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CORRESPONDENCE

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

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To the Editor,

Approximately 5% of coronavirus disease (COVID-19) patients will require admission to an intensive care unit (ICU).[1] 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).[2] 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.[3] 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 vasopressors (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 $mg{\cdot}L^{-1}$ 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.[4] Other coronaviruses have an inverted "V" distribution of viral shedding, peaking ten days after the

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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_aO2/F_IO2 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 $PaO2/F_IO2$ ratio < 100, Moderate ARDS defined as PaO_2/F_IO_2 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; PaO_2/F_IO_2 = arterial partial pressure of oxygen/fraction of inspired oxygen.

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.

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