

Coronavirus Pandemic

Corticosteroids prescription for mild-moderate COVID-19 in Primary Care

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Dear Editor,

Corticosteroids are very accessible drugs, and nowadays, they have been the mainstay of treatment for severe COVID-19. However, some physicians have been motivated to prescribe them for mild and moderate cases, mainly in settings where other therapies such as monoclonal antibodies or remdesivir for early COVID-19 are unavailable.

We have recently received a considerable number of COVID-19 patients that began corticosteroid therapy in a mild-moderate disease at our tertiary referral center. A day-by-day case in our referral center looks as follows:

A 43-year-old man, a health care worker, was admitted to our emergency department for a history of shortness of breath. He was previously healthy with no chronic diseases. Three days after close contact with a COVID-19 positive relative, he was tested with nasopharyngeal swab RT-PCR and confirmed a SARS-CoV-2 infection. He was isolated at home by medical advice. On day five, he had the only headache with a blood oxygen saturation of 93%. However, by a primary care physician's recommendation, he started dexamethasone 16 mg intramuscularly daily. Six days later, he began with a fever, shortness of breath, and cough with purulent sputum; because of that, he was brought by relatives to seek medical attention.

At the time of admission, the vital signs were heart rate 115 bpm, temperature 38.5 °C, blood pressure 80/60 mmHg, and blood saturation of 82%. A computed tomography scan of the chest showed ground-glass opacity and condensation with peribronchial lines in the right lower lobe. Biochemical data and completed blood

count showed the following relevant findings: Glucose, 332 mg/dL; DHL, 530 mg/dL; high-sensitive C-reactive protein (CRP), 25 mg/L; procalcitonin, 12 ng/mL; leukocytes, $17.6 \times 10^9/L$; neutrophils, $15.2 \times 10^9/L$; lymphocytes, $1.4 \times 10^9/L$. He evolved to acute respiratory distress syndrome that required invasive ventilation. *Klebsiella pneumoniae* was yielded from a bronchoalveolar lavage fluid culture, although he received appropriate antibiotic treatment, tocilizumab, convalescent plasma, and insulin. He died after ten days.

Discussion

The COVID-19 pandemic has promoted intensive research in treatments to prevent and lowering mortality associated with SARS-CoV-2 infection. In this regard, since June 2020, corticosteroids are an option of treatment because of the recovery trial results [1], about low doses of dexamethasone, which reduced deaths up to one-third in ventilated patients and one-fifth in other patients receiving oxygen. These findings were additionally supported by a meta-analysis of six randomized controlled trials besides the recovery trial, showing that corticosteroids reduced 28-day mortality in critically ill COVID-19 patients (summary odds ratio [OR] = 0.66) [2]. Therefore, in the most recent guidelines, dexamethasone is recommended in severe and critical COVID-19 patients with moderate certainty of evidence [3]. However, their use in mild disease has been controversial.

Nowadays, because of the wide availability, easy administration, and low cost, corticosteroids are broadly prescribed even for mild-moderate COVID-19,

mostly in primary care attention. However, in the seminal recovery trial, patients without oxygen requirements and less than seven days since symptoms onset showed no benefit of corticosteroid therapy; these showed even a trend to harm [1]. Furthermore, a recent meta-analysis focused on COVID-19 patients with several levels of severity showed that the subgroup of patients not requiring oxygen had a higher risk of mortality (RR = 1.23; 95% confidence interval [CI] = 1.00 - 1.62) [4]. Furthermore, a systematic review using propensity score matching showed that in mild-moderate COVID-19 patients, those that received corticosteroids showed a more extended hospitalization and more days of viral shedding [5].

Regarding corticosteroids dosage, a study in hospitalized patients with non-severe COVID-19 divided into two groups, one received low-dose corticosteroid therapy, and the other did not. The first group had a higher virus clearance time (median of 18 vs. 11 days, $p < 0.001$) and a long time hospital stay (median 23 vs. 15 days, $p < 0.001$) [6]. Dexamethasone 20 mg daily has been used recently in acute respiratory syndrome (ARDS) with lower mortality in corticosteroid groups at 60 days of follow-up (21% vs. 36%, between-group difference -15.3%; $p = 0.0047$). Despite its adverse effects such as hyperglycemia and superinfections, anti-inflammatory and antifibrotic properties could reduce lung damage in ARDS [7]. Remarkably, in COVID-19, low-dose corticosteroids have shown similar efficacy in terms of mortality in comparison to higher dosage (*e.g.*, methylprednisolone > 80 mg/day, dexamethasone > 15 mg/day, hydrocortisone > 400 mg/day) [2]. The latter dosages have been related to a delayed viral shedding, a higher rate of invasive mechanical ventilation, and delayed recovery on chest-computed tomography, suggesting high doses of corticosteroids should be avoided [8].

The optimal timing of corticosteroid prescription is still controversial, and the indication "in patients requiring oxygen" may be ambiguous. However, an exciting report trying to clarify the timely medication found that only the patients requiring ≥ 3 L/min and CRP ≥ 100 mg/L who received corticosteroids had less risk of death or intubation [9]. This finding suggests a rationale for corticosteroid prescription based on a combination of oxygen supplementation with inflammatory biomarkers.

Conclusions

Health care providers might feel motivated to prescribe corticosteroids in patients with mild-moderate COVID-19. However, the current evidence suggests

that corticosteroid prescription for mild-moderate cases should be avoided. Close monitoring of progressive COVID-19 may be enough to detect patients at the appropriate time of starting corticosteroid therapy. For mild or moderate COVID-19 cases, it is necessary to follow the first do no harm principle.

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Author contribution

Dr. Ordinola and Lopez Luis have access to the data. Both authors contributed equally in the preparation, reviewing, writing and editing of the manuscript.

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