Critical Care Explorations

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The Combination of Tocilizumab and Methylprednisolone Along With Initial Lung Recruitment Strategy in Coronavirus Disease 2019 Patients Requiring Mechanical Ventilation: A Series of 21 Consecutive Cases

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Objective: To describe the outcomes with use of a combination of tocilizumab and methylprednisolone administered around the time of endotracheal intubation in patients with confirmed coronavirus disease 2019-associated hypoxemic respiratory failure requiring mechanical ventilation.

Data Sources: Retrospective chart review.

Study Selection/Data Extraction: Twenty-one consecutive patients with confirmed coronavirus disease 2019-associated hypoxemic respiratory failure requiring mechanical ventilation. Initial ventilator parameters were positive end-expiratory pressure 14 cm H_2O and target plateau pressure 29 cm H_2O to maximize lung recruitment. Methylprednisolone (125 mg every 6hr for 24 hr with tapering to 60 mg every 12 hr) was administered shortly after patients were intubated (median 11 hr after intubation).

Data Synthesis: No patient in the cohort died while hospitalized (mortality, 0%; 95% CI, 0%–18%) and 18 patients have been discharged from the acute care setting. Twenty of 21 patients (95%) have been liberated from mechanical ventilation after a median duration of 8 days (range, 4–30 d). Following 48 hours of methylprednisolone, the A-a O_2 gradient decreased from 455 ± 103 to 228 ± 109 mm Hg (difference 227 ± 108 mm Hg; $p < 0.01$).

Conclusions: Our positive experience with tocilizumab in combination with methylprednisolone started early after endotracheal intubation may be one avenue for reducing the morbidity and mortality seen with severe coronavirus disease 2019 and merits further exploration in clinical studies.

Key Words: artificial respiration; coronavirus disease 2019; cytokine release syndrome; glucocorticoids; respiratory distress syndrome; viral pneumonia

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The world is experiencing a pandemic of coronavirus disease 2019 (COVID-19) caused by a novel coronavirus (severe acute respiratory syndrome-coronavirus disease-2 [SARS-CoV-2]) that arose in China in late 2019 (1). Although the majority of patients will have a mild course of illness, approximately 6% of patients develop a critical form of COVID-19 (2, 3). Those affected by these severe forms may progress to an Acute Respiratory Distress Syndrome (ARDS)-like pattern

requiring oxygen and ventilatory support, including invasive mechanical ventilation (IMV) (2, 4). Overall mortality estimates for critically ill COVID-19 patients requiring IMV range from 18% to 97%, although these reports included many patients who remained in intensive care at the time of publication (5–10). The proximate cause of death for many of these cases was refractory hypoxemia with acute respiratory failure (11).

The pathogenesis of severe COVID-19 disease is thought to be a progression from initial viral prodromal phase to a vigorous inflammatory host response leading to pneumonia and respiratory failure (4, 12, 13). While much of the initial pharmacotherapeutic discussion has revolved around antiviral agents, there have been limited data regarding anti-inflammatory and immunomodulatory therapy (12–14). One hypothesis is that attenuating the robust inflammatory response seen in critically ill COVID-19 patients could mitigate the severity of lung inflammation, thereby improving pulmonary gas exchange, hastening time to extubation, and potentially reducing mortality.

CASE SERIES

Twenty-one consecutive patients with COVID-19 who required IMV between March 18 and May 2, 2020 were included in this case series. All patients tested positive for SARS-CoV-2 via nasopharyngeal polymerase chain reaction (PCR) and had disease consistent with COVID-19. COVID-19 patient cases were discussed daily with a multidisciplinary team of physicians and pharmacists versed in the treatment of highly infectious, critically ill patients (15). Patients who were deteriorating (increased work of breathing or a respiratory rate in excess of 25 breaths per minute) and had oxygen needs exceeding 6 L O_2/min via nasal cannula to maintain an oxygen saturation of at least 90% (usually corresponding to a $Pao_2/Fio_2 < 200$) underwent elective endotracheal intubation. IMV was initiated with a target PEEP of 14 cm H_2O and a goal plateau pressure to 29 cm H_2O to optimize lung recruitment and avoid alveolar overdistension. In addition to standard ICU care, patients received a combination of IV tocilizumab 400 mg and IV push methylprednisolone around the time of intubation (12, 13). Methylprednisolone was administered as 125 mg every 6 hours IV push for 4 doses followed by 60 mg every 12 hours with slow tapering over a total of 10 days. Patients were also treated with either aggressively dosed enoxaparin (40 mg or 0.5 mg/kg bid) or therapeutic IV heparin (target anti-Xa, 0.3–0.7 IU/mL) (16). Nineteen patients received at least one SARS-CoV-2-targeted antiviral with purported effect against the virus (either hydroxychloroquine or remdesivir) (14). Remdesivir was obtained either via compassionate use or expanded access and was only administered after a patient was on IMV. This case series was conducted in accordance with the amended Declaration of Helsinki and with local ethics committee input. As this was a retrospective chart review with minimal risk to the patients, informed consent was not obtained.

Patients

The median age of the patients was 56 years (range, 37–85 yr) and 14 (67%) were men (**Table 1**). The median body mass index (BMI)

TABLE 1. Baseline Demographics and Characteristics for 21 Patients

Age (yr)	56 (37–85)
Male	14 (67%)
Ethnicity	
White	7 (33%)
Black	6 (29%)
Hispanic	8 (38%)
BMI (kg/m2)	29 (24–50)
Past medical history	
Hypertension	11 (52%)
Diabetes	13 (62%)
Hyperlipidemia	7 (33%)
Chronic kidney disease	1 (5%)
Chronic liver disease	1 (5%)
COVID-19 symptoms	
Fever	14 (67%)
Cough	21 (100%)
Dyspnea	15 (71%)
Symptom onset to admission (d)	8 (3–28)
Admission to endotracheal intubation (d)	2 (0–4)
SOFA score	
On admission	3 (1–10)
24 hr after intubation	5 (2–12)
APACHE II score	
On admission	10 (5–19)
24 hr after intubation	13 (3–24)
Initial ventilator parameters and lung mechanics	
Plateau pressure (cm H2O)	30 (24–36)
Static compliance (mL/cm H2O)	39 (23–74)
Tidal volume (mL/kg)	8 (5–10)
PEEP (cm H2O)	14 (7.5–14)
Driving pressure (cm H2O)	19 (10–29)
Admission laboratory tests[a]	
Absolute lymphocyte count (k/μL)	0.73 (0.27–2.88)
Blood D-dimer (μg/mL FEU)	1.24 (0.39–3.12)
Ferritin (ng/mL)	954 (91–6220)
C-reactive protein (mg/dL)	6.9 (4.7–14.8)
Lactate dehydrogenase (units/L)	486 (269–1142)

APACHE II = Acute Physiology and Chronic Health Evaluation, II, PEEP = positive end-expiratory pressure, SOFA = Sequential Organ Failure Assessment.

[a]Institution laboratory reference ranges: Absolute lymphocyte count: 0.85–3.2 k/μL; Blood D-dimer: ≤ 0.5 μg/mL FEU; Ferritin: 5–204 ng/mL; C-reactive protein: ≤ 0.49 mg/dL; Lactate dehydrogenase: 125–275 units/L.

Data presented as percentages or medians and ranges.

of the cohort was 29 kg/m² (range, 24–50 kg/m²). All patients were treated in an ICU, although 12 were initially admitted to a medical floor prior to the ICU. Patients were intubated a median of 2 days into their hospital admission (range 0–4 d). On the day following endotracheal intubation, the median Sequential Organ Failure Assessment (SOFA) score was 5 (range 2–12). Only one patient required the use of a vasopressor agent for longer than 4 hours.

Immunomodulatory Therapy

Tocilizumab was given to all patients, 10 of whom received the drug prior to intubation. Methylprednisolone was started a median 11 hours (range 1.5–141 hr) following intubation. One patient received methylprednisolone 5 hours prior to intubation. This large range is explained by continued refinements made to our treatment scheme. After the first four patients demonstrated an apparent response to methylprednisolone, this treatment was pushed closer in proximity to intubation and averted a need for repeat tocilizumab dosing (range −5 to 27 hr after intubation).

Outcomes

As of this report, 20 of the 21 patients (95%) have been successfully liberated from IMV. The patient who remains on IMV has the potential for tracheostomy creation. The median duration of mechanical ventilation was 8 days (range 4–30 d). One patient self-extubated and required reintubation. Another patient was extubated but developed postextubation respiratory distress related to fluid overload and required reintubation within 12 hours. Eighteen patients (86%) have been discharged with two requiring postdischarge oxygen supplementation therapy and one discharged to a skilled nursing unit. No patient from this cohort has died while hospitalized (mortality, 0%; 95% CI, 0%–18%). Over this same time frame, six patients have avoided endotracheal intubation altogether with use of tocilizumab combined with methylprednisolone along with oxygen supplementation (data not included in case series).

Although there were no control subjects in the case series, the first four patients received multiple doses of tocilizumab and initiated methylprednisolone later in their disease courses (71–141 hr after intubation). Importantly, three of the first four patients required salvage therapy (prone positioning and epoprostenol), whereas none of the latter patients did. For the first four patients, the median duration of IMV was 10.5 days (range 9–30 d). This was reduced to a median 6 days (range 4–18 d) for the latter 17 patients.

Outcomes were also compared between different antiviral regimens patients received. Ten patients received at least one dose of hydroxychloroquine followed by a 10-day regimen of remdesivir, five patients received hydroxychloroquine monotherapy, four patients received remdesivir monotherapy, and two patients were not administered an antiviral. Median durations of IMV were 9.5, 9, 6.5, and 5 days, respectively. The one patient remaining on IMV received a combination of hydroxychloroquine followed by 10 days of remdesivir.

Pulmonary Parameters and Inflammatory Markers

Following 48 hours of methylprednisolone, the A-a O_2 gradient improved from 455 ± 103 to 228 ± 109 mm Hg (difference, 227 ± 108 mm Hg; $p < 0.01$) (**Fig. 1**). The Pao_2/Fio_2 did not significantly increase at 48 hours and was highly variable (198 ± 99 to 214 ± 101 mm Hg [difference 16 ± 121 mm Hg; $p = 0.55$]). Calculated static compliance was minimally increased (43 ± 15 to 49 ± 12 mL/cm H_2O; $p = 0.14$). Serum C-reactive protein levels were significantly reduced after 48 hours of methylprednisolone treatment (from 16.4 ± 9.5 to 5.2 ± 3.7 mg/dL; mean difference, 11.2 ± 6.8 mg/dL; $p = 0.002$). Ferritin and blood D-dimer levels did not significantly change over this time frame.

Adverse Effects

Hyperglycemia was observed in all patients over the first 72 hours following methylprednisolone initiation but was managed with insulin. Only one patient had blood glucose values in excess of 180 mg/dL despite use of an IV insulin infusion. Aside from hyperglycemia, two patients developed ventilator-associated pneumonia and one developed bacterial tracheobronchitis, which were all successfully treated. One patient was readmitted 7 days after discharge for hemoptysis and cavitary lung disease and is currently being treated for reactivation of a nontuberculosis mycobacterial infection.

DISCUSSION

With the reported high mortality among critically ill patients with COVID-19 requiring IMV, novel approaches to stem the tide of the poor outcomes associated with this disease are needed. In this report, we describe the outcomes of a cohort of consecutively admitted patients with severe COVID-19 pneumonia and progressive hypoxemia requiring IMV in an ICU who were treated with tocilizumab and methylprednisolone. Three of these patients received salvage therapy with prone positioning and administration of pulmonary vasodilators prior to the addition of methylprednisolone. Following methylprednisolone, all patients demonstrated improvements in gas exchange parameters and 20 have subsequently been extubated. Eighteen patients have been discharged and hospital mortality is 0%. We find these results encouraging and merit further investigation.

We used a ventilator strategy with slightly higher target plateau pressure of 29 cm H_2O compared with that used in Seattle-area hospitals (median, 25 cm H_2O) and a medium-high PEEP of 14 cm H_2O, similar to that used in an Italian cohort, to attain an open and recruited lung (6, 7). The aforementioned Seattle-area hospitals used a mean PEEP of 10 cm H_2O and their patients had a median BMI of 33.8 kg/m² (6). Importantly, the median BMI of patients that died was 35.7 kg/m² (20.5–45.2 kg/m²), whereas survivors had a BMI of 28.5 kg/m² (22.6–48.7 kg/m²), stressing the need for optimal alveolar recruitment.

While significant interest surrounds candidate antiviral regimens targeted at SARS-CoV-2, no agent has conclusively demonstrated a mortality benefit in critically ill patients requiring IMV (14). Remdesivir may be the most promising anti-SARS-CoV-2 agent; however, there are limited published data in critically ill patients requiring IMV (10, 14) In a report on compassionate use

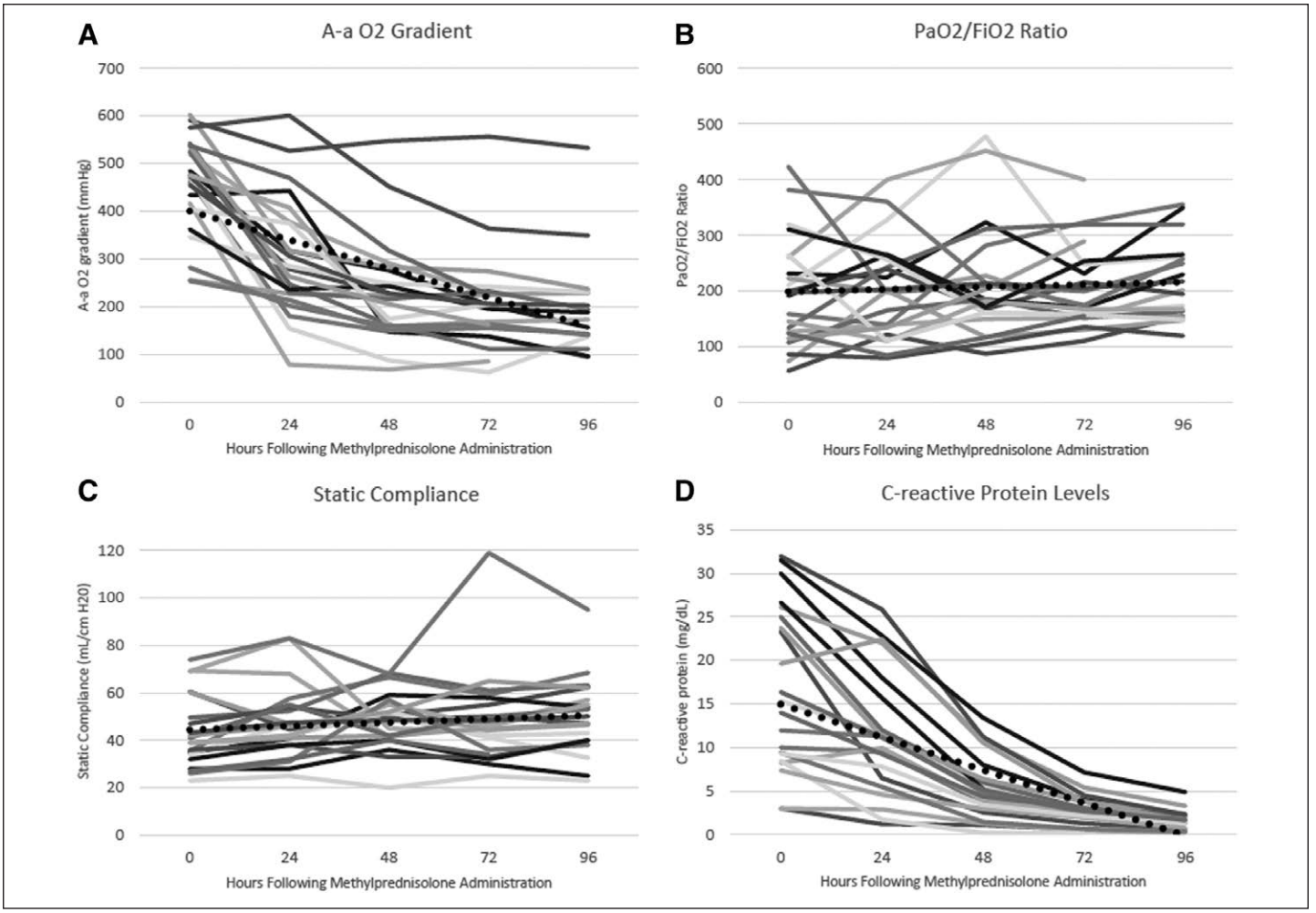

Figure 1. Changes in A-a o_2 gradient (**A**), Pao_2/Fio_2 ratio (**B**), calculated static compliance (**C**), and C-reactive protein levels (**D**) for all 21 patients over the first 96 hours following administration of methylprednisolone. *Dotted lines* on the graph represent the cohort mean.

of remdesivir, mortality in the 34 patients requiring IMV was 18% (10). Therefore, to address the high mortality seen with this variant of disease, our investigations may need to shift away from antiviral therapy alone.

The role of glucocorticoid therapy in severe COVID-19 remains controversial and unproven (2, 17, 18). Glucocorticoid use in SARS-CoV infection was associated with prolonged viral clearance and increased morbidity and mortality; however, severity of illness and receipt of other therapies confound such results (19, 20). In MERS-CoV infection, glucocorticoid use was not associated with a difference in mortality but did delay RNA clearance (21). Similar to SARS-CoV studies, MERS-CoV patients who received glucocorticoids had higher rates of respiratory failure requiring salvage therapy. Due to the equivocal or potentially deleterious findings from prior novel coronavirus outbreaks, many organizations have recommended against the use of glucocorticoids for COVID-19 (2, 18). While the data are limited, glucocorticoid use in COVID-19 patients with ARDS was associated with a significant reduction in mortality (8). A recent randomized controlled trial demonstrated early treatment with dexamethasone in traditional ARDS demonstrated a reduction duration of IMV and mortality (22). These data have led others, including the Surviving Sepsis Campaign, to recommend the use of glucocorticoids in COVID-related ARDS (17, 23). Methylprednisolone is a familiar agent to physicians with known, manageable side effects and is frequently used in other pulmonary conditions, although the optimal dose, timing, and specific glucocorticoid agent for treatment of COVID-19 is not known. A randomized trial (CoDEX) in Brazil using dexamethasone for COVID-19-associated ARDS is currently enrolling, which will provide additional data in a more robust clinical study (24). While hyperglycemia and bacterial infections were seen in this series, the benefit of glucocorticoid therapy likely outweigh those risks given the published mortality estimates (5–10).

Tocilizumab is an interleukin-6 (IL-6) receptor antagonist that should reduce the cytokine release syndrome seen in severe COVID-19 (12, 13, 25). Elevations in serum IL-6 levels, along with other proinflammatory cytokines, may be responsible for a maladaptive immune response, leading to progressive respiratory failure and pulmonary intravascular coagulopathy and microthrombi (13). All of our patients were treated with tocilizumab in combination with methylprednisolone, so it is unknown if the pharmacological action of the agent is complementary, duplicative, or additive with glucocorticoids or if monotherapy with just

an IL-6 receptor antagonist is beneficial. Theoretically, glucocorticoids should suppress IL-6 production in addition to other proinflammatory mediators (13). Thus, in areas without access to tocilizumab or a similar IL-6 inhibitor agent, preference should likely be given to glucocorticoid use.

In conclusion, the early use of methylprednisolone and tocilizumab in COVID-related ARDS, in addition to optimal mechanical ventilation using high initial PEEP of 14 cm H_2o and plateau pressure of 29 cm H_2 o, appears to be one viable treatment to curb the mortality seen in severe disease. We await larger studies, including the currently enrolling CoDEX trial, to contextualize these encouraging observations.

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