corticosteroids. Considering our findings and the growing body of scientific evidences [5,6] on steroid efficacy in improving survival in COVID-19 patients, reluctance toward steroid use for the management of COVID-19 may negatively impact patient outcomes.

Methods

For this retrospective analysis, we considered all patients admitted between February 25th 2020 and May 19th 2020 to the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele (Milan, Italy) with moderate or severe COVID-19, a definite outcome (discharge or death), complete information on therapies administered during hospitalization, and the availability of at least two nasopharyngeal swabs (one at hospital admission and ≥1 thereafter).

We obtained data from the COVID-BioB clinical database of the IRCCS San Raffaele Hospital. The study was approved by the Ethics Committee of San Raffaele Hospital (protocol No. 34/int/2020) and was registered on ClinicalTrials.gov (NCT04318366). All patients signed an informed consent form. Our research was in compliance to the Declaration of Helsinki.

COVID-19 was diagnosed in all patients with a SARS-CoV-2 positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR; Roche Cobas Systems) assay result from a nasopharyngeal swab and compatible signs, symptoms, and/or radiological findings. All nasopharyngeal samples were submitted to the San Raffaele Scientific Institute Laboratory for RT-PCR testing, yielding qualitative results (positive or negative).

Moderate COVID-19 was defined as the presence, during hospitalization, of: 1) at least one arterial oxygen partial pressure (PaO_2)/fraction inspired oxygen (FiO_2) ratio < 300 mmHg, as determined by arterial blood gas analysis; or 2) supplemental oxygen use; or 3) a peripheral saturation of oxygen < 94%.

Severe COVID-19 was defined as: requiring the need of mechanical ventilation (both invasive and non-invasive). Only steroid treatment within 7 days of admission was considered for this analysis. Patients on chronic steroid therapy were excluded.

Use of corticosteroids in patients with COVID-19 was at the discretion of the different medical teams. All corticosteroids were converted to methylprednisolone-equivalent doses and dosing was reported in mg/Kg. Other treatments considered in the analysis included biological agents (tocilizumab, sarilumab, mavrilimumab, and anakinra), hydroxychloroquine, and antiretrovirals (lopinavir/ritonavir and darunavir/cobicistat).

The primary outcome of this study was the time to nasopharyngeal swab negativization defined by: i) the occurrence of two consecutive negative swabs after hospital admission (baseline), in cases of multiple nasopharyngeal swabs; or ii) the occurrence of a negative swab prior to discharge or death, in cases without multiple nasopharyngeal swabs. In patients treated with corticosteroids, swab negativization (if shown) was attributed to corticosteroid treatment only if it had occurred after steroid introduction.

Statistical analyses

Results were reported as median (interquartile range, IQR) and frequency (%).

Distributions of continuous variables were compared between patients treated with or not treated with steroids using the Wilcoxon rank-sum test or the chi-square/Fisher exact test for categorical variables.

Time to nasopharyngeal swab negativization was estimated by the use of Kaplan-Meier curves; estimates were provided according to different factors and compared by the log-rank test. Follow-up started at baseline and ended at the date of first nasopharyngeal swab negativization, or the date of discharge, or death (whichever occurred first), and was right censored 60 days after baseline owing to the low number of cases thereafter; there were no competing events.

A multivariable Cox proportional hazard model was fitted to determine factors associated with the risk of nasopharyngeal swab negativization; the adjusted hazard ratio (aHR) with the corresponding 95% CI were reported. The included covariates were fitted as time-fixed and measured at baseline. The assumption of

the proportional hazard was examined by use of interactions of the predictors and the function of time; it was confirmed for all covariates.

For the analyses, two-sided p-values <0.05 were considered statistically significant. All analyses were performed using the SAS Software, release 9.4 (SAS Institute, Cary, NC).

Declarations

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTERESTS

None to declare.

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AUTHORS' CONTRIBUTIONS

VS and MG conceived the study, collected and reviewed data, wrote the first draft of the manuscript; AC, PRQ, MR, PS, MM, MT, LD, AL AZ and FC collected and reviewed data, reviewed and edited the manuscript; AP and LG collected and reviewed data and performed statistical analyses

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Figures

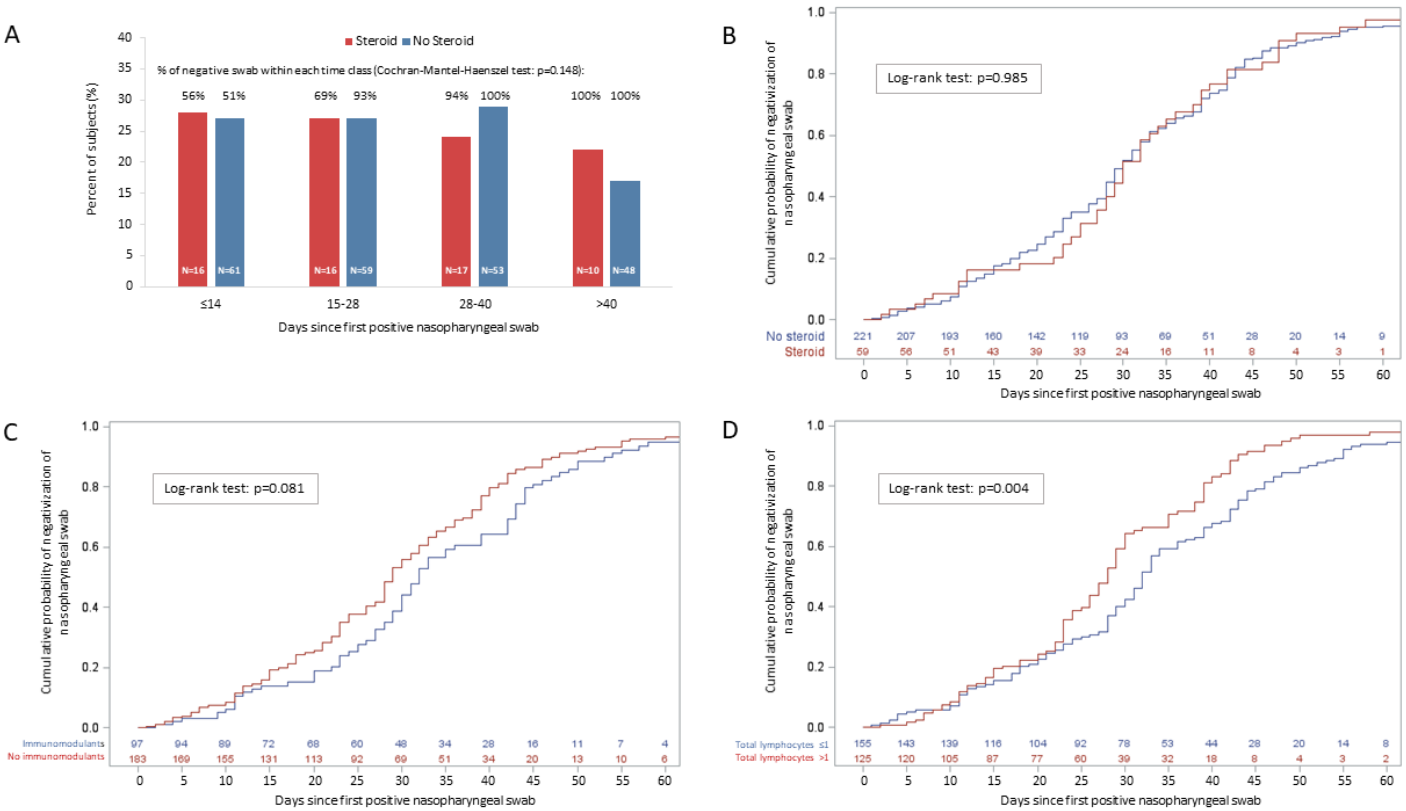

Figure 1

Distribution of follow-up nasopharyngeal swabs according to days since first positive swab and use of steroid (panel A); time to negativization of nasopharyngeal swab according to the use of steroid (panel B); use of immunomodulatory drugs (panel C); lymphocyte count at admission stratified on the overall median value (panel D).