Moving to the Head of the "Claza"—Targeting Interleukin-6 for COVID-19 Pneumonia

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Over the last 2 years, critically ill patients with COVID-19 pneumonia and acute respiratory distress syndrome (ARDS) have filled ICUs throughout the United States and the world. The mortality of COVID-19–associated ARDS has been substantial, with death occurring in approximately 10% of hospitalized patients and 60% of those requiring mechanical ventilation (1). The immense clinical need for effective therapies for COVID-19 spawned a large number of quickly completed clinical trials to attempt to identify new potentially life-saving treatment options. In this issue of *Critical Care Medicine*, Lonze et al (2) report results of a double-blinded placebo-controlled clinical trial of the direct interleukin (IL)–6 inhibitor clazakizumab for treatment of COVID-19 pneumonia.

The study by Lonze et al (2) presents data from a multicenter randomized trial of clazakizumab in hospitalized patients with severe COVID-19 and hyperinflammation. Eligible patients had polymerase chain reaction–proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with hypoxemia defined by either Pao_2/Fio_2 less than 200 or saturation of less than 90% on a minimum of 4 L supplemental oxygen or need for increased oxygen supplementation in the 24 hours prior to study enrollment; in addition, two markers of hyperinflammation were required and could include C-reactive protein (CRP) greater than 35 mg/L, ferritin greater than 500 mg/mL, D-dimer greater than 1,000 ng/mL, lactate dehydrogenase greater than 200 U/L, neutrophil:lymphocyte ratio greater than 4, or elevated troponin in the absence of cardiac disease. The primary endpoint of the seamless phase II/III study was 28-day ventilator-free survival. The phase II study enrolled 81 hospitalized patients with severe COVID-19 and hyperinflammation in a trial of low dose clazakizumab (12.5 mg), high dose clazakizumab (25 mg), or placebo. The phase III study enrolled 97 patients in a trial of high-dose clazakizumab compared with placebo. The final analyzed cohort included 152 patients, with 74 patients in the placebo group and 78 in the high-dose clazakizumab group. The odds ratio for 28-day ventilator-free survival in the clazakizumab group was 3.84 compared with placebo (95% CI, 1.54–10.62). Patients who received clazakizumab had a 28-day ventilator-free survival of 70.5% compared with 55.4% in those who received placebo. Clazakizumab also improved several clinically relevant secondary outcomes including overall 28-day and 60-day survival, likelihood of improving clinical status (>2-point increase in World Health Organization [WHO] score), reduced need for intubation or ICU admission, and shorter durations of mechanical ventilation and ICU care. Importantly, a post hoc analysis showed that the treatment benefit of clazakizumab was

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restricted to those patients who had not yet developed severe hypoxemia (Pao_2/Fio_2 < 300) at the time of treatment initiation.

Clazakizumab was previously studied in a limited number of patients with rheumatoid arthritis refractory to methotrexate and in renal transplant recipients with antibody-mediated rejection (3,4). The rationale underlying testing clazakizumab in COVID-19 is that direct inhibition of IL-6 may have more potent effects than IL-6 receptor (IL-6R) antagonism with tocilizumab (5–8). Direct IL-6 inhibition targets the IL-6 axis more proximally than IL-6R antagonists and may reduce amplification of inflammatory signaling cascades. Clazakizumab limits IL-6 binding to both membrane-bound IL-6R and soluble IL-6R (sIL-6R). Because IL-6 complexed to sIL-6R activates inflammatory pathways without involvement of membrane-bound IL-6R, clazakizumab may block IL-6-dependent signaling more potently than IL-6R antagonists. In addition, through this mechanism, clazakizumab can also inhibit IL-6-dependent effects on cells that do not express IL-6R. It has been shown that sIL-6R is elevated in patients with COVID-19 and facilitates robust proinflammatory effects even in the presence of only modest plasma levels of IL-6 (9–11). Clazakizumab was most effective in patients who had not developed severe hypoxemia, whereas tocilizumab also showed efficacy in patients requiring ICU admission. Thus, targeting the IL-6 pathway more proximally may have benefit earlier in disease progression than IL-6R antagonism.

One challenge of optimizing medical therapy for patients hospitalized with COVID-19 is understanding which individual patients have the greatest potential benefit from new therapies. Here, the benefit of clazakizumab was limited to those with mild hypoxemia, with no significant impact of therapy when started after onset of severe critical illness. This result emphasizes the need for rapid patient assessment and implementation of appropriate treatment prior to clinical deterioration requiring escalation of oxygen support. Here, the authors attempted to define the ideal timeframe for clazakizumab by including patients with changing oxygen supplementation needs and by performing a post hoc analysis in patients with different severity of hypoxemia at study enrollment. The study by Lonze et al (2) also only included patients with elevated systemic inflammatory markers. It is clear that the higher dose of clazakizumab is sufficient to exert anti-inflammatory effects because the median CRP of clazakizumab-treated patients decreased by 62% within 3 days of therapy administration. However, it remains uncertain which biomarkers of inflammation will best predict treatment responses or what level of IL-6 is needed to indicate the potential for clinical response.

The study by Lonze et al (2) illustrates several important aspects of clinical trial design and performance. First, the seamless phase II/III study design allowed for rapid dose optimization. In the phase II portion of the current study, the higher dose of clazakizumab was deemed by the data safety and monitoring board to be superior than the lower dose, thereby altering the study design of the subsequent phase III study. The study design facilitated this shift in strategy and may have contributed to the power to detect a clinical benefit of clazakizumab by shifting patients into fewer treatment groups. Second, because of the COVID-19 pandemic, the study and clinical outcomes were monitored remotely by research staff who were off-site with inpatient treatment delivery by on-site physicians, bedside nurses, and pharmacists at each study location. This structure for clinical trial oversight is interesting and has the potential to facilitate future clinical trial participation by hospitals with limited research infrastructure. Finally, assessing treatment responses with a standard scale of clinical improvement (WHO ordinal scale) provides an excellent nonmortality endpoint. Despite early clinical improvement and survival, many patients with critical illness have had extended ICU and hospital courses, often requiring weeks or months of mechanical support; there may be substantial downstream benefits on post-ICU recovery that are not yet measurable in COVID-19 survivors.

There remain some important clinical questions as the critical care community continues to develop treatment plans for COVID-19 and ARDS. The study by Lonze et al (2) was conducted in 2020 prior to circulation of variants of SARS-CoV-2, and it is uncertain whether the benefit of immunotherapy would have the same magnitude of effect as the virus evolves. It is also unknown whether IL-6 pathway blockade will be beneficial in non–COVID-19 ARDS. In the setting of rapidly changing hospital guidance during a pandemic, it is challenging for a study to account for variability in patient management during the study period. The optimal method to address this beyond increased sample

size is not well established; in the study by Lonze et al (2), inclusion of study site in the randomization plan and in data analysis was sufficient to detect a benefit of clazakizumab despite differential use of steroids and remdesivir in the study population.

Overall, the study by Lonze et al (2) provides support for direct IL-6 inhibition as a treatment option for patients with COVID-19 pneumonia and evidence of systemic inflammation. The treatment is most effective prior to onset of severe illness and can be administered rapidly. Amidst the devastation of the COVID-19 pandemic, rapid completion of robust clinical trials has highlighted the strength of the critical care community to thoroughly investigate several therapies like clazakizumab to move the most effective therapies to the head of the "claza" for incorporation into patient management algorithms.

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Do We Need an ICU for All Elective Postcraniotomy Patients? A Critical Appraisal*

KEY WORDS: intensive care unit; postcraniotomy; resource allocation

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Evidence of craniotomies (temporary removals of a part of the skull to expose the brain) dates back to the neolithic period with suggestion that approximately 50% of patients survived the operation based on signs of regenerated bone in many of the recovered skulls (1). ICUs, however, are far more contemporary and were formally established in the 1950s (2). With the advent of sophisticated surgical tools and techniques, intraoperative hemostatic

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