Internal and Emergency Medicine (2021) 16:1913–1919
https://doi.org/10.1007/s11739-021-02800-1

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High-dose dexamethasone treatment for COVID-19 severe acute respiratory distress syndrome: a retrospective study

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Received: 28 January 2021 / Accepted: 27 June 2021 / Published online: 17 July 2021

Abstract

Low-dose dexamethasone reduces mortality in patients with coronavirus disease 2019 (COVID-19)-related acute respiratory distress syndrome (ARDS). We retrospectively analyzed the efficacy of high-dose dexamethasone in patients with COVID-19-related ARDS and evaluated factors affecting the composite outcome (death or invasive mechanical ventilation). From March 4th to April 1st 2020, 98 patients with COVID-19 pneumonia were included. Those who after at least 7 days from symptom onset presented a worsening of the respiratory function or of inflammatory biomarkers were started on intravenous high-dose dexamethasone (20 mg daily for 5 days, followed by 10 mg daily for 5 days). Most patients were males (62%) with a mean age of 69 years. Hypertension and cardiovascular disease (CVD) were prevalent. Following dexamethasone treatment, a significant improvement in PaO_2/FiO_2 (277.41 [178.5–374.8] mmHg vs. 146.75 [93.62–231.16] mmHg, $p < 0.001$), PaO_2 (88.15 [76.62–112.0] mmHg vs. 65.65 [57.07–81.22] mmHg, $p < 0.001$), and SpO_2 (96 [95–98]% vs. 94 [90–96]%, $p < 0.001$) was observed. A concomitant decrease in C-reactive protein and ferritin levels was found (132.25 [82.27–186.5] mg/L vs. 7.3 [3.3–24.2] mg/L and 1169 [665–2056] ng/mL vs. 874.0 [569.5–1434] ng/mL, respectively; $p < 0.001$ for both vs. baseline). CVD was found to increase the risk of the composite outcome (RR 7.64, 95% CI 1.24–47.06, $p = 0.028$). In hospitalized patients with COVID-19-related ARDS, high-dose dexamethasone rapidly improves the clinical status and decreases inflammatory biomarkers. CVD was found to increase the risk of the composite outcome. These data support the importance of randomized clinical trials with high-dose dexamethasone in COVID-19 patients.

Keywords COVID-19 · SARS-CoV-2 · ARDS · Dexamethasone · Inflammation · PaO_2 · FiO_2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the pandemic of coronavirus disease 2019 (COVID-19) [1]. Although most patients experience mild symptoms, a small proportion of them develops severe, viral interstitial pneumonia with increasing hypoxia that can cause acute respiratory distress syndrome (ARDS), multiorgan failure, and death [2–5].

McGonagle et al. [6] hypothesized that, in the first stages, the virus induces a temporary immunodeficiency status (i.e., interferon suppression and lymphopenia) [7]. The second step consists in the activation of anti-viral mechanisms, that may trigger an exaggerated immune response characterized by a cytokine storm, i.e. high levels of interleukin (IL)-6 [8] and other cytokines like IL-1, tumor necrosis factor (TNF)-α, IL-18, and granulocyte–macrophage

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colony-stimulating factor (GM-CSF) [2, 9–11]. All these events may then culminate and/or sustain immunothrombosis, that is responsible for poor outcomes [12].

Numerous collaborative trials investigated the effectiveness of remdesivir and some immunomodulating agents with contrasting or neutral results [13–18]. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial has investigated the role of low-dose dexamethasone (6 mg daily up to 10 days) on top of usual care vs. usual care alone in patients with SARS-CoV-2 infection [19]. A reduced 28-day mortality was found in the dexamethasone group compared with the usual care group, with the largest benefit among those patients receiving invasive mechanical ventilation or any oxygen support at the time of randomization. Few weeks before the outbreak of COVID-19 pandemic, a multicenter Spanish study demonstrated that early administration of high-dose dexamethasone in patients with established moderate-to-severe ARDS reduced the duration of mechanical ventilation and overall mortality [20].

The aim of our work was to retrospectively review the efficacy of high-dose dexamethasone in patients with SARS-CoV-2 pneumonia-related ARDS admitted to a COVID-19 hub in Lombardy (Italy) during the first wave of the disease.

Materials and methods

Design

From March 4th to April 1st, 2020, all adult patients (≥ 18 years) with confirmed COVID-19 pneumonia (laboratory real-time-polymerase chain reaction [RT-PCR] SARS-CoV-2 positivity and/or chest computed tomography [CT] scan suggestive for interstitial pneumonia) admitted to the High-Intensity Care of the Internal Medicine Department (Ospedale di Circolo – Fondazione Macchi, ASST dei Sette Laghi, Varese, Italy) were included in the present retrospective study. Patients were admitted to our High-Intensity Unit if they (i) tested positive for severe SARS-CoV-2 infection or had confirmed pneumonia on chest X-ray or highly suspected findings for COVID-19 on chest CT scan; (ii) had respiratory failure requiring oxygen administration and (iii) did not require intubation according to anesthesiologist evaluation. Based on low-evidence guidelines available during the first weeks of the pandemic, they were treated with lopinavir/ritonavir, hydroxychloroquine, low-molecular weight heparin (LMWH), oxygen and, in case of a suspected bacterial superinfection, antibiotic therapy (e.g., azithromycin, ceftriaxone or levofloxacin). After at least 7 days from symptom onset, those who presented a worsening of the respiratory function, increasing value of C-reactive protein (CRP) compared with baseline, and an arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO_2/FiO_2) < 300 mmHg were treated with intravenous dexamethasone (20 mg once daily from day 1 to day 5, followed by 10 mg once daily from day 6 to day 10).

Clinical examination, including pulse oximetric saturation (SpO_2) assessment, blood tests, and arterial blood gas analysis were performed according to routine clinical practice.

The study was conducted in accordance with the Declaration of Helsinki (revised version 2000) and was approved by the local Institutional Review Board.

Oxygen delivery

At the time of the enrollment in the study, all patients were provided with oxygen support, including nasal cannula (airflow between 2 and 6 L/min), Venturi mask (airflow between 8 and 10 L/min), non-rebreather mask (airflow 15 L/min), and continuous positive airway pressure (CPAP).

Definitions

Cardiovascular (CV) disease included a history of myocardial infarction or unstable angina. Cerebrovascular disease included a history of ischemic or hemorrhagic stroke or transient ischemic attack. Obesity was defined according to a body mass index (BMI) ≥ 30 kg/m^2. Chronic kidney disease (CKD) was defined for an estimated glomerular filtration rate < 60 mL/min/1.73 m^2, according to the Cockcroft–Gault equation [21]. Chronic liver disease was defined as the progressive deterioration of liver function for more than six months secondary to toxins, alcohol abuse, infection, autoimmune disease, genetic and metabolic disorders. Fever was defined for a body temperature > 37.5 °C. The composite outcome was defined by the occurrence of death or admission to the intensive care unit (ICU), whatever came first.

Study endpoints

The primary endpoint of the study was the assessment of the respiratory function—expressed as PaO_2/FiO_2—after 10 days of dexamethasone treatment. Secondary endpoints included (i) the evaluation of SpO_2 throughout the treatment period, (ii) the occurrence of the composite outcome, and (iii) the assessment of factors predicting the composite outcome.

Statistical analysis

The distribution of continuous data was examined using the Shapiro–Wilk test. Non-normally distributed continuous variables are expressed as median and interquartile range [IQR], while normally distributed variables are presented as mean ± standard deviation (SD). Data with a non-Gaussian

distribution were analyzed using the Mann–Whitney *U* test, while categorical variables were compared using a Chi-squared test or Fisher's exact test, as appropriate. Variations of continuous variables between two time points were tested with Wilcoxon signed rank test, while the McNemar's test was used for categorical variables. Given the limited number of events of the composite outcome ($n=13$), we used a backward stepwise regression analysis to determine independent predictors for the composite outcome. Risk ratio (RR) and the corresponding 95% confidence interval (95% CI) are presented. For all statistical analyses, a two-sided p value <0.05 was considered as statistically significant. Analyses were performed using IBM SPSS Statistics for Mac, version 26.0 (IBM CO., Armonk, NY, USA) and GraphPad Prism, version 8.2 for Windows (GraphPad Software, La Jolla, CA, USA, www.graphpad.com).

Results

Characteristics of the cohort

Ninety-eight consecutive patients were included in the present study, the majority being males ($n=61$, 62.2%) and with a mean age of 69 years (Table 1). A small number of patients (5, 5.9%) tested negative for SARS-CoV-2 but presented interstitial pneumonia on imaging that was highly suggestive for COVID-19. Before hospitalization, most common symptoms were fever ($n=93$, 94.9%) and dyspnea ($n=80$, 81.6%). Laboratory tests showed increased values of all acute-phase reactants, including CRP), ferritin, and fibrinogen (Table 1).

Hypertension was the most frequent comorbidity, followed by CV disease ($n=41$, 41.8%) and obesity ($n=36$, 36.7%).

At baseline (i.e., pre-high-dose dexamethasone treatment), all patients were on oxygen therapy. Most of them were on a non-rebreather (34.8%) or a Venturi mask (30.8%). Fifteen patients (16.5%) were on CPAP. Details on oxygen delivery are summarized in Supplementary Fig. 1.

Oxygen values during the study period

After 10 days of high-dose dexamethasone treatment, a statistically significant improvement in PaO_2/FiO_2 (277.41 [178.5–374.8] vs. 146.75 [93.62–231.16], $p<0.001$), PaO_2 (88.15 [76.62–112.0] mmHg vs. 65.65 [57.07–81.22] mmHg, $p<0.001$), and SpO_2 (96 [95–98]% vs. 94 [90–96]%, $p<0.001$) was found (Fig. 1A–C and Supplementary Table 1). This held true also at day 3 and day 5 when compared with baseline (Fig. 1A–C).

A reduction in supplemental oxygen therapy, evaluated through FiO_2 values, was recorded at the 10th day of treatment compared with baseline (0.35 [0.26–0.50] vs. 0.50 [0.28–0.80], $p<0.001$) (Supplementary Fig. 2). A decrease in the number of patients using a non-rebreather mask was

Table 1 Patients' characteristics at baseline (i.e., before high-dose dexamethasone treatment)

	Overall cohort ($n=98$)
Anthropometric parameters	
Males *n* (%)	61 (62.2%)
Females *n* (%)	37 (36.7%)
Age, years	69 ± 13
Weight, kg	75 [65–84]
Height, m	1.69 ± 0.09
BMI, kg/m^2	25.4 [22.9–29.2]
Comorbidities	
Hypertension, *n* (%)	57 (58.2%)
Cardiovascular diseases, *n* (%)	41 (41.8%)
Diabetes, *n* (%)	20 (20.4%)
Obesity, *n* (%)	36 (36.7%)
Cerebrovascular diseases, *n* (%)	19 (19.4%)
COPD, *n* (%)	11 (11.2)
Cancer, *n* (%)	12 (12.2%)
Liver disease, *n* (%)	3 (3.1%)
CKD, *n* (%)	8 (8.2%)
Autoimmune diseases, *n* (%)	2 (2.0%)
Symptoms at onset	
Cough, *n* (%)	59 (60.2%)
Fever, *n* (%)	93 (94.9%)
Dyspnea, *n* (%)	80 (81.6%)
Gastrointestinal symptoms, *n* (%)	13 (13.3%)
Days from symptom onset	9 [7–12]
Pre-steroid treatment	
Antiviral drugs, *n* (%)	44 (44.9%)
Hydroxychloroquine, *n* (%)	90 (91.8%)
Azithromycin, *n* (%)	22 (22.4%)
Levofloxacin, *n* (%)	51 (52.0%)
Ceftriaxone, *n* (%)	46 (46.9%)
LMWH, *n* (%)	93 (94.9%)
Tocilizumab, *n* (%)	5 (5.1%)
Laboratory tests	
WBC (× 10^3/mL)	7.21 [5.9–9.4]
RBC (× 10^6/mL)	4.41 ± 1.86
Hemoglobin (g/dL)	13.01 ± 1.86
PLT (× 10^3/mL)	208.5 [160.7–265.0]
CRP (mg/L)	132.2 [82.3–186.5]
Ferritin (ng/mL)	1169.0 [665.0–2,056.0]
Fibrinogen (mg/dL)	615.0 [505.5–689.0]
D-dimer (μg/L)	1980 ± 2919.3

BMI body mass index; *COPD* chronic obstructive pulmonary disease; *CKD* chronic kidney disease; *CRP* C-reactive protein; *LMWH* low-molecular-weight heparin; *PLT* platelets; *RBC* red blood cells; *WBC* white blood cells

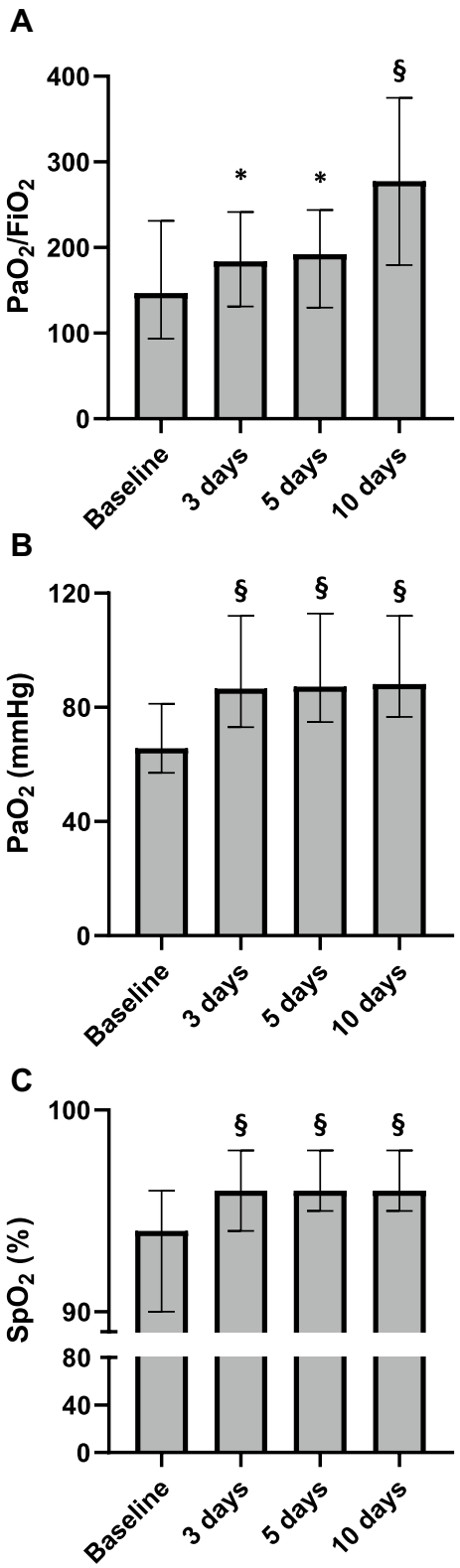

Fig. 1 Improvement of respiratory function over the treatment period. A progressive and statistically significant improvement in PaO_2/FiO_2 (panel A), PaO_2 (panel B), and SpO_2 (panel C) was observed starting from day 3 of dexamethasone treatment. *PaO_2* arterial oxygen partial pressure, *PaO_2/FiO2* arterial oxygen partial pressure to fractional inspired oxygen ratio, *SpO2* pulse oximetric saturation. $^{*}p<0.05$ and $^{\S}p<0.001$ vs. baseline for Wilcoxon signed rank test

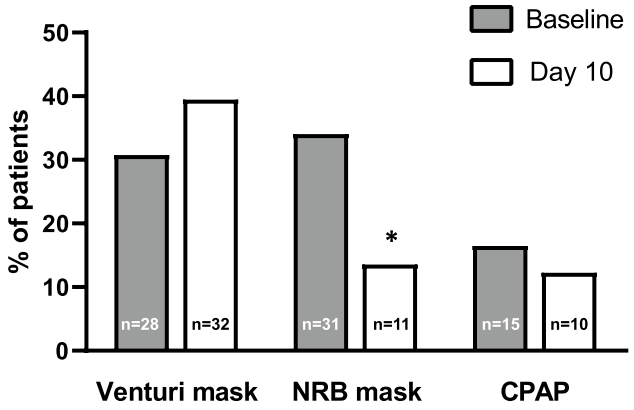

Fig. 2 Oxygen support throughout the study period. The number of patients using a non-rebreather mask significantly decreased from baseline to day 10 ($p=0.004$). A non-statistically significant reduction in the use of CPAP was observed. As well, a non-statistically significant increase in the proportion of patients using a Venturi mask was recorded. *CPAP* continuous positive airway pressure. $^{*}p<0.05$ vs. baseline for McNemar's test

found from baseline to day 10 (34.1%, $n=31$ vs. 13.6%, $n=11$, $p=0.004$), while a non-statistically significant reduction in the number of patients on CPAP was observed across the same time lapse (Fig. 2). A non-statistically significant increase in the proportion of patients on Venturi mask was observed from baseline to day 10 (Fig. 2).

Clinical response during dexamethasone treatment

After 10 days of high-dose dexamethasone, 9 out of 98 patients (9.2%) died, whereas 4 (4.1%) were admitted to the ICU for invasive mechanical ventilation.

A statistically significant reduction in the number of patients with fever (94.9% vs. 6.1%, $p<0.001$), dyspnea (81.6% vs. 20.4%, $p<0.001$), and cough (60.2% vs. 21.4%, $p<0.001$) was recorded, while no change was observed in gastrointestinal symptoms (13.3 vs. 5.1%, $p=0.077$) (Fig. 3). With regard to laboratory tests, CRP and ferritin significantly decreased after 10 days (132.25 [82.27–186.5] mg/L vs. 7.3 [3.3–24.2] mg/L and 1169 [665–2056] ng/mL vs. 874.0 [569.5–1434] ng/mL, respectively; $p<0.001$ for both), while fibrinogen did not (615.0 [505.5–689.0] mg/dL vs. 387.0 [282.0–535.0] mg/dL, $p=0.109$) (Fig. 4A–C).

Using a backward stepwise analysis (including age, sex, weight, baseline ferritin, baseline PaO_2/FiO_2, CV disease, hypertension, diabetes, cerebrovascular disease, chronic liver and kidney disease, obesity, COPD, and cancer), CV disease was found to increase the risk of occurrence of the composite outcome (RR 7.64, 95% CI 1.24–47.06, $p=0.028$), while weight appeared to reduce this risk (RR 0.90, 95% CI 0.81–1.00, $p=0.041$).

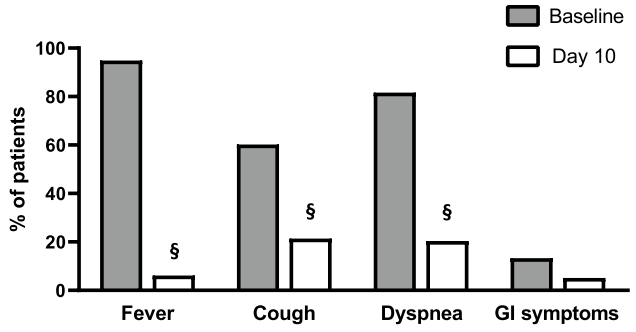

Fig. 3 Symptoms over treatment period. Across the 10-day treatment period, the majority of patients experienced an improvement in fever, cough, and dyspnea, while no difference was found for gastrointestinal symptoms. *GI* gastrointestinal. $^{§}p < 0.001$ vs. baseline for McNemar's test

Adverse events

The number of adverse events (AEs) was low. The most frequent AE was delirium ($n = 18$, 18%), followed by new-onset atrial fibrillation ($n = 4$, 4%), hyperglycemia ($n = 3$, 3%), and herpes zoster ($n = 1$, 1%). No infections were recorded during the treatment period.

Discussion

In our retrospective, observational study involving nearly 100 consecutively hospitalized patients with ARDS secondary to SARS-CoV-2 pneumonia and treated with intravenous infusion of dexamethasone for 10 days, we found a significant improvement in the respiratory function, evaluated through PaO_2/FiO_2, as well as a rapid reduction of oxygen needs. The treatment had very few AEs, most of them represented by delirium, which is commonly experienced in patients treated with glucocorticoids [22].

A wealth of evidence points to the exaggerated host inflammatory response as the main cause for SARS-CoV-2-related ARDS, similar to what happens in macrophage activation syndrome or chimeric antigen receptor-T-cell-related cytokine release syndrome [9, 23]. Indeed, after the initial "viremic phase", in a subgroup of patients infiltrating monocytes, macrophages, neutrophils, lung epithelial and endothelial cells start producing large quantities of inflammatory cytokines—i.e., IL-6, TNF-α, IL-18, GM-CSF, and interferon-γ—that determine severe ARDS [6, 8, 10, 11, 24]. This concept has promoted a large number of clinical trials testing immunomodulating agents, with controversial or neutral results [8, 25].

From *in vitro* and *in vivo* studies, glucocorticoids are well known to inhibit pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6 [26]. Accordingly, high-dose

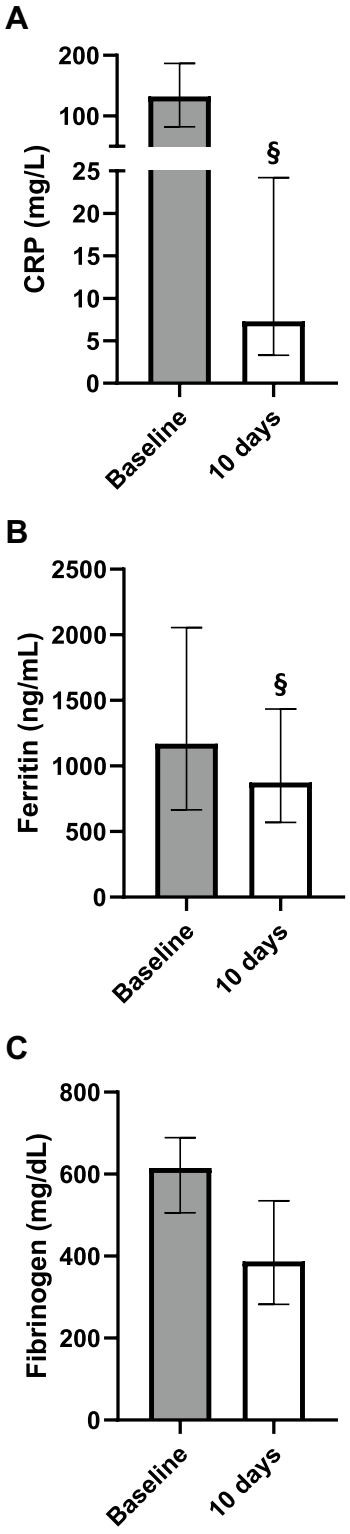

Fig. 4 Inflammatory biomarkers over treatment period. Following the 10-day dexamethasone treatment, a striking improvement in CRP and ferritin levels was observed (panels A–B), while only a trend for a decrease in fibrinogen was recorded (panel C). *CRP* C-reactive protein, *GI* gastrointestinal, $^{§}p < 0.001$ vs. baseline for Wilcoxon signed rank test

glucocorticoids could be used in patients who develop a hyperinflammatory response (defined by the concomitant presence of ARDS, worsening of the respiratory function, and increasing value of CRP at least 7 days after symptoms onset) to prevent ARDS or its progression. Previous studies in patients with SARS and Middle East respiratory syndrome (MERS) treated with glucocorticoids were generally controversial. Most of them described a potential harm rather than a benefit due to a delay in viral clearance, with only few of them showing beneficial results [27–29].

Villar et al. demonstrated that high-dose dexamethasone shortened the duration of mechanical ventilation and reduced overall mortality in patients with moderate-to-severe ARDS [20]. The RECOVERY trial has shown that low-dose dexamethasone for 10 days provided a 20% reduction in 28-day mortality in COVID-19-related ARDS patients, especially among those on invasive mechanical ventilation and on oxygen support [19]. Tomazini et al. investigated the efficacy of intravenous high-dose dexamethasone (20 mg daily for 5 days, followed by 10 mg daily for other 5 days) plus standard care vs. standard care alone in patients with COVID-19 and moderate-to-severe ARDS. They concluded that the use of dexamethasone plus standard care increased the number of ventilator-free days compared with standard care alone [30]. A prospective meta-analysis evaluating systemic administration of glucocorticoids compared with usual care or placebo in critically ill patients with COVID-19 has shown to lower 28-day all-cause mortality as well [31]. Our data with high-dose dexamethasone confirmed the above-mentioned findings with a rapid improvement in terms of respiratory function starting from day 3, as highlighted by the increase in the PaO_2/FiO_2 and SpO_2. After 10 days of treatment, most of the patients had their symptoms (fever, dyspnea, and cough) improved along with a low rate of AEs, in particular no infection was recorded.

Finally, when considering patients' comorbidities, we found that a history of CV disease was the only factor negatively affecting patients' outcome. This is not unexpected, as CV disease was recognized as a negative prognostic factor in other studies [5, 32, 33].

In spite of these positive results, recently some papers came out questioning the positive effects of high-dose glucocorticoids, either dexamethasone or methylprednisolone [34–36]. However, other studies supported the beneficial effects of an immediate blunting of hyperinflammation using high-dose glucocorticoids in terms of increased survival [37–39].

Our study, however, is not without limitations. The retrospective nature, the limited number of patients, and the absence of a control group cannot allow to demonstrate a definitive efficacy of glucocorticoid treatment. Given the challenging period during which the study was conducted, some data were incomplete or missing.

In conclusion, this retrospective observational study in hospitalized patients treated with high-dose dexamethasone during the hyperinflammatory phase of COVID-19 showed a rapid and significant improvement in clinical and laboratory parameters along with a low rate of AEs. Randomized clinical trials are eagerly needed to confirm our positive, preliminary data with high-dose dexamethasone in COVID-19 patients. Indeed, REMED is a prospective, phase II, open-label, randomized controlled trial comparing the efficacy of dexamethasone 20 mg vs. 6 mg daily (NCT04663555, EudraCT No.:2020-005,887-70) [40].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11739-021-02800-1.

Authors' contribution ABa, FT, BP, AA, RC, SF, AMM, and DDG collected the data and designed the database. AV, Aba, and ABo performed the statistical analyses and drafted the first version of the manuscript. FT, NM, OP, AMM, DDG, and FD critically revised the manuscript. AV and ABa equally contributed as first authors to this work. All authors approved the final version of the manuscript.

Declarations

Conflict of interest Dr. Bonaventura and Dr. Vecchié received a travel grant from Kiniksa Pharmaceuticals Ltd. to attend the 2019 AHA Scientific Sessions and receive honoraria from Effetti s.r.l. (Milan, Italy) to collaborate on the medical website www.inflammology.org. The remaining authors have nothing to disclose related to this study.

Statements on human and animal rights The study was conducted in accordance with the Declaration of Helsinki (revised version 2000) and was approved by the local Institutional Review Board.

Informed consent Patient consent was collected before study inclusion.

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