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ABSTRACT & COMMENTARY

Is There a Role for Immunomodulatory Therapy in COVID-19 Cytokine Storm?

By Kathryn Radigan, MD

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SYNOPSIS: In this retrospective analysis of COVID-19 patients hospitalized with cytokine storm, the use of corticosteroids combined with tocilizumab was associated with superior survival when compared to no immunomodulatory treatment; a combination of corticosteroids and anakinra; or corticosteroids, tocilizumab, or anakinra alone. Patients who received corticosteroids, either alone or in combination with anakinra, also experienced lower hospital mortality compared to no treatment.

SOURCE: Narain S, Stefanov DG, Chau AS, et al. Comparative survival analysis of immunomodulatory therapy for coronavirus disease 2019 cytokine storm. *Chest* 2021;159:933-948.

COVID-19 cytokine storm (CCS), often identified by elevations in ferritin, C-reactive protein (CRP), and lactate dehydrogenase (LDH), is a marker of COVID-19 illness severity and increased mortality. Immunomodulatory therapies, such as tocilizumab and anakinra, have been repurposed in an attempt to improve survival in COVID-19 patients with CCS. Narain and colleagues performed a retrospective analysis of the electronic health records of 14,489 COVID-19 patients across the Northwell Health System between March 1, 2020, and April 24, 2020. Patients were subdivided into six groups: no immunomodulatory treatment, corticosteroids only, tocilizumab only, anakinra only, corticosteroids and tocilizumab, and corticosteroids and anakinra. The primary outcome was hospital mortality. Inclusion criteria were COVID-19 positivity as determined by polymerase chain reaction testing of nasopharyngeal swabs, age > 18 years, and meeting CCS criteria with either an elevated ferritin (> 700 ng/mL), CRP (> 30 mg/dL), or LDH (> 300 U/L).

Hospitalized COVID-19 patients treated with combination corticosteroids and tocilizumab had lower mortality compared with patients receiving

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no immunomodulatory treatment (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.35-0.55; $P < 0.0001$), patients treated with corticosteroids alone (HR, 0.66; 95% CI, 0.53-0.83; $P = 0.004$), or patients treated with corticosteroids and anakinra (HR, 0.64; 95% CI, 0.50-0.81; $P = 0.003$). Compared to no immunomodulatory treatment, there was improved hospital survival when corticosteroids were given alone (HR, 0.66; 95% CI, 0.57-0.76; $P < 0.0001$), with tocilizumab (HR, 0.43; 95% CI, 0.35-0.55; $P < 0.0001$), and with anakinra (HR, 0.68; 95% CI, 0.57-0.81; $P < 0.0001$). A randomized clinical trial comparing tocilizumab plus corticosteroids to corticosteroids alone is necessary to define patients with the greatest benefit from combination therapy.

■ COMMENTARY

Recently, the United States has reported more than 33 million COVID-19 cases and more than a half a million deaths.[1] Repurposed immunomodulatory drugs aimed at cytokine storm in COVID-19 have been used in an attempt to improve mortality. Corticosteroids were of initial interest mainly because of their profound anti-inflammatory and immunoregulatory properties. The RECOVERY trial found that dexamethasone 6 mg daily for 10 days reduced the death rate in mechanically ventilated patients by 35% and in oxygen-dependent patients by 20% compared to patients who received standard care. There was no benefit in patients who were not receiving respiratory support.[2]

Interleukin-6 (IL-6) also was of significant interest because it was known to be an important mediator of inflammation and was specifically higher in patients with more severe COVID-19.[3] It was theorized that IL-6 blockade in patients not yet requiring mechanical ventilation would interrupt the cytokine storm associated with COVID-19. Tocilizumab, a recombinant anti-IL-6 receptor monoclonal antibody, was hypothesized to disrupt the cytokine storm associated with COVID-19 with subsequent prevention of the most severe disease consequences, including acute respiratory distress syndrome. Unfortunately, early studies in the pandemic that evaluated tocilizumab monotherapy were negative. Stone and colleagues conducted a randomized, double-blind, placebo-controlled trial and found that tocilizumab had no significant effect on the risk of intubation, death, worsening of disease, or the time of discontinuation of supplemental oxygen.[4] In this trial, glucocorticoids were administered to 23 patients (18 [11%] in the tocilizumab group and five [6%] in the placebo group). In contrast, subsequent open-label trials and non-randomized case series suggested that IL-6 receptor blockade had substantial positive effects on patients with COVID-19, such as a reduced rate of mechanical ventilation and decreased hospital mortality.[5,6]

The current study supports the practice of corticosteroids, either alone or with tocilizumab or anakinra, since it was associated with reduced hospital mortality for patients with cytokine storm. Although this current study was retrospective, subsequent studies, including the RECOVERY and the REMAP-CAP studies, were prospective and also found tocilizumab to be beneficial. The RECOVERY trial was a randomized, controlled, open-label, platform trial evaluating several possible treatments in 21,550 patients hospitalized with COVID-19 in the United Kingdom.[7] A subset of patients with hypoxemia and CRP levels ≥ 75 mg/L were offered enrollment in a second randomization to receive tocilizumab or usual care. In all, 4,116 (19%) of the participants underwent a second randomization into the tocilizumab intervention arm. In these hospitalized patients with hypoxia and systemic inflammation, tocilizumab improved survival and the chances of discharge from the hospital alive, and reduced the chances of progressing to require invasive mechanical ventilation compared to usual care. Notably, in contrast to previous trials, 82% of the trial participants also were on glucocorticoids, mainly dexamethasone. Tocilizumab resulted in a 6% reduction in mortality when given with dexamethasone but no reduction in mortality when given alone.

The REMAP-CAP study, also a randomized controlled trial, revealed that treatment with the IL-6 receptor antagonists, tocilizumab and sarilumab, was associated with better outcomes, such as shorter time to clinical improvement and survival, in patients with severe to critical COVID-19 who were exhibiting rapid respiratory decompensation.[8] Tocilizumab (n = 353) and sarilumab (n = 48) each reduced in-hospital mortality in patients enrolled within 24 hours of intensive care unit (ICU) admission compared with standard of care (28% vs. 22% vs. 36%, respectively; adjusted odds ratio [OR], 1.64; 95% credible interval [CrI], 1.14-2.35, for tocilizumab; OR, 2.01; 95% CrI, 1.18-4.71, for sarilumab). In the REMAP-CAP study, corticosteroids were given to 88% of patients, and remdesivir was given to 33% of patients. Since enrollment occurred within 24 hours of ICU admission and within a median of 1.2 days of hospitalization (interquartile range [IQR], 0.8-2.8 days), results suggest the benefit of tocilizumab may occur specifically in patients who are experiencing rapid respiratory decompensation.

The National Institutes of Health (NIH) panel currently acknowledges there may be some hospitalized patients who are receiving conventional oxygen therapy with progressive hypoxemia associated with significant systemic inflammation who may benefit from tocilizumab.[9] The panel currently recommends using tocilizumab 8 mg/kg in combination with dexamethasone 6 mg daily for up to 10 days in hospitalized patients within three days of admission who are: admitted to the ICU within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation, or high-flow nasal cannula (HFNC) oxygen (> 0.4 FiO_2/30 L/min of oxygen flow), or not admitted to the ICU, but have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC and who have significantly increased markers of inflammation (CRP ≥ 75 mg/L). Some panel members would consider the administration of tocilizumab to patients with rapidly increasing oxygen needs while on dexamethasone and who have a CRP ≥ 75 mg/L but who do not yet require noninvasive ventilation or HFNC oxygen.

In general, tocilizumab should be avoided in the significantly immunosuppressed, in patients with alanine aminotransferase greater than five times the upper limit of normal, in patients at high risk for gastrointestinal perforation, and/or in those who have uncontrolled serious bacterial, fungal, or coinciding viral infection. Ivermectin also should be considered for patients who are from strongyloidiasis-endemic areas. Similarly, the Infectious Diseases Society of America (IDSA) suggests adding tocilizumab to standard of care (i.e., glucocorticoids) for hospitalized adults who have progressive severe or critical COVID-19 and have elevated markers of systemic inflammation.[10]

Although the benefit of tocilizumab in hospitalized patients who require more aggressive ventilator support or are progressing with significantly increased markers of inflammation appears to be more clear, larger prospective randomized controlled trials with a head-to-head comparison of tocilizumab plus corticosteroids vs. corticosteroids alone may be beneficial to further define patient populations with greatest benefit. ■

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ABSTRACT & COMMENTARY

Interleukin-6 Antagonists in the Treatment of Severe COVID-19 Pneumonia

By Vibhu Sharma, MD, MS

Associate Professor of Medicine, University of Colorado, Denver

SYNOPSIS: These two trials had disparate findings with respect to interleukin-6 inhibition, with REMAP-CAP showing a benefit and COVACTA showing none.

SOURCES: The REMAP-CAP Investigators; Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491-1502.

Rosas IO, Brau N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *N Engl J Med* 2021;384:1503-1516.

The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) trial randomized patients with severe COVID-19 pneumonia to tocilizumab, sarilumab, or placebo. This was the immune modulation therapy domain among multiple other domains in the study, including corticosteroid, antibiotic, and macrolide domains. Critically ill patients requiring organ support were enrolled. Organ support was defined as respiratory organ support in the form of heated high flow nasal cannula (HHFNC) oxygen > 30 L/minute, noninvasive ventilation (NIV), or invasive mechanical ventilation, or cardiac organ support in the form of vasopressors. Patients had to be enrolled within 24 hours of starting organ support in a critical care setting. Tocilizumab dosing could be repeated once within 12-24 hours at the discretion of the treating physician. Sarilumab was administered once at a dose of 400 mg. Overall, 895 patients underwent randomization at 113 sites across six countries. Approximately one-third of patients in each group were receiving HHFNC, with the rest on either NIV or invasive mechanical ventilation. Approximately one-quarter of patients in each group received vasopressors, except approximately 10% in those randomized to sarilumab.

REMAP-CAP used a Bayesian design with no sample size calculated; in this clinical trial type, interim analyses occur as randomization continues. A Markov chain Monte-Carlo simulation calculates odds of the primary outcome occurring — in this case, the odds of survival and the number of organ failure-free days up to day 21 as predicted by treatment group (tocilizumab, sarilumab, or placebo). A cumulative logistic model is fit to project possible outcomes using patient outcomes of those previously recruited (based on two-week epochs) and refining the model as recruitment continued. This technique has been used to predict stock prices using historical price data. Simplistically, an odds ratio of greater than one generated by the model implies improved survival or organ failure-free days. The trial was to conclude with a superiority conclusion if the posterior probability was greater than 99% that an intervention was more effective than the others or an inferiority conclusion when the posterior probability was less than 0.25% that a given intervention was better than the others. A calculated posterior probability of 99% that the odds ratio for the primary outcome was greater than one implied intervention efficacy compared to placebo. The intervention was deemed futile if the posterior probability that the odds ratio was greater than 1.2 was less than 5%, and equivalent if the posterior probability that the odds ratio was between 0.8 and 1.2 was greater than 90%.

The median number of organ support-free days was 10 (interquartile range [IQR], -1 to 16 days) in the tocilizumab group, 10 (IQR 0-16 days) in the sarilumab group, and 0 (IQR, -1 to 15 days) in the placebo group. The mean adjusted odds for organ failure-free survival were 1.65 (95% credible interval

[CrI], 1.25 to 2.14) for tocilizumab and 1.76 (95% CrI, 1.17 to 2.91) for sarilumab compared to control, with posterior probabilities of > 99% for both, implying efficacy. Similarly, the mean adjusted odds for in-hospital survival were 1.64 (95% CrI, 1.14 to 2.35) for tocilizumab and 2.01 (95% CrI, 1.18 to 4.71) for sarilumab compared to placebo, implying efficacy for the mortality outcome.

The second trial (COVACTA) randomized 438 patients with COVID-19 acute respiratory distress syndrome (ARDS) (SaO_2 < 93% or a PaO_2/FiO_2 < 300) to intravenous tocilizumab or placebo. The primary outcome was clinical status at day 28 on an ordinal scale: 1) discharged alive or ready to discharge; 2) hospitalization on a medical floor without oxygen; 3) medical floor with oxygen; 4) noninvasive ventilation or heated high flow oxygen; 5) intubation/mechanical ventilation; 6) extracorporeal membrane oxygenation (ECMO) or mechanical ventilation plus other life support; and 7) death. The baseline score on the ordinal scale was the score immediately prior to randomization. Secondary outcomes included clinical status at day 14 on the ordinal scale, day 28 mortality, number of ventilator-free days by day 28, the time to improvement from baseline by at least two categories on the ordinal scale, and the time to hospital discharge or readiness for discharge. This trial found no difference in clinical status between the tocilizumab and placebo groups at day 28; however, the trial did find a "possible benefit for tocilizumab in the time until hospital discharge (or readiness for discharge) and in the duration of ICU stay, both of which require additional study."

■ COMMENTARY

The REMAP-CAP study found a mortality benefit to IL-6 antagonism with odds that are not impressive. Although the statistical technique used was robust, the odds ratios generated suggest a marginal benefit at best. Importantly, in this trial, patients received the first dose of the intervention drug (or placebo) within approximately a day of admission and within 13 hours of admission to the intensive care unit. PaO_2/FiO_2 ratios were approximately 100 at enrollment, implying moderate to severe ARDS. With respect to COVACTA, the mortality rate was identical in the tocilizumab and placebo groups; however, there was a signal toward a shorter length of hospital stay with tocilizumab. Approximately 40% of patients were mechanically ventilated and of these patients, the median time to initiation of the intervention drug was three days, with a range of 0-28 days, implying (possibly) that initiation was too delayed for any meaningful benefit in some patients. Patients were recruited a mean of 12 days from the onset of COVID symptoms, but the range was wide (up to 50 days for some), at which point, given the natural history of the disease, a benefit from immune modulation is unlikely. In the COVACTA trial, more patients in the placebo group received steroid therapy (29%) compared to the tocilizumab group (19%). It is clear that mortality is reduced by steroid therapy, and it is possible that the survival rates in the placebo group may have been inflated as a result of more patients receiving steroids. In addition, more Black and Native American patients received placebo purely as a result of the chance of randomization.

The RECOVERY trial was a much larger trial than COVACTA, enrolling more than 4,000 patients.[1] This trial found a survival benefit for tocilizumab regardless of the amount of respiratory support among hospitalized patients with hypoxia (oxygen saturation < 92% on room air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein [CRP] ≥ 75 mg/L). Importantly, in this trial, positive outcomes were seen for the nine patients not receiving any oxygen and 1,859 patients receiving low-flow oxygen randomized to the tocilizumab group. The benefits were sustained for patients receiving corticosteroids and other subgroups as well (i.e., receiving noninvasive mechanical ventilation, invasive ventilation, or ECMO). A smaller trial assessed the use of tocilizumab in non-critically ill patients and found a smaller chance of reaching the primary endpoint (a composite of the percentage of patients who died, received invasive ventilation, or received noninvasive ventilation) among those with CRP levels > 150 mg/L.[2] These patients with elevated CRP levels also were more likely to be alive at 90 days. Both REMAP-CAP and COVACTA excluded patients with active infection, tuberculosis, or those with imminent death. There were no excess infections in patients receiving IL-6 antagonism, suggesting that in the appropriately selected patient, IL-6 antagonism is safe. The current state of evidence suggests benefit to patients not yet critically ill with elevated inflammatory markers (CRP 75 mg/L to 150 mg/L). Although some patients may benefit later in the disease course, the key may be initiating IL-6 antagonism early in the course of disease in appropriately selected patients. ■

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ABSTRACT & COMMENTARY

Dexmedetomidine Compared to Propofol for Sedation in Mechanically Ventilated Patients with Sepsis

By Vibhu Sharma, MD

Associate Professor of Medicine, University of Colorado, Denver

SYNOPSIS: The MENDS2 trial found that dexmedetomidine, when used for light sedation, had outcomes similar to those for propofol.

SOURCE: Hughes CG, Mailloux PT, Devlin JW, et al.; MENDS2 Study Investigators. Dexmedetomidine or propofol for sedation in mechanically ventilated adults with sepsis. *N Engl J Med* 2021;384:1424-1436.

The MENDS2 (Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients with Acute Respiratory Failure) study randomized mechanically ventilated adults with sepsis to dexmedetomidine or propofol, targeting a Richmond Agitation-Sedation Scale (RASS) of 0 to -2 (i.e., light sedation or the ability to open eyes to verbal stimulation). Groups were assigned in a 1:1 ratio using computer-generated blocks stratified by age and enrollment site. All caregivers (clinicians and bedside nurses) were blinded to the study group assignment. The actual range achieved in each group was a RASS of -3 to -1. The dexmedetomidine dose administered ranged from 0.2 mcg to 1.5 mcg per kilogram body weight per hour and propofol was administered at 5 mcg to 50 mcg per kilogram per minute. Sedation was titrated at 30-minute intervals to a target RASS, and sedation was stopped for daily spontaneous awakening trials (SATs) and spontaneous breathing trials (SBTs) or in the event bradycardia or hypotension developed. There was rigorous adherence to the Society of Critical Care Medicine (SCCM) intensive care unit (ICU) liberation bundle in both groups.

Approximately one-third of patients were admitted to a surgical ICU; the rest were admitted to a medical ICU. All were mechanically ventilated and needed continuous sedation. Major exclusion criteria included: baseline cognitive dysfunction, a moribund state, conditions considered contraindications to the use of dexmedetomidine (e.g., bradycardia requiring intervention or second-/third-degree heart block), requirement for neuromuscular blockade, allergies to either medication, or indications for benzodiazepines. Of 432 patients recruited, 422 were randomized: 214 to dexmedetomidine and 208 to propofol. Approximately half of the patients in each group had vasopressor-dependent shock. Median doses of medications administered were 0.27 mcg per kilogram of body weight per hour of dexmedetomidine and 10.2 mcg per kilogram per minute of propofol. The mean duration of use of either sedative was three days. For the purposes of the study, the authors requested and received Food and Drug Administration (FDA) approval for an investigational new drug application for dexmedetomidine administered for more than 24 hours and for doses up to 1.5 mcg per kilogram per hour.

The primary study end point was days alive without delirium or coma during the intervention periods of 14 days. Delirium was assessed using the Confusion Assessment Method for the ICU (CAM-ICU) bedside tool when the patient was maximally awake at the end of a daily awakening and spontaneous breathing trial. Pain was measured using the Critical Care Pain Observation Tool and was treated using either bolus opioid dosing or a continuous fentanyl infusion. Secondary end points included: death at 90 days, ventilator-free days at 28 days, and global cognition using the age-adjusted total score on the Telephone Interview for Cognitive Status questionnaire total (TICS-T) at six months. The latter is a validated score that enables assessment of cognition over the phone with scores ranging from 0 to 100, with lower scores indicating worse cognition.

Overall, the trial found no difference between the groups in terms of the primary end point of number of days alive without delirium or coma over the 14-day intervention period. In addition, there were no differences in ventilator-free days at 28 days, death at 90 days, or global cognition at six months between the dexmedetomidine and propofol groups. Safety end points were similar in the two groups.

■ COMMENTARY

Dexmedetomidine has been shown to be superior to lorazepam infusion with respect to the incidence of delirium and coma among mechanically ventilated critically ill patients.[1] Prior to this randomized trial, propofol had not been compared directly to dexmedetomidine exclusively in patients with suspected or documented infection who were mechanically ventilated. This trial failed to demonstrate any differences in primary or secondary outcomes between propofol and dexmedetomidine, suggesting that either drug may be used to target light sedation when used in addition to rigorous adherence to the SCCM ICU liberation bundle. Most importantly, there was no difference in the incidence of delirium in the hospital or the incidence of cognitive dysfunction at long-term follow-up with the use of either drug.

There are some practical aspects that deserve to be mentioned. Bradycardia was more common in the dexmedetomidine group (26%) compared with the propofol group (6%). Compared to propofol, dexmedetomidine was associated with more temporary infusion interruption due to bradycardia (2% vs. 12%, respectively) and hypotension (15% vs. 21%, respectively). In contrast, oversedation was a more common reason for a temporary hold on infusion with propofol (20%) compared with dexmedetomidine (14%).

In patients with shock admitted to the intensive care unit, the hemodynamic effect of sedation is an important consideration for clinicians. The study authors did not delineate the proportion of patients with moderate to severely reduced cardiac dysfunction in either group. For that subpopulation, the effects of bradycardia and hypotension induced by dexmedetomidine may be exaggerated. Among patients without septic shock, a small study showed that both propofol and dexmedetomidine have similar frequencies for negative hemodynamic effects; however, propofol was associated with a greater degree of hypotension when it did occur.[2] In this study, only a small number of patients had heart failure. Findings were similar in those with septic shock.[3] Another study assessed the incidence of severe hemodynamic derangements while using propofol and dexmedetomidine infusions in a neurocritical care population and found severe hypotension and bradycardia occurred at similar frequencies.[4]

In the aggregate, it appears that there are no relevant differences with respect to the primary end points of delirium- and coma-free days between the two drugs when used for light sedation. Caution may be warranted with dexmedetomidine in the face of bradycardia. ■

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CME/CE QUESTIONS

1. **What treatment regimen currently is recommended by the National Institutes of Health for hospitalized COVID-19 patients admitted to the intensive care unit and who require mechanical or noninvasive ventilation?**
   a. Tocilizumab 8 mg/kg in combination with dexamethasone 6 mg daily for up to 10 days
   b. Tocilizumab 8 mg/kg in combination with dexamethasone 6 mg daily for up to 30 days
   c. Tocilizumab 1 mg/kg in combination with dexamethasone 12 mg daily for up to five days
   d. Dexamethasone 10 mg daily for up to 30 days

2. **In the retrospective analysis by Narain et al, compared to no immunomodulatory therapy, the combination of corticosteroids with tocilizumab resulted in what outcome?**
   a. More hemorrhagic complications
   b. More liver function abnormalities
   c. More life-threatening complications
   d. Superior survival

3. **Based on the results from multiple studies (REMAP-CAP, COVACTA, RECOVERY), which of the following is true regarding interleukin-6 inhibition in COVID-19 pneumonia?**
   a. An increased risk of infection as was seen in REMAP-CAP and COVACTA.
   b. Tocilizumab and sarilumab improved mortality in REMAP-CAP.
   c. A benefit to tocilizumab was seen across all levels of inflammation.
   d. Tocilizumab was not associated with benefit in those patients not on oxygen.

4. **Which one of the following was a frequent adverse effect seen in the MENDS2 trial?**
   a. Bradycardia with dexmedetomidine
   b. Oversedation with dexmedetomidine
   c. Increased vasopressor needs with propofol
   d. Bradycardia with propofol

5. **Which of the following was the primary end point of treatment with either propofol or dexmedetomidine in the MENDS2 trial?**
   a. Death at 90 days
   b. Days free of mechanical ventilation
   c. Global cognition at six months
   d. Delirium-free days within the two-week interval

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.