IL-6 Receptor Antagonist Therapy for Patients Hospitalized for COVID-19

Who, When, and How?

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Although substantial progress has been made in the treatment and prevention of COVID-19, more effective treatments for patients with COVID-19 who require hospitalization are still needed. One promising immunomodulatory strategy is inhibition of interleukin 6 (IL-6), based on the hypothesis that SARS-CoV-2 creates injury to the lung and other organs in part through activation of cytokine and downstream proinflammatory networks. While several clinical trials have investigated the effect of IL-6 receptor antagonists (IL-6ra) in patients with COVID-19, the results have not been consistent, with some trials reporting benefit and others no benefit. In this issue of JAMA, investigators from the World Health Organization Rapid Evidence Appraisal for COVID Therapies (REACT) Working Group have provided a much-needed meta-analysis of 27 randomized trials of IL-6ra that included 10,930 patients with COVID-19 who were treated between October 2020 and January 2021.1

The primary results indicate that all-cause mortality was reduced in patients hospitalized for COVID-19 and treated with IL-6ra compared with those treated with placebo or usual care. By day 28 after randomization, 1,407 deaths occurred among 6,449 patients randomized to receive IL-6 antagonists and 1,158 deaths occurred among 4,481 patients randomized to usual care or placebo (summary odds ratio [OR], 0.86 [95% CI, 0.79-0.95]; P = .003 based on a fixed-effects meta-analysis). Importantly, a significant mortality benefit was only found when IL-6ra were coadministered with glucocorticoids (summary OR for the association of IL-6 antagonist treatment with 28-day all-cause mortality, 0.78 with concomitant glucocorticoid administration vs 1.09 without glucocorticoid administration). The benefits of IL-6ra were most evident among patients who received respiratory support with oxygen by nasal cannula, face mask, high-flow nasal oxygen (OR for death, 0.81 [95% CI, 0.67-0.98]), or noninvasive ventilation (OR, 0.83 [95% CI, 0.72-0.96]) vs those who required invasive mechanical ventilation (IMV) (OR, 0.95 [95% CI, 0.78-1.16]). Furthermore, there was not a clear benefit associated with IL-6ra use for reducing 90-day mortality or the duration of IMV among patients who already required mechanical ventilation at the time of randomization.

The beneficial outcomes associated with IL-6ra therapy did not differ according to patient age, sex, race and ethnicity, use of cardiovascular support defined by the need for vasopressors, or the level of C-reactive protein. Also, there was no evidence for an increase in the risk of secondary infections associated with IL-6ra at 28 days, although ascertainment of infectious adverse events varied and was quite limited in some trials (eTable 3 in Supplement 1).2 In terms of the specific pharmacologic agents, the data were strongest for tocilizumab, perhaps because more of the tocilizumab-treated patients had received glucocorticoids; more data will be needed to fully evaluate the comparative efficacy of tocilizumab and sarilumab.

The meta-analysis by the REACT investigators has several strengths. The study includes more than 90% of patients with COVID-19 enrolled in IL-6ra trials, and the analysis plan was predefined and published before the collection of outcome data, reducing the risk of bias.2 In addition to the primary outcome, the study focused on clinically relevant secondary outcomes, including progression to IMV or death. The benefits associated with IL-6ra were consistent across several subgroups, including patients treated with glucocorticoids, vasopressors, kidney replacement therapy, and a range of supplemental levels of respiratory support. The authors conducted several post-hoc sensitivity analyses that showed the ORs were similar to the primary analysis for key end points, including an analysis that excluded results from the RECOVERY trial to mitigate disproportionate effect due to this study’s large size (4,116 participants) and analyses restricted only to peer-reviewed published trials, open-label trials, or placebo-controlled trials. The primary analysis relied on a fixed-effects model, which the authors contend is more appropriate than a random-effects model, because the latter approach gives more weight to smaller compared with larger trials. Regardless, the random-effects analysis indicated a similar OR, suggesting an association between IL-6ra use and reduced 28-day mortality.

An important limitation to this meta-analysis is lack of accounting for the baseline risk of death. In most randomized trials of sepsis or acute respiratory distress syndrome, baseline risk of death is usually assessed with a severity of illness score, such as APACHE (Acute Physiology and Chronic Health Evaluation) or SOFA (Systemic Organ Failure Assessment), because these scores help to interpret the effect of the intervention and reduce confounding by an imbalance of baseline comorbidities. Severity of illness scores have not been validated for patients hospitalized with COVID-19, and it is possible that prognosis among these hospitalized patients may depend more on the severity of respiratory failure as defined by oxygen support and ventilatory assistance. An additional limitation is the lack of detailed reporting on the level of respiratory support at the time of randomization, which precludes a granular understanding of how IL-6ra efficacy is
affected by oxygen requirements. For example, in this study, the use of noninvasive ventilation and high-flow nasal oxygen was combined as 1 analytic category.

Effective treatments for COVID-19 continue to evolve; anti-inflammatory agents, such as dexamethasone, 3 JAK inhibitors, 4–6 antiviral drugs including remdesivir, 7 and now at least 1 combination of monoclonal antibodies, 8 have been associated with improved time to recovery and a mortality benefit in certain groups of patients hospitalized for COVID-19. Also, among noncritically ill patients hospitalized with elevated D-dimer levels, therapeutic anti-coagulation with heparin decreased COVID-19 disease progression. 9 Given this background of existing therapeutics, how should IL-6ra best be used to benefit patients hospitalized for COVID-19?

First, the meta-analysis by the REACT investigators highlights that IL-6ra have only been effective to date when given with concomitant glucocorticoids and thus should be reserved for patients who already have started taking glucocorticoids.

Second, how should the level of respiratory support guide the use of IL-6ra? The mortality benefit associated with IL-6ra use was lower among patients who received IMV vs those who did not receive IMV. IL-6ra for critically ill patients may be most effective when given early in the disease course, whereas benefit may be unlikely when patients have received ventilatory support for several days or more. For example, REMAP-CAP demonstrated a hazard ratio of 1.6 for improved 90-day survival in patients who received IL-6ra in the first 24 hours after admission to the intensive care unit. 10 In addition, appropriate use of IL-6 inhibition in patients with low oxygen requirements is not clear. The OR for death was 0.75 among those who required oxygen at a rate of 15 L/min or less, which encompasses a broad group of patients, ranging from those with progressive severe hypoxemia to those with minimal oxygen needs. Questions remain about the appropriate threshold for initiating glucocorticoids in patients with limited oxygen requirements, and the addition of IL-6ra is likely unnecessary for those with modest oxygen needs and a relatively stable course.

Third, how should IL-6ra be compared with other available interventions? The JAK inhibitors baricitinib and tofacitinib have largely shown benefit for patients who are not receiving mechanical ventilation but who require high levels of oxygen support 4 and in conjunction with glucocorticoid use. 5 While IL-6ra require intravenous administration, JAK inhibitors are given orally, are usually less costly than IL-6-ra, and may be more widely available globally. How these drugs compare head to head is not known, and combination treatment with IL-6ra and JAK inhibition is not recommended pending data from ongoing studies. Monoclonal antibodies against SARS-CoV-2 are reemerging as an option early in hospitalization, specifically for patients who have not mounted an endogenous antibody response. 8 The additive benefit or risk of combining immunomodulators such as IL-6ra with monoclonal antibody therapy against SARS-CoV-2 is unknown and requires more data on endogenous antibody responses, viral kinetics, and infectious complications.

Fourth, the mortality among patients hospitalized for COVID-19 in the US has greatly declined over the course of the pandemic, with nonintensive care unit mortality well below the 25% assumed mortality from this meta-analysis. 11 The 4% absolute risk reduction in mortality from 25% to 21% with IL-6 inhibition added to glucocorticoids may not translate to patients with a lower baseline mortality risk and likely do not justify the additional expense and risk for toxicities for patients hospitalized with modest oxygen requirements and a stable clinical course.

In conclusion, IL-6ra hold promise for patients hospitalized for COVID-19 with progressive disease and substantial oxygen requirements but are not yet merited for widespread use among patients with mild disease nor with prolonged invasive mechanical ventilation.

ARTICLE INFORMATION
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REFERENCES
9. Lawler PR, Goligher EC, Berger JS, et al; The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation in non-critically ill patients...
Intake of Ultraprocessed Foods Among US Youths
Health Concerns and Opportunities for Research and Policy

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Technological advancements in food production, preparation, and processing have yielded improvements in the quality of life, food safety, and health. Yet, the proliferation of highly processed, ready-to-eat or ready-to-heat products, commonly referred to as ultraprocessed foods, has elicited concern because they tend to have poorer nutrient profiles and can replace more nutrient-dense, whole food options in the diet.

In this issue of JAMA, Wang et al1 present trends in the consumption of ultraprocessed foods among US youths using data from 1999-2018 National Health and Nutrition Examination Surveys (NHANES). Foods were categorized based on the NOVA framework, the current gold standard for classifying processed foods.2 NOVA-classified ultraprocessed foods are industrially produced and contain ingredients that will rarely be included in culinary preparations. The industrial production of ultraprocessed foods uses modern technology to create visually appealing and hyperpalatable products comprising materials extracted from food, such as casein and whey; substances derived from food constituents through further processing, such as soy protein isolates and maltodextrin; and nonculinary additives, such as flavor enhancers and emulsifiers.2,3 During the 20-year study period, the estimated percentage of total energy consumed from ultraprocessed foods increased from 61.4% to 67.0% (difference of 5.6%), whereas the estimated percentage of total energy consumed from unprocessed or minimally processed foods decreased from 28.8% to 23.5% (difference of −5.3%). The estimated percentage of energy from consumption of sugar-sweetened beverages decreased (from 10.8% to 5.3%), but the percentage of energy from other subgroups of ultraprocessed foods increased, especially ready-to-heat and -eat meals (from 2.2% to 11.2%).

The potential implications for future health are significant. Childhood is a critical period for biological development and the establishment of dietary behaviors.4 Recent systematic reviews and meta-analyses have found that higher intake of ultraprocessed foods is associated with a range of adverse health outcomes in adults5 and with overweight or obesity in children.6 However, these analyses included only a limited number of cross-sectional and cohort studies because investigation of ultraprocessed foods is still in the early stages. Perhaps the strongest support for a causal effect of ultraprocessed foods comes from a crossover feeding study by Hall et al7 that found participants on a diet high in ultraprocessed foods consumed more calories and gained more weight in a 2-week period, compared with individuals on a whole food-based diet, despite matching the foods by calories, energy density, macronutrient composition, sugar, sodium, and fiber.

However, the interpretation of many of the studies of ultraprocessed foods is challenging because the effects of processing generally cannot be separated from the composite nutrients of ultraprocessed foods. As shown by Wang et al,1 ultraprocessed foods are higher in carbohydrates, added sugars, and sodium and are lower in fiber and protein. In the controlled study by Hall et al,7 the investigators were unable to identify factors associated with increased energy intake by participants receiving the ultraprocessed food diet, and it remains unclear whether their results reflect some unique pathway related to processing or differential consumption of nutrients. Epidemiological studies have found associations between intake of ultraprocessed foods and adverse health outcomes after adjustment for total energy and dietary quality, but the potential for residual confounding remains due to high correlations between ultraprocessed foods and nutrient content.

As Wang et al1 point out, a conceptual advancement would be to consider the level and characteristics of processing as just one of multiple dimensions (including nutrients and food groups) used to classify foods as healthy or unhealthy. For example, the Pan American Health Organization recommends that policies to reduce unhealthy food intake should target products that are ultraprocessed and high in added nutrients of concern.8 This joint approach to assessing both nutrients and processing avoids a common critique of NOVA, which is that some products classified as ultraprocessed may be relatively healthy, whereas other products that are minimally processed may be relatively less healthy. For example, in the study by Wang et al,1 all industrial-made bread was classified as ultraprocessed despite the potential for some of these products to be low in nutrients of concern and rich in whole grains.

In addition, classification of ultraprocessed foods is complex because it requires data on a full list of ingredients. This is a challenge, given that most large epidemiological studies rely on food frequency questionnaires that lack the information necessary to classify processing levels. Wang et al9 benefited by having access to detailed food data from the NHANES diet assessment. However, even more detailed information may be needed, including product-specific...