Corticosteroids for critically ill COVID-19 patients with cytokine release syndrome: a limited case series

Stephen Su Yang, MDCM, FRCPC • Jed Lipes, MDCM, FRCPC

To the Editor,

Approximately 5% of coronavirus disease (COVID-19) patients will require admission to an intensive care unit (ICU). Among these patients, the most severe cases may be mediated by a late-onset systemic inflammatory response with cytokine dysregulation referred to as cytokine release syndrome (CRS). Clinically, this results in fever, acute respiratory distress syndrome, multiorgan failure, and/or hemodynamic collapse due to distributive shock. Late-onset severe COVID-19 patients may respond to anti-inflammatory therapy without worsening the initial early viral infection. We describe a case series of 15 COVID-19 patients admitted to ICU who received corticosteroids in the context of CRS. Cytokine release syndrome was identified as worsening hypoxemia or vasoplegia with rising C-reactive protein (CRP) or interleukin-6 levels without alternative clinical explanation. The Research Ethics Board at our local site approved this retrospective case series.

The characteristics of these patients are provided in the Table. The median [interquartile range (IQR)] age was 72 [62-74] yr (range, 45-75 yr), and nine of the 15 patients (60%) were male. The indications for steroid administration were hypoxic respiratory failure (67%), vasoplegic shock on multiple vaspressors (20%), or both respiratory and cardiovascular failure (20%). Two non-intubated patients received steroids for impending respiratory failure with increasing inflammatory markers concerning for CRS. The median [IQR] day of steroid administration after symptoms onset was 14 [12–15] days. Nine patients (60%) received methylprednisolone, four patients (27%) received hydrocortisone, and two patients (13%) received dexamethasone. The median [IQR] dose of corticosteroids during the first 24 hr in methylprednisolone equivalents was 160 [83-160] mg. In almost all cases, there was a decrease in vasopressor requirement or an improvement in oxygenation after steroid administration. There was an average fall in CRP of 236 mg/L with steroid administration (eFig. 1, available as Electronic Supplementary Material [ESM]). An average increase in the arterial partial pressure of oxygen/fraction of inspired oxygen (i.e., P/F) ratio of 44 was detected 24 hr after steroid administration (eFig. 2, available as ESM).

Currently, four patients were discharged home, four patients remained in ICU, four patients were transferred to the medical ward, and three patients are deceased. We present a subset of COVID-19 patients who presented with progressive respiratory failure along with progressive inflammatory biomarkers consistent with severe CRS. We found a significant clinical and biochemical association between corticosteroids and improved surrogate outcomes in late-onset CRS associated with COVID-19. Corticosteroids are indicated to treat CRS occurring from immune or chimeric antigen receptor therapy, but its use in weathering the cytokine storm in viral infection remains controversial, particularly if given early. Other coronaviruses have an inverted “V” distribution of viral shedding, peaking ten days after the
onset of symptoms and then decreasing rapidly. Consequently, the clinical deterioration occurring after ten days may be caused by dysregulated inflammation and not the virus itself, offering a window of opportunity for therapeutic intervention.4

Our report is limited by several important factors. There was no control group and therefore no randomization of intervention, we examined surrogate outcomes of uncertain clinical relevance, and there was likely selection bias in determining who received steroids and what dose they received. We report very few patients from a single centre, making it difficult to generalize our results to other hospitals even after consideration of the biases present. Additionally, exact criteria for CRS are not available and the prognostic importance of CRS in COVID-19 patients remains to be determined.

The fear of giving corticosteroids is related to a possible risk of decreased viral clearance with unclear clinical significance.5 Our report suggests the possibility of short-term clinical improvements with corticosteroids and it highlights the need for urgent high-quality studies to determine whether steroid administration may meaningfully affect the outcomes of critically ill COVID-19 patients.

Conflicts of interest None.

Funding statement None.

### Table Characteristics of 15 critically ill patients with COVID-19 who received corticosteroids

| No | Age (yr) | Sex | Time from symptoms to steroids (days) | Steroid administered | Dosage of steroid over first 24 hr – Methylprednisolone equivalents (mg) | Indication | Clinical change 24 hr post therapy | CRP (mg L\(^{-1}\)) | \(P_{O2}/F_{O2}\) ratio | Current condition |
|----|---------|-----|--------------------------------------|----------------------|------------------------------------------------------------------------|------------|-----------------------------------|----------------|----------------|------------------|
| 1  | 72      | M   | 12                                   | Methylprednisolone   | 160                                                                     | Vasoplegia | Improved hemodynamics             | 348→163       | N/A            | Ward              |
| 2  | 72      | M   | 16                                   | Methylprednisolone   | 160                                                                     | Severe ARDS | Moderate ARDS                     | 341→9         | 73→130         | ICU              |
| 3  | 62      | M   | 10                                   | Hydrocortisone       | 40                                                                     | Severe ARDS | Moderate ARDS                     | 455→217       | 77→150         | Ward              |
| 4  | 66      | M   | 14                                   | Methylprednisolone   | 160                                                                     | Severe ARDS | Severe ARDS                       | 378→121       | 71→77          | Deceased         |
| 5  | 53      | F   | 8                                    | Methylprednisolone   | 160                                                                     | Severe ARDS | Moderate ARDS                     | 466→150       | 92→100         | ICU              |
| 6  | 63      | F   | 14                                   | Hydrocortisone       | 60                                                                     | Severe ARDS & vasoplegia | Moderate ARDS and improved hemodynamics | 556→49       | 83→110         | ICU              |
| 7  | 66      | M   | 16                                   | Hydrocortisone       | 60                                                                     | Vasoplegia | Improved hemodynamics             | 293→85        | N/A            | ICU              |
| 8  | 78      | M   | 13                                   | Methylprednisolone   | 160                                                                     | Severe ARDS & vasoplegia | Moderate ARDS and improved hemodynamics | 425→149       | 60→110         | Deceased         |
| 9  | 55      | M   | 14                                   | Dexamethasone        | 106.7                                                                   | 5L NP      | 1L NP                            | 210→61        | N/A            | Home             |
| 10 | 74      | M   | 13                                   | Dexamethasone        | 106.7                                                                   | 5L NP      | 4L NP                            | 297→104       | N/A            | Home             |
| 11 | 72      | F   | 14                                   | Methylprednisolone   | 160                                                                     | Severe ARDS | Moderate ARDS                     | 115→48        | 87→155         | Home             |
| 12 | 75      | M   | 12                                   | Hydrocortisone       | 40                                                                     | Vasoplegia | Improved hemodynamics             | N/A           | N/A            | Deceased         |
| 13 | 45      | F   | 12                                   | Methylprednisolone   | 160                                                                     | Severe ARDS | Moderate ARDS                     | 80→22         | 82→145         | Home             |
| 14 | 75      | F   | 22                                   | Methylprednisolone   | 120                                                                     | Severe ARDS | Severe ARDS                       | N/A           | 81→81          | Ward              |
| 15 | 73      | F   | 17                                   | Methylprednisolone   | 160                                                                     | Severe ARDS | Moderate ARDS                     | 368→87        | 94→183         | Ward              |

Severe ARDS defined as \(P_{O2}/F_{O2}\) ratio < 100, Moderate ARDS defined as \(P_{O2}/F_{O2}\) ratio ≥ 100 and < 200. ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; CRP = C-reactive protein; ICU = intensive care unit; N/A = not available; NP = nasal prongs; \(P_{O2}/F_{O2}\) = arterial partial pressure of oxygen/fraction of inspired oxygen.
Editorial responsibility  This submission was handled by Dr. Philip M. Jones, Associate Editor, Canadian Journal of Anesthesia.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; https://doi.org/10.1001/jama.2020.2648.

2. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020;https://doi.org/10.1016/j.ijantimicag.2020.105954.

3. Lee N, Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. J Clin Virol 2004; 31: 304-9.

4. Gomersall CD. Pro/con clinical debate: steroids are a key component in the treatment of SARS. Pro: yes, steroids are a key component of the treatment regimen for SARS. Crit Care 2004; 8: 105-7.

5. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med 2018; 197: 757-67.

Publisher’s Note  Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.