Corticosteroid therapy for patients with COVID-19 pneumonia: a before–after study

Firouzé Bani-Sadr, Maxime Hentzien, Madeline Pascard, Yohan N'Guyen, Amélie Servettaz, Laurent Andreoletti, Lukshe Kanagaratnam, Damien Jolly

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Firouzé BANI-SADR[1], Maxime HENTZIEN[1], Madeline PASCARD[2], Yohan N'GUYEN[1], Amélie SERVETTAZ[1], Laurent ANDREOLETTI[3], Lukshe KANAGARATNAM[2], Damien JOLLY[2]

1- Department of Internal Medicine, Clinical Immunology and Infectious Diseases, Reims University Hospital, Reims, France

2- Department of Research and Public Health, Reims University Hospital, Reims, France

3- Department of Virology, Reims University Hospital, Reims, France

Corresponding author:

Prof. Firouzé BANI-SADR
Department of Internal Medicine, Infectious Diseases, and Clinical Immunology
CHU Robert Debré
rue du Général Koenig
51092 Reims, France
Telephone number: (+33) 3 26 78 71 89
Fax number: (+33) 3 26 78 40 90
E-mail address: fbanisadr@chu-reims.fr

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Abstract

Background: Anti-inflammatory drugs such as corticosteroids may beneficially modulate the host inflammatory response to CoVID-19 pneumonia.

Aims: To evaluate the impact of addition of corticosteroids to the hospital protocol for treatment of suspected or confirmed CoVID-19 pneumonia on rates of death or intensive care unit (ICU) admission.

Methods: A before-after study was performed to evaluate the effect of addition of corticosteroids to our institution's COVID-19 treatment protocol on hospital mortality.

Results: Between March 3rd and April 14th 2020, 257 patients with CoVID-19 diagnosis were included. As corticosteroids were wide used since 27 March 2020, two periods were considered for the purposes of our study: the before period from March 3rd to 20th (n= 85) and the "after period" (n=172) from March 26th to April 14th 2020.

The "after" period was associated with a lower risk of death (HR 0.47; 95% CI, 0.23 - 0.97; p=0.04), and a lower risk of intensive care admission or death before ICU admission (HR 0.37 95% CI 0.21 - 0.64; p=0.0005) by multivariate analysis adjusted for age, National Early Warning score and institutionalization status.

Conclusions: In the "after period", the addition of corticosteroids to our institution's CoVID-19 treatment protocol was associated with a significant reduction in hospital mortality.

Introduction

There is evidence that severe CoVID-19 patients present overwhelming inflammatory reactions with high levels of cytokines and inflammatory biomarkers, leading to lung injury [1,2]. Anti-inflammatory drugs such as corticosteroids may beneficially modulate the host immune response to CoVID-19 pneumonia. With an average of 2-3 days between the occurrence of dyspnea and intensive care unit (ICU) admission, we postulate that corticosteroid treatment initiated as soon as the patient has shortness of breath or needs oxygen therapy, might be effective in preventing acute respiratory distress syndrome and death [3]. Therefore, since 27 March 2020, we have systematically included corticosteroids in the treatment of patients with CoVID-19 pneumonia. Prednisone or methylprednisolone at a dose of 1 mg/kg equivalent per day (0.5 mg/kg for patients also receiving antiviral therapy with ritonavir as coadministration of corticosteroid and ritonavir lead to an increase corticosteroid plasma concentrations and their half-life) for 3 to 4 weeks, according to the severity of pneumonia, with dose tapering over the last week, was added to our initial therapeutic protocol for hospitalized CoVID-19 patients [4]. This protocol included antiviral therapy (lopinavir plus ritonavir or darunavir plus ritonavir) and/or hydroxychloroquine, empiric broad-spectrum antibiotic treatment for 14 days and preventive anticoagulation for 14 to 21 days. The long duration of corticosteroid treatment was chosen by analogy with that recommended for severe pneumocystis pneumonia in order to additionally prevent pulmonary fibrosis [5]. As lopinavir-ritonavir treatment was not available after mid-March due to a drug shortage in our hospital, most of our patients received another HIV protease inhibitor (darunavir-ritonavir) after this date.

In order to evaluate the impact of addition of corticosteroids to the hospital protocol for treatment of suspected or confirmed CoVID-19 pneumonia, we compared rates of death

(primary outcome) or intensive care unit (ICU) admission and/or death before ICU admission (secondary outcome) in a before-and-after study, with the introduction of corticosteroids in our therapeutic protocol as the event defining the start of the “after” period.

Patients and Methods

Between March 3rd and April 14th 2020, 319 patients with CoVID-19 diagnosis defined as a positive result on an polymerase-chain reaction testing of a nasopharyngeal sample or presence of characteristic findings on chest CT scan were followed in the University Hospital of Reims, France [6]. Two periods were considered for the purposes of our study: the first, from March 3rd to 20th, corresponded to the “before” period, and the admission of the first cases to our center. During the “before” period, corticosteroid therapy was not recommended. The second period comprised March 26th through April 14th 2020, (“after”), with wide use of corticosteroid therapy in this period following our decision to introduce it systematically due to the biological rationale of its use in the inflammatory phase. Patients with initiation of corticosteroid therapy during the transition period (from March 21st to March 25th 2020) were not included in the before-after analysis. Patients with fewer than 7 days between symptom onset and April 14th, 2020 - that was the end point date of follow up - were not included.

Individual follow-up was defined as the time from first symptoms to death during hospitalization for the primary outcome and to ICU admission or death before ICU admission for the secondary outcome**.** ICU admission alone was not considered as an outcome, since we did not exclude patients aged over 80 years and/or with comorbidities, who were less likely to have access to ICU care. Data are expressed as mean ± standard deviation, or number (percentage), as appropriate. Quantitative variables were compared between the

two periods using the Student t test and qualitative variables using the Chi square test or Fisher's exact test, as appropriate. For the impact of the period on death and on ICU admission and/or death, we constructed Kaplan Meier curves and compared them using the log rank test. For multivariate analysis, we used Cox proportional hazard models systematically adjusted for age, National Early Warning score and institutionalization status at hospital admission [7].

Results

At the time of data extraction, a total of 319 patients were included in the cohort, namely 85 patients in the "before" period (until March 20th, 2020), 62 patients in the transition period (March 21st – 25th), and 172 patients in the "after" period (March 26th through April 14th). Eleven patients (12.9%) received corticosteroid therapy in the "before period", 20 (32.3%) in the transition period and 119 (69.2%) in the "after" period. The main characteristics of the 257 patients in the "before" and "after" periods are summarized in Table 1. Patients in the "after" period were significantly more frequently nursing home residents, had higher prevalence of dementia, a longer time from symptom onset to hospitalization, less frequently received lopinavir and/or hydroxychloroquine, and more often required oxygen therapy than in the "before" period. Patients in the "after" period also had higher serum creatinine. The mean duration of follow-up was 16.0 ± 7.0 days, and was similar between periods (16.0 ± 8.7 versus 16.1 ± 6.2; p=0.92). Of note, deceased patients hospitalized in medical ward were older than those who were transferred to ICU (mean age 83.9 (±11.3) versus 69.6 (±7.2) years).

The "after period" was not associated with a lower risk of death (hazard ratio (HR) =0.86; 95% confidence interval (CI), 0.47-1.56; p=0.62) by bivariate analyses but was associated by

multivariate analysis adjusted for age, National Early Warning score and institutionalization status (HR = 0.47; 95% CI 0.23 - 0.97; p=0.04).

The “after period” was associated with a lower risk of ICU admission and/or death before ICU admission by bivariate analyses (HR=0.25; 95% CI = 0.11-0.55) and by multivariate analysis adjusted for age, National Early Warning score and institutionalization status (HR =0.37 95% CI 0.21 - 0.64; p=0.0005).

Discussion

In this before-and-after study of 319 hospitalized CoVID-19 patients, after adjustment for age, National Early Warning score and institutionalization status, the "after" period (n=172) -during which corticosteroids were routinely recommended for patients presenting with CoVID-19 pneumonia at our institution- was associated with a lower risk of death (HR =0.47; 95% CI 0.23 - 0.97; p=0.04), and a lower risk of ICU admission and/or death before ICU admission (HR =0.37 95% CI 0.21 - 0.64; p=0.0005).

To this day, corticosteroids are not recommended by the World Health Organization for the treatment of CoVID-19 pneumonia due to their potential adverse effects, such as secondary infections and prolonged virus shedding [8]. However, with our improving knowledge of the role played by overwhelming inflammation in severe CoVID-19 patients, immunomodulatory drugs such as Interleukin-6 or -1 blockade or anti-tumor necrosis factor therapy are being evaluated and all are in favor of a beneficial effect of immunomodulatory drugs during the inflammatory phase of CoVid-19 infection [1,9]. Corticosteroids are old medicines that are inexpensive and accessible to the whole world. In our study, they were associated with a decrease of over 50% in mortality, and in the rate of death and/or ICU admission, even

though patients were more dependent and more often required oxygen in the “after” period at the censoring date (although follow-up duration was similar between the two groups).

We acknowledge that a before-and-after study yields a low level of evidence, the difference may be the result of overall better patient care with improvements in thrombosis prophylaxis and some of these patients remained hospitalized at end of follow-up and were thus censored for outcomes. Furthermore, the favorable outcome observed with corticosteroids may be partly due to the use of concurrent antiviral drugs in our patients. Another limitation of our study is that CoVID-19 pneumonia diagnosis was more often performed by chest CT scan in patients who received corticosteroids group than in patients who did not. Positive reverse transcriptase polymerase-chain reaction is the gold standard for confirming diagnosis of COVID-19 but its performance presents variable sensitivities, ranging from 37% to 71% [10]. Although chest CT scan is highly sensitive for detecting COVID-19 pneumonia, overlapping CT image features with others viral pneumonia and other respiratory diseases make an exclusion diagnosis difficult and could be therefore a source of bias in our study [10]. Finally, the unavailability of safety data should be acknowledged as a limitation.

Nevertheless, these preliminary data support the initiation of clinical trials testing corticosteroids during the inflammatory phase of CoVID-19, and may potentially lead to a change in treatment recommendations.

Reims COVID Study Group

Ailsa ROBBINS, Kévin DIDIER, Pauline ORQUEVAUX, Violaine NOEL, Paola MARIANETTI, Juliette ROMARU, Dorothée LAMBERT, Jean Luc BERGER, Sandra DURY, Maxime DEWOLF, Jean Hugues SALMON, Jérôme COSTA, Julia SIMON, Natacha NOEL, Sara BARRAUD, Marion BARROIS, Hédia BRIXI, Quentin LAURENT-BADR, Manuelle VIGUIER, Clélia VANHAECKE, Laurence GUSDORF, Isabelle QUATRESOUS, Aline CARSIN-VU, Véronique BRODARD, Antoine HUGUENIN, Morgane BONNET, Aurore THIERRY

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Author contributions*:*

All authors participated in the design of the study protocol and data collection. MH, LK, MP, DJ performed the data management and statistical analyses. FBS, MH and DJ wrote the first manuscript draft. All authors participated in interpretation of the data and writing of the final manuscript and all authors approved the final manuscript. FBS was responsible for the overall supervision of the study.

182 **Table I: Main characteristics of patients in the periods before and after introduction of**
183 **corticosteroids for CoVID-19 pneumonia in Reims University Hospital**

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	Before (N=85) n (%) or mean ± SD		After (N=172) n (%) or mean ± SD		p
Received corticosteroids	11	12.9	119	69.2	<0.0001
Age	70.1	±15.1	71.8	±16.4	0.44
Male sex	46	54.1	51.7	41.7	0.72
Charlson comorbidity score	1.8	±2.0	2.05	±1.94	0.42
Dementia	8	9.4	33	19.2	0.04
Nursing home resident	8	9.4	47	27.3	0.001
Time from symptom onset to hospitalization (days)	5.8	±4.2	7.5	±4.9	0.009
Diagnosis by positive PCR	80	94.1	143	83.1	0.01
Diagnosis by chest CT scan	5	5.9	29	16.9	
Risk factor of severity	71	83.5	156	90.7	0.09
- Immunocompromised	11	12.9	22	12.8	0.97
- Cardiovascular disease	41	48.2	94	54.7	0.33
- Complicated diabetes	7	8.2	23	13.4	0.23
- Cirrhosis	1	1.2	3	1.7	0.99
- Chronic respiratory disease	22	25.9	32	18.6	0.18
- Chronic renal disease	4	4.7	16	9.3	0.20
- Cancer	7	8.2	10	5.8	0.46
- BMI>40	2	2.4	13	7.7	0.15
- National Early Warning Score	6.2	3.8	6.9	3.2	0.12
Biological characteristics					
- Lymphocyte count G/L	1.1	±0.56	1.1	±1.0	0.73
- Lymphopenia<1G/L	43	51.2	91	53.9	0.69
- Neutrophil count, G/L	5.0	±3.6	5.6	±4.0	0.26
- C-reactive protein, mg/L	98.0	±90.2	89.9	±77.1	0.46
- Serum creatinine, □mol/L	103.5	±106.2	137.7	±174.3	0.05
Treatment use with expected antiviral activity	63	75.0	135	79.4	0.43
- Lopinavir	46	54.8	13	7.9	<0.0001
- Darunavir	27	32.5	133	78.2	<0.0001
- Hydroxychloroquine	11	13.3	10	6.0	0.049
Antibiotic therapy	80	95.2	162	95.9	0.99
Evolution					
- Required oxygen therapy	52	61.9	125	76.7	0.01
- Maximum oxygen flow in medical ward †	5.0	±7.6	5.7	±5.2	0.48
- Death	17	20.0	31	18.0	0.70
- ICU admission and/or Death	29	34.1	40	23.6	0.07

185 †Among those who received oxygen therapy.

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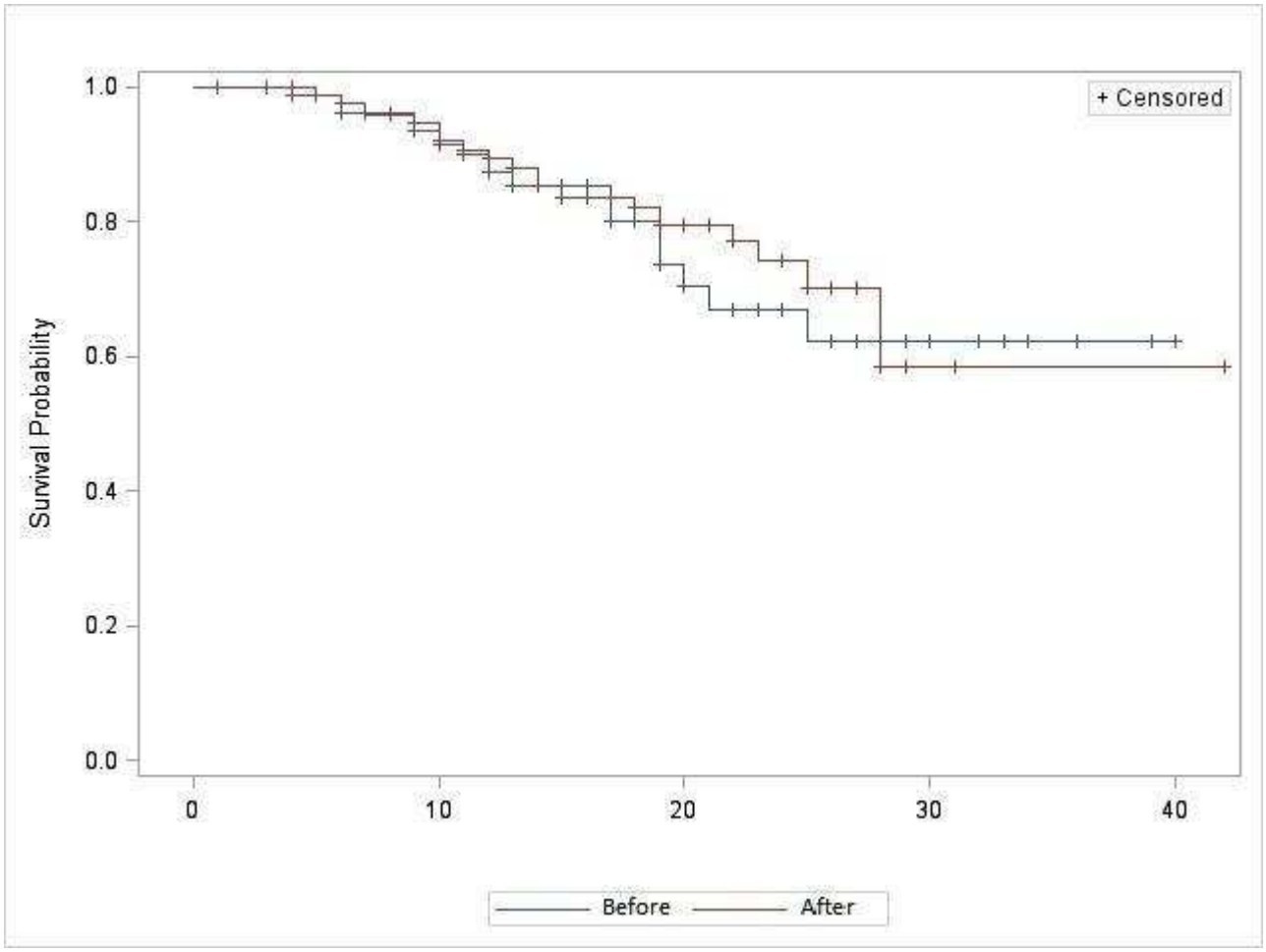
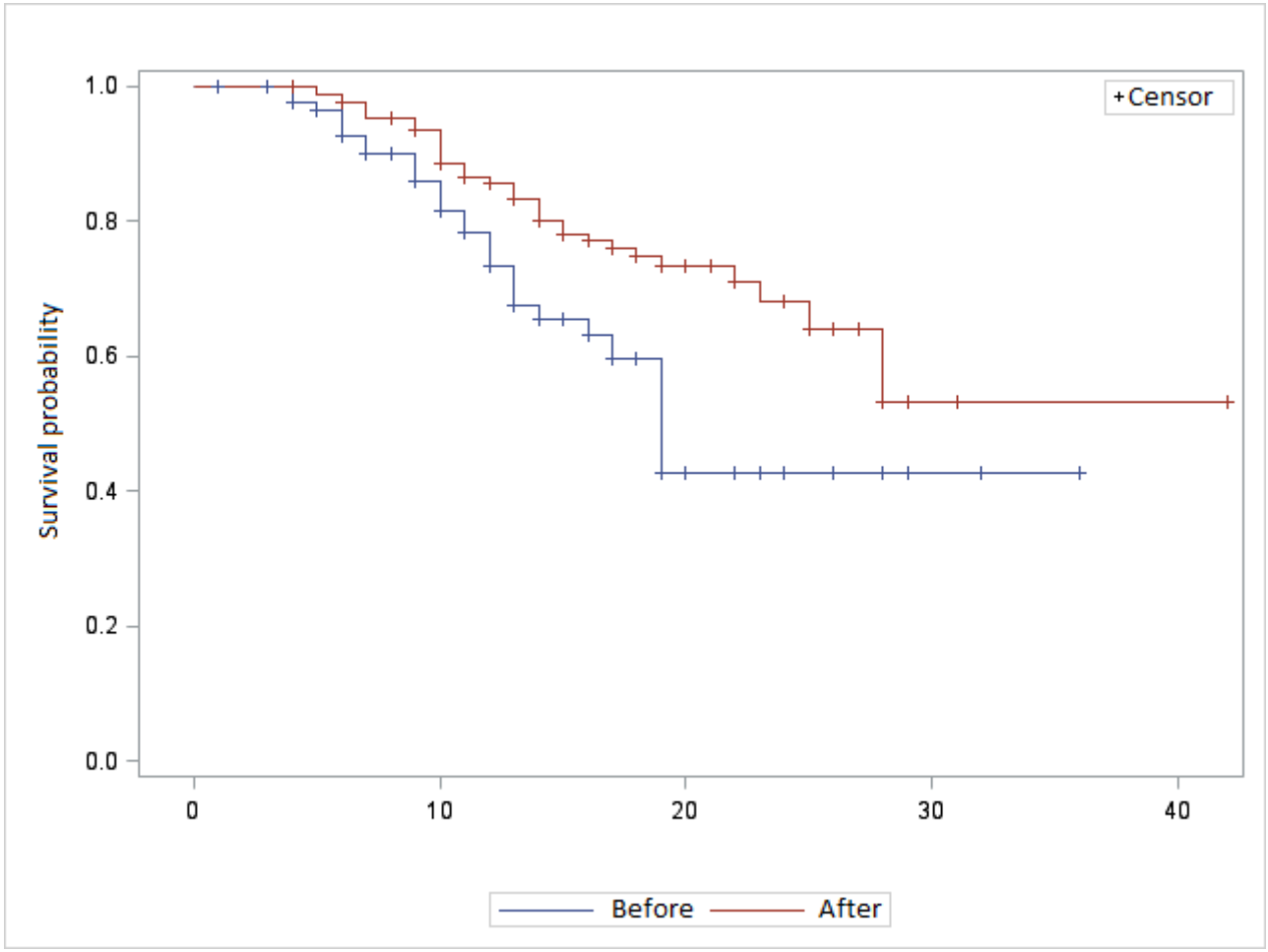
Fig 1: Kaplan Meier curves for death before ICU admission between patients "before" and "after" implementation of corticosteroids for CoVID-19 pneumonia in Reims University Hospital



Kaplan Meier curves for ICU admission and/or death before ICU admission between patients "before" and "after" implementation of corticosteroids for CoVID-19 pneumonia in Reims University Hospital



The "before" period was until March 20th, 2020 and the "After" period began on March 26th, 2020. Log -rank: (p=0.006)

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