PERSPECTIVE

Applied Clinical Pharmacology in a Crisis: Interleukin-6 Axis Blockade and COVID-19

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The global pandemic of coronavirus disease 2019 (COVID-19) represents an emergent threat to the public health. Mitigation strategies have been employed to varying effect in many Western nations. Treatment strategies to effectively address COVID-19 and equitably distribute resources are needed, especially in overwhelmed hospitals.

Coronavirus disease 2019's (COVID-19's) high mortality, ~ 7% at 14 days despite the use of leading antiviral candidate remdesivir,[1] may in part be driven by interleukin 6 (IL-6)-mediated hyperinflammation. Because of its clinical and biochemical resemblance to the cytokine storm of cytokine release syndrome (CRS), there is hope that immunosuppressive therapies commonly used to treat CRS—such as the IL-6 receptor–targeted monoclonal antibodies tocilizumab or sarilumab or the IL-6–targeted monoclonal antibody siltuximab—can be repurposed toward COVID-19.[2] Serum IL-6 and C-reactive protein (CRP) are markedly elevated in patients with COVID-19, and the degree of elevation correlates with disease severity.[3] Retrospective analysis of patients with severe-to-critical COVID-19 pneumonitis receiving anti–IL-6 therapies demonstrated rapid resolution of both clinical and biochemical signs of hyperinflammation with only a single dose.[4] On the basis of these retrospective data, a global

placebo-controlled phase III trial (A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)) studying tocilizumab in the treatment of severe-to-critical COVID-19 pneumonitis using the CRS dose of 8 mg/kg has opened.[5] Even if anti–IL-6 therapies are proven efficacious, however, aggregate demand for them could rapidly outstrip available supply, as in the cases of remdesivir, hydroxychloroquine, and chloroquine.

To overcome expected supply/demand mismatches, the *effective* supply of the medications must be increased by increasing manufacturing and extending available anti–IL-6 therapy as much as possible. Toward this problem, the new field of interventional pharmacoeconomics offers a promising approach.[6] Monoclonal antibody dosing for chronic oncologic and rheumatologic conditions is aimed at maintaining therapeutic concentrations for weeks in outpatients. Conversely, in the inpatient setting, a patient's primary

problem is expected to be temporary. In this case, lower medication doses at higher frequency are preferable as they reduce the total amount of medication used and the frequency and/or duration of adverse events. Moreover, minimizing the immunosuppression of patients with COVID-19, some of whom are expected to have long inpatient hospital stays, may help to reduce risks of nosocomial and secondary infection. This pharmacological line of reasoning represents a plausible strategy to optimize anti–IL-6 therapies in COVID-19 and merits further investigation.

Our initial focus is tocilizumab, given its approved usage for CRS after chimeric antigen receptor (CAR) T-cell therapy and its preliminary evidence of efficacy in COVID-19.[4] Tocilizumab, an intravenous drug dosed every 4 weeks at a labeled dose of 8 mg/kg, was originally developed for outpatient rheumatoid arthritis therapy, with its approval based on improvement in the American College of Rheumatology 20 score.[7] Dose-finding studies revealed a dose-related reduction in Disease Activity Score in 28 joints beyond 4 weeks at doses 4 mg/kg and 8 mg/kg. In its subsequent new drug application for the CAR T-cell–related CRS indication, though, no formal dose-finding study was performed. Tocilizumab was approved based on its resolution of CAR T-cell–related CRS within 14 days, using the 8 mg/kg dose, provisioned up to four times and at least 8 hours between doses.[7] No common CRS biomarkers such as ferritin or CRP response were included as part of tocilizumab's supplemental Food and Drug Administration (FDA) filings.[7] The FDA's own review stated: "... Some patients in the Treated Population had resolution of CRS by day 14 after receiving tocilizumab 4 mg/kg, suggesting that a dose lower than

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recommended might be effective" (emphasis ours).[7]

The standard tocilizumab dose of 4 to 8 mg/kg every 4 weeks is a pharmacologically sound and convenient strategy for outpatient administration in clinical situations in which consistently maintaining serum drug concentrations greater than the half maximal effective concentration (EC_{50}) is important, such as in rheumatoid arthritis. Conversely, most patients with signs of COVID-19–related hyperinflammation would be expected to require at most 1 week of higher serum drug concentration (e.g., exceeding the EC_{90}), but prolonged serum concentration exceeding the EC_{50} could increase a patient's risk of developing secondary infections. The clinical circumstances of COVID-19 therefore suggest

that the most appropriate dose is significantly lower than 8 mg/kg. Previous modeling of tocilizumab's exposure–response relationship in patients with rheumatoid arthritis estimated the EC_{50} for CRP response to be 0.878 µg/mL—approximately 20% of the EC_{50} for the disease activity score, which was 4.60 µg/mL.[8] The modeled EC_{90} (when the Hill slope is 1) is nine times the EC_{50}, or approximately 8 µg/mL to achieve clinically significant CRP response. In comparison, the peak concentration after one dose of 8 mg/kg is approximately 75 µg/mL.[9] Although tocilizumab's clearance is concentration dependent, the peak concentration would be predicted to be correlated with dose, suggesting that it would be approximately 7.5 µg/mL at a mere 10% of the standard CAR T-cell dose.

In the context of COVID-19, we hypothesize that doses of anti–IL-6 axis therapies much lower than those used for chronic rheumatologic and oncologic conditions are effective in reducing COVID-19–related inflammation. Moreover, we hypothesize that a strategy aimed at early administration of this low-dose therapy may help to prevent the need for intensive care utilization and invasive ventilation. We propose the development of a titration treatment regimen for supportive care of hospitalized patients who are at risk for clinical decompensation and utilization of intensive care resources (**Figure 1**). Patients with COVID-19 who have evidence of incipient severe or critical disease, as evidenced by rising PaO2/FiO2 (arterial oxygen partial pressure/fractional
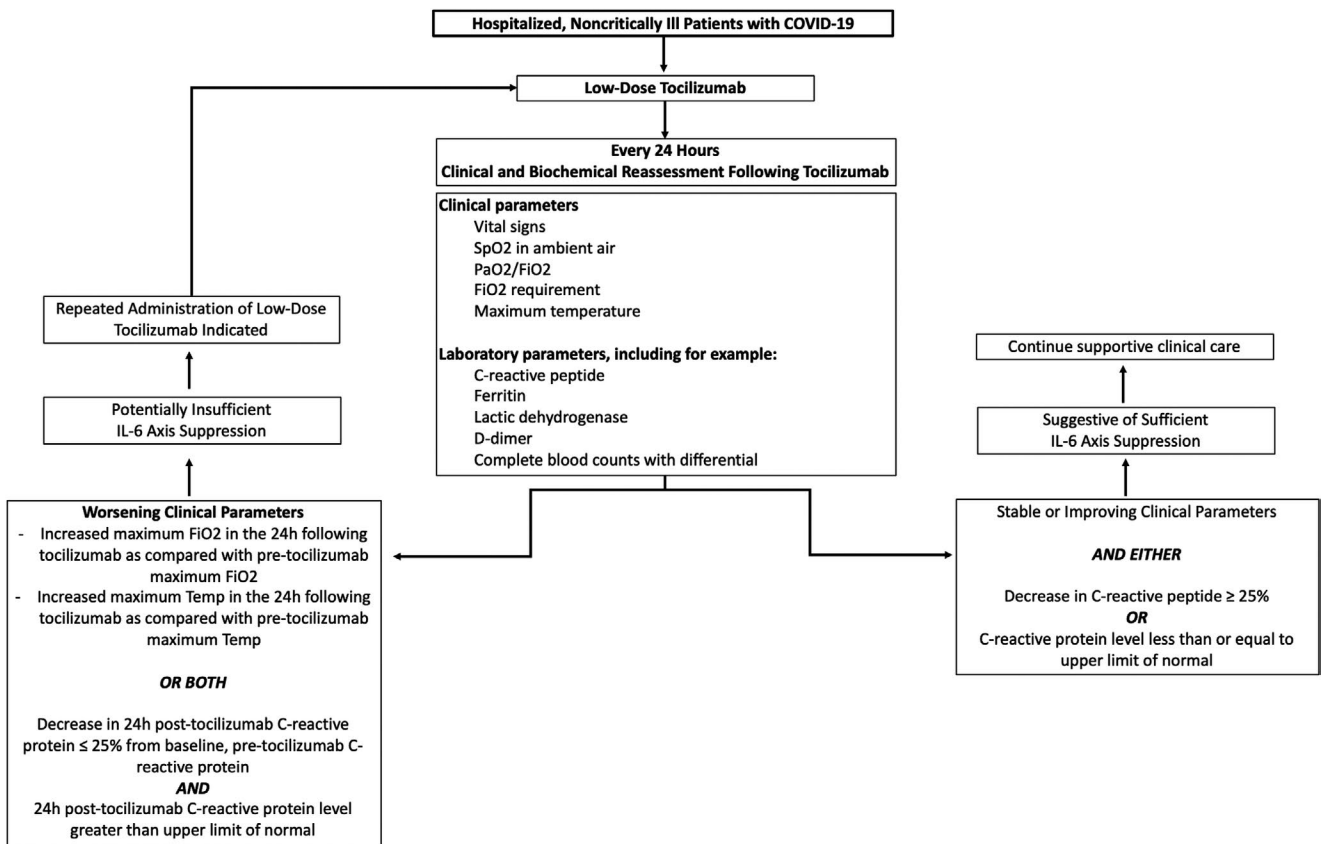

Figure 1 Proposed treatment strategy for patients with moderate or severe COVID-19 with high risk for clinical decompensation using tocilizumab titration. Most hospitalized patients with COVID-19 infections are potential recipients of IL-6 axis-suppressing therapy, with priority for those patients at high risk for decompensation and death. Following baseline clinical and laboratory-based risk stratification, patients will receive an initial dose of tocilizumab. Studies need to be performed to determine the minimum effective dose in this context, but it may be 100 mg or lower. Supportive clinical care continues for 24 hours after the initial tocilizumab dose, at which point repeat clinical and biochemical assessments are performed. If clinical stability or clinical improvement *and* biochemical evidence of IL-6 axis suppression, continuation of supportive clinical care without repeat dosing is indicated. If clinical decompensation *or* biochemical evidence of insufficient IL-6 axis suppression, patients receive an additional dose of tocilizumab, with reconsideration of additional doses at 24-hour intervals. COVID-19, coronavirus disease 2019; h, hours; PaO2, arterial oxygen partial pressure; SpO2, peripheral blood oxygen saturation; Temp, temperature.

inspired oxygen) ratio, persistent fever, or rising or markedly elevated serum inflammatory markers, or known epidemiologic risk factors for clinical decompensation, as well as those with known severe and critical COVID-19, are prime candidates for treatment with tocilizumab. Given tocilizumab's underlying pharmacokinetics as well as the much lower IL-6 concentrations observed in COVID-19 compared with CRS,[10] single doses significantly lower than 8 mg/kg (the COVCACTA dose) may be effective. Based on the rate at which clinical and biochemical improvements in COVID-19–related hyperinflammation are seen in tocilizumab-treated and siltuximab-treated patients,[4] rapid readout within 24 hours is possible, thereby supporting rational use of a titration strategy (**Figure 1**). Patients with clinical worsening (as suggested by rising PaO2/FiO2 ratio, persistent or rising fever, or developing or increasing need for vasopressor support) or biochemical evidence of insufficient IL-6 axis-suppression (for example, CRP decrease of less than 25% in the 24 hours following tocilizumab dose[4]) can be re-dosed at 24–48 hour intervals. Similar approaches may also be used to safely reduce the labeled doses of other IL-6 axis-suppressing therapies to more COVID-19–appropriate doses, thereby increasing effective supply.

Testing this hypothesis is made challenging by a host of factors, including a definition of the optimal patient population, the urgency of the COVID-19 pandemic, and the need for rapid results. A randomized, controlled trial including standard dose tocilizumab, low-dose tocilizumab, and placebo would be the gold-standard design to overcome the first barrier, but would do so at the expense of timeliness. Instead, a nonrandomized, adaptive phase II study evaluating a variety of doses, in which rapid clinical and pharmacodynamic end points are assessed, is an alternative strategy to provide context for the interpretation of the COVACTA trial and real-world evidence studies of off-label tocilizumab use.[5] Relevant end points such as 28-day mortality outcomes as well as those relevant to intensive care unit utilization (e.g., time to mechanical ventilation etc.) should be measured in a low-dose tocilizumab study, but many single-center studies may not be adequately powered to detect differences. The bigger purpose, however, is to show that low-dose tocilizumab is pharmacodynamically viable. At the time of this writing, to our knowledge, only one tocilizumab-related and COVID-19–related dose-finding study has been opened.[11]

The emergence of COVID-19 represents a public health threat not seen in the United States and Western Europe in generations. To minimize loss of life, people and materiel must move in lockstep. In the current resource-limited situation, ingenuity is needed to maximize effective supply and distribute that supply to areas most in need. We hypothesize that an evidence-based treatment strategy for tocilizumab in COVID-19 hyperinflammation will both conserve supply and optimize the therapeutic index of this valuable drug. In this way, leveraging lessons learned from value-oriented and equality-focused approaches to medicine represent a promising mechanism by which COVID-19 mitigation efforts can be maximized.

CONFLICTS OF INTEREST
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