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Systemic corticosteroid therapy in the post-acute period of COVID-19 pneumonia with torpid clinical and radiological evolution

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Abstract

COVID-19 pneumonia generates both immediate damage due to the viral effects and distant damage due to inflammatory immune deregulation. Systemic corticosteroid therapy has proven to be beneficial in the first part of the process, but its usefulness in post-acute damage is still unclear. The number of affected patients makes it imperative to find a treatment that reduces potential pulmonary sequelae. This series of cases included 18 patients admitted to polyvalent private medical institutions of Buenos Aires City: 15 were male and 3 were female; age 58.4 ± 13.6 years. History of most common comorbidities: AHT (4 patients), obesity (6 patients) and smoking (4 patients). Five patients had no medical history. All patients showed dyspnea, oxygen desaturation, and persistent or progressive tomographic abnormalities 14 days after their infection. All of them received dexamethasone according to current regulations. Subsequently, given the poor evolution, they were administered oral and/or intravenous corticosteroids with the same treatment used for secondary organizing pneumonia (OP). A transbronchial biopsy was performed in 6 of the patients, showing an OP pattern in 3 of them. Four weeks after the beginning of the treatment, all of the patients showed clinical improvement expressed by decreased dyspnea and the fact that they didn't require oxygen anymore and that all chest tomographies showed clearly reduced pulmonary parenchymal involvement. Systemic corticosteroids administered in the post-acute period of COVID-19 have a clinical and radiological beneficial effect.

Key words: COVID-19 pneumonia - Secondary organizing pneumonia - Systemic corticosteroid therapy

Abbreviations

COVID-19	SARS-CoV-2 infection
NYHA	New York Health Association
O_2	oxygen
OP	organizing pneumonia
CAT	computed axial tomography
MRA	mechanical respiratory assistance
FBC	fibrobronchoscopy
BAL	bronchoalveolar lavage
TBB	transbronchial biopsy
DAD	diffuse alveolar damage
CIP	cell interstitial pneumonia
mg/kg	milligrams per kilogram of body weight

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Introduction

Since the beginning of the COVID-19 pandemic, there has been a lot of debate about the usefulness of corticosteroids for the treatment. From the beginning, they were thought to have even a potential harmful effect[1]; subsequently they showed their usefulness in patients with severe acute pneumonia with requirement of oxygen therapy or some type of ventilatory support[2]. Patients who overcome the acute phase of the disease may show clinical and radiological alterations[3-4-5] in the post-acute period, with their long-term evolution not clearly known yet. It is very important to have tested treatments in order to accelerate recovery and reduce potential sequelae[6]. Corticosteroids would counteract the inflammatory process triggered by the viral infection and perpetuated by an "uncontrolled" immune system[7]. This case report tried to give at least an initial response to this hypothesis, describing the clinical and radiological evolution of patients who received that treatment.

Materials and Methods

For this report, we included 18 patients with severe[8] COVID-19 pneumonia who 14 days after the beginning of the symptoms persisted with significant clinical alterations (dyspnea FC III – IV according to the NYHA scale, not explained by any other cause), altered oximetry readings (oxygen desaturation (O_2) breathing ambient air, not present before COVID-19) and/or tomographic alterations (bilateral parenchymal infiltrates suggestive of organizing pneumonia (OP) or late appearance of new infiltrates not explained by an infection of a different etiology). The patients were evaluated and treated in 3 polyvalent private medical institutions of the Autonomous City of Buenos Aires.

All the patients received treatment with dexamethasone during the acute period, according to what was described in the Recovery study[2], indicating in some cases other therapeutic measures based on what was approved at the moment of the hospitalization (convalescent plasma, hyperimmune equine serum, hydroxychloroquine, antiretroviral medicines).

We performed chest tomographies (CAT) upon hospitalization, in cases of clinical changes showing worsening of the patient's respiratory condition, at the beginning of corticosteroid treatment and 4 weeks after the beginning of such treatment. We used intravenous pulse corticosteroids (methylprednisolone, 500 mg a day, 3 doses) in patients with mechanical respiratory assistance (MRA) or spontaneous breathing with high O_2 requirement through high flow cannula or mask with reservoir bag. Patients with O_2 requirement per conventional nasal cannula or less than 5 liters/minute were prescribed oral corticosteroids (meprednisone, 0.5 to 0.75 mg/kg/day). This regimen was administered after the intravenous dose in patients who required pulse dosing. The treatment was extended for 3 to 6 months, like other organizing pneumonias[9], with progressive decrease depending on the clinical, oximetric and radiological response. Patients with suspected aggregated infections underwent a bronchoscopy (FBC) with bronchoalveolar lavage (BAL) and transbronchial biopsies (TBB), provided that it was clinically possible and safe, in order to dismiss the suspicion and also to try and record the anatomopathological characteristics of the inflammatory process shown in the images.

Ethical consideration

This draft is a series of case reports. Merely descriptive approaches focused on the interpretation of the results have been adopted, trying to reach valid conclusions. It hasn't been produced in the context of a research trial with control groups or randomized treatments. The patients signed their informed consent upon hospitalization and before performing the bronchoscopy. It follows the guidelines of the Personal Data Protection Act No. 25,236, particularly sections 1, 5 subsection D, 8 and 11, subsection D.

Results

15 out of the 18 patients included were male and 3 female, with a mean age of 58.4 ± 13.6 years. There were five patients without a pathological history. The other 13 had clinical and oncological medical history **(Table 1)**. All the patients were administered dexamethasone, 6 mg/day intravenously or orally for 10 days, according to the Recovery study. Mean time from the onset of symptoms until the beginning of corticosteroid, "non-dexamethasone" treatment was 28.1 ± 10 days. Given the severity of their clinical condition, 7 patients initially received intravenous treatment with methylprednisolone (5 patients with high-flow nasal cannula or mask with reservoir bag and 2 with MRA). Those treated with oral corticosteroids received meprednisone, 50 ± 12 mg/day.

6 patients underwent FBC with BAL and TBB. No germs were isolated. The anatomopathological report showed OP pattern in 3 patients: it was associated with diffuse alveolar damage (DAD) in 2 cases, and with lymphocytic inflammation or cell interstitial pneumonia (CIP) in 1 patient. One patient showed isolated DAD changes, another patient had acute neutrophil inflammatory damage and the remaining one reported CIP.

Six of the 18 patients required home O_2 supply after hospital discharge, due to dyspnea or desaturation. One month after discharge, none of the patients continued with the indication of O_2 supply.

The chest CAT performed 4 weeks after hospital discharge showed in all of the patients a clear reduction of the parenchymal involvement, and the most frequent finding was ground-glass persistence associated with septal thickening **(Figures 1 and 2)**. Only 1 patient had traction bronchiectasis and another one showed images compatible with pneumatocele.

TABLE 1. General Characteristics of Patients

Sex	Comorbidities	Age	Ferritin DD/pCr	ARM	DXM	DOS until non- DXM CT	Mepredn OR	Methyl pred IR	TBB	0_2upon discharge	0_2 after one month
M	No PH	51	NA	No	Yes	39	40	No	OP+ DAD	Yes	No
M	AHT SM PC IMBT	73	867/697/52	No	Yes	33	60	Yes	NA	Yes	No
M	ICM DBT DPM	85	433/437/13	No	Yes	16	40	No	NA	No	No
M	AHT	57	NA	No	Yes	17	60	Yes	NA	No	No
M	0B	53	1650/498/110	No	Yes	42	60	No	OP+ CIP	No	No
M	No PH	51	NA	No	Yes	34	40	No	Acute pneumonia	Yes	No
F	OCP	73	491/1061/88	No	Yes	31	60	Yes	OP+ DAD	Yes	No
F	NHL	57	NA	No	Yes	44	60	No	CIP	No	No
F	No PH	62	NA	Yes	Yes	44	40	Yes	DAD	Yes	No
M	No PH	24	NA	Yes	Yes	22	40	Yes	NA	No	No
M	LS DLP	49	NA	No	Yes	25	40	No	NA	No	No
M	AHT DLP SM	67	484/409/37	No	Yes	33	40	No	NA	No	No
M	AHT 0B	60	1650/605/42	No	Yes	19	20	No	NA	No	No
M	No PH	64	1187/331/49	No	Yes	22	60	No	NA	No	No
M	MMOB	59	416/563/157	No	Yes	16	60	Yes	NA	Yes	No
M	0B	38	1095/473/51	No	Yes	14	60	No	NA	No	No
M	OBSM	62	603/209/178	No	Yes	25	60	Yes	NA	No	No
M	0BSM AF	66	NA	No	Yes	30	60	No	NA	No	No

M: masculine. F: f eminine. No PH: no pathological history. AHT: arterial hypertension. SM: sm oking . PC: prostate cancer. IMBT: inferior maxillary bone tumor. ICM: ischemic cardiomyopathy. DBT: diabet es. DPM: definitive pacemaker. Ob: obesity. OCP: ocular pemphigoid. NHL: non-Hodgkin lymphoma. LS: liver steatosis. DLP: d ysli pidemia. M M : multiple myeloma. AF: atrial fibrillation. Ferritin ng/ml. DD: D dimer ng/ml. pCR: e-reactive protein mg/L. DOS: date of onset of symptoms. Non-DXM CT: non-dexamethasone corticosteroid therapy. Mepredn OR: oral meprednisone, initial dose. Methylpred IR: intravenous pulse methylprednisolone. TBB: transbronchial biopsy. OP: organizing pneumonia. DAD: diffuse alveolar damage. CIP: cell interstitial pneumonia. NA: not available/not performed. O_2: oxygen.

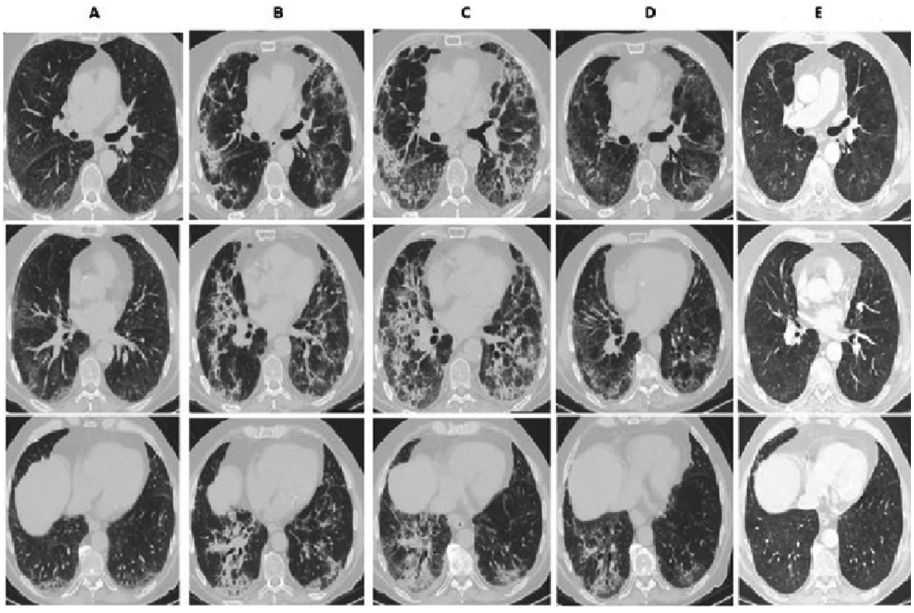

Figure 1. 73-year old man. Column A: 11 days since the onset of symptoms . B: 26 days since the onset of symptoms. C: 30 days since the onset of symptoms/ 1st day of intravenous methylprednisolone. O: 40 days since the onset of symptoms. 7th day of oral meprednisone (60 mg/day). E: 119 days since the onset of symptoms, receiving meprednisone, 10 mg/day.

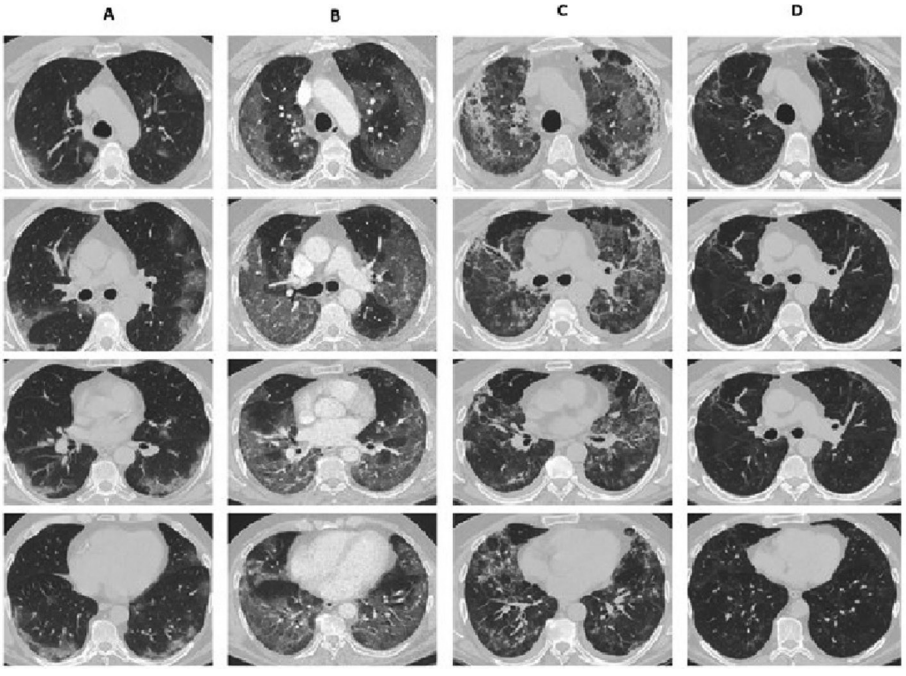

Figure 2. 67-year old man. Column A: 5 days since the onset of symp t oms. B: 9 days sincde the onset of symptoms. C: 32 days since the onset of symptoms/ 1st day of oral meprednisone (40 mg/day). D: 63 days since the onset of symptoms, receiving meprednisone, 20 mg/day.

Discussion

When the presence of the SARS COV 2 infection became known, it was assumed that the clinical presentation was the expression of the viral infection and the post-acute period was the consequence of an immune system deregulation, more commonly known as "cytokine storm"[7]. Corticosteroid therapy during the infectious acute phase showed its usefulness in the Recovery study,[2] which described an improvement in survival with the use of dexamethasone in patients requiring some type of respiratory assistance. Other authors reported similar benefits using higher doses of methylprednisolone[10-12]. Once the acute infectious process is resolved, like other more common etiologic agents[13], COVID-19 may evolve towards a clinical condition compatible with secondary organizing pneumonia[14-15.] This is shown in the tomographic characteristics observed during the evolution of the infection[6]. In the anatomopathological necropsy reports and in some "in vivo" biopsy reports, the damage pattern was confirmed, associated with other observed patterns such as diffuse alveolar damage and acute fibrinous and organizing pneumonia (AFOP)[14, 17].

At the moment, the natural evolution of the clinical and radiological consequences post-acute COVID-19 infection is unknown. But given the number of patients affected by this pandemic, it is imperative to find some treatment that accelerates recovery and reduces respiratory abnormalities as potential sequelae to the minimum. According to various reports[3, 4, 18], 39% of patients remained asymptomatic one month after hospital discharge, up to 63% showed spirometric alterations 3 months after the infection and 30% after one year, and 25% of the patients still showed radiological alterations one year post-infection.

Myall et al[18] described in their work one approach that is similar to the one described in this report, but they began corticosteroid therapy 6 weeks after discharge in patients whose clinical or radiological findings were suggestive of persistent pulmonary lesion, mainly OP. In that case they indicated only 3 weeks of treatment with oral corticosteroids and their results showed symptomatic, radiological and spirometric improvement. The French guidelines[19] for the management of post-COVID respiratory sequelae also supported this approach, considering all the patients who remained asymptomatic or with radiological or spirometric alterations up to even 1 year post-infection as capable of being treated. According to these guidelines the treatment is more similar to the conventional treatment of organizing pneumonia, starting with prednisone, 0.5 mg/kg for one month and then reducing 10 mg every month.

Future studies shall define if corticosteroid therapy has to be administered during the immediate post-acute period or subsequently if there is no clinical or radiological improvement. They must also evaluate whether there is a group of patients that need the corticosteroid therapy of the acute period to continue for more than 10 "formal" days in cases of radiological or clinical markers suggestive of the subsequent "negative" evolution described herein. Finally, it would be adequate to define the dose and duration of the corticosteroid therapy considering that the underlying cause of the inflammatory process has been resolved (acute viral infection), and which are the adverse effects related to prolonged use.

This retrospective work about a series of cases has clear limitations: the lack of a control group and randomization of the indicated treatment. Treatment decision making was defined by the attending physician, who clinically analyzed each separate case. Still, the favorable results that were described allow us to suggest that systemic corticosteroid therapy indicated after the acute period would have a beneficial effect, both clinical and radiographic, in patients with torpid evolution of severe pneumonia caused by COVID-19, provided that the presence of pulmonary tromboembolism or bacterial or fungal superinfection or other causes of dyspnea and/or pulmonary infiltrates (heart failure, drug-induced pulmonary toxicity, exacerbation of underlying pulmonary diseases) that may justify the clinical condition beyond the unfavorable evolution of the patient's COVID-19 has been properly dismissed. It is necessary to conduct prospective studies duly designed to clearly establish the benefit suggested in this work, defining clear inclusion criteria, forms of therapy, dose and duration.

Conclusion

Systemic corticosteroid therapy administered after the acute period would have a potential beneficial effect in patients with severe pneumonia caused by SARS COV 2 who 14 days after the onset of symptoms still show clinical or radiological manifestations suggestive of damage generated by the immune response to the virus.

Conflicts of interest: The author declares that there is no conflict of interest.

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