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Immunomodulators in Mechanically Ventilated Patients With COVID-19: Lessons Learned From Underpowered Trials*

KEY WORDS: acute respiratory distress syndrome; baricitinib; clinical trials; COVID-19; ruxolitinib

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Despite remarkable advances in supportive care, antiviral, and immunomodulatory therapies through rigorous clinical trials (1), patients with severe COVID-19 continue facing high burden of complications, including prolonged cognitive and physical sequelae, hospitalization, and risk of death. Mortality is higher in patients with risk factors for complications and those needing ICU care (2). Early in the pandemic, the use of the antiviral agent remdesivir demonstrated faster clinical recovery, decreased disease progression (3), and, ultimately, provided survival benefit (4, 5). However, clinical outcomes required further improvement, partly because disease severity was also related to a dysregulated host immune response. Several immunomodulatory agents from distinctive pharmacologic families, such as glucocorticoids, interleukin-6 (IL-6) signaling blockers, and Janus Kinase (JAK) and signal transducer and activator of transcription (STAT) inhibitors, have all shown survival benefits in patients with severe COVID-19 infection. Nonetheless, nuance remains regarding their optimal target population, safety profile, and the degree of certainty for the evidence supporting each drug's mortality benefit, especially in the critically ill population.

COVID-19 patients with severe hypoxemia leading to acute respiratory distress syndrome (ARDS) requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) experience disproportionately high mortality. One of the regimens recommended by treatment guidelines is dexamethasone and tocilizumab (6, 7), as those agents have been associated with better survival in patients with hypoxemia and organ dysfunction (8, 9), although double-blind, placebo-controlled randomized trials have not found a survival benefit from tocilizumab or dexamethasone in this population. Indeed, a recent Bayesian meta-analysis that included 15 randomized clinical trials compromising greater than 5,000 patients treated with tocilizumab and corticosteroids concluded that uncertainty remains about the magnitude of a survival benefit for the subgroup of patients requiring invasive mechanical ventilation (10).

***See also p. 1701.**

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Baricitinib, a JAK1 and JAK2 inhibitor, became the first Food and Drug Administration-approved immunomodulatory agent for COVID-19 following evidence from several randomized controlled trials (RCTs) demonstrating a consistent and marked reduction in 28-day mortality in patients with severe COVID-19 infection (11–15). To date, three RCTs have demonstrated that baricitinib significantly reduces mortality compared with placebo plus standard of care (SOC) (COV-BARRIER and (Baricitinib in Participants With COVID-19 [COV-BARRIER] and COV-BARRIER-2 trials) (11, 12) or SOC alone (the Randomised Evaluation of COVID-19 Therapy [RECOVERY] baricitinib trial) (13) and significantly decreases progression to intubation or death compared with placebo plus SOC (Adaptive COVID-19 Treatment Trial [ACTT]-2) (14). Furthermore, baricitinib has proven to represent a feasible and safer initial immunomodulatory choice in hospitalized patients with COVID-19 based on the efficacy and safety results of two double-blind, placebo-controlled RCTs: ACTT-2 and ACTT-4 (14, 15). In contrast with tocilizumab, whose treatment effect is dependent on corticosteroids (significant statistical interaction) (9, 10), baricitinib works independently of the presence or absence of corticosteroids (no interaction). Another JAK-inhibitor agent, tofacitinib, an orally administered selective JAK1 and JAK3 inhibitor with functional selectivity for JAK2, was evaluated in a double-blind, placebo-controlled randomized trial of non-ICU hospitalized patients in Brazil, the Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 (STOP-COVID) trial (16). Compared with placebo, tofacitinib led to a lower mortality or respiratory failure through day 28. In the critically ill population, the COV-BARRIER-2 (12) compared the efficacy of baricitinib to placebo in 101 patients on invasive mechanical ventilation or ECMO and showed that in combination with corticosteroids, baricitinib significantly reduced 28-day mortality. This survival benefit was consistent with the mortality reduction observed in nonventilated patients in the COV-BARRIER study (11). Consequently, the most recent update of the National Institute of Health (NIH) COVID-19 treatment guidelines recommend baricitinib (or tofacitinib if by mouth baricitinib and IV tocilizumab are not available) in combination with dexamethasone, for patients who require mechanical ventilation or ECMO, if not initiated beforehand (7). Whether the survival benefits from the JAK-STAT signaling pathway inhibition can be extended to other JAK-inhibitors (e.g., ruxolitinib) remains uncertain.

Ruxolitinib is a potent, selective inhibitor of the JAK1 and JAK2 licensed for treating patients with intermediate- or high-risk myelofibrosis, including polycythemia vera and steroid-refractory graft versus host disease. In this issue of *Critical Care Medicine*, Rein et al (17) evaluated the safety and efficacy of ruxolitinib in patients with COVID-19–associated ARDS requiring invasive mechanical ventilation (the Ruxolitinib in Patients With COVID-19–Associated Cytokine Storm study [RUXCOVID] study). The study, a randomized, placebo-controlled, double-blind trial, was conducted in the United States (29 sites) and Russia (4 sites). Hospitalized patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection were eligible if they were greater than or equal to 12 years old and mechanically ventilated with severe hypoxemia (Pao_2/Fio_2 of ≤ 300 mm Hg) within 6 hours of randomization. A randomization schema of 2:2:1 was used to maximize exposure to the interventional arms; randomization was stratified by ARDS severity and study site. Subjects were randomized to receive either ruxolitinib 15 mg, ruxolitinib 5 mg (both bid), or a matching placebo. Among all participants at baseline, 27% had severe ARDS (defined as a Pao_2/Fio_2 <100 mm Hg). The study was planned for a sample size of 500 patients (200 randomized in each ruxolitinib arm and 100 to placebo) to achieve 83% power to detect a 20% mortality difference in the intervention arm, assuming a baseline 60% mortality rate in the placebo arm based on emergent mortality data early in the pandemic. Nonetheless, the study's sponsor halted enrollment in December 2020, 7 months following patient recruitment. A total of 211 patients (mean age 63.4 yr, 65% male, 71% White) were enrolled: ruxolitinib 15 mg (n = 77), ruxolitinib 5 mg (n = 87), and placebo (n = 47). The primary endpoint (28-d mortality) did not differ between groups, 51%, 53%, and 70%, for ruxolitinib 15 mg, ruxolitinib 5 mg, and placebo, respectively, with an (odds ratio [OR], 0.46 [95% CI, 0.201–1.028]) one-sided p = 0.029 in the 15 mg arm, and (OR, 0.42 [95% CI, 0.171–1.023]) one-sided p = 0.028 in the 5 mg arm, compared with placebo. Other treatments were allowed and balanced across groups: corticosteroids (90%), remdesivir (55%), corticosteroid plus remdesivir (51%), and convalescent plasma (18%). Analysis of secondary outcomes, including ventilator-free,

ICU-free, and vasopressor-free days, showed a numerical improvement in favor of ruxolitinib but failed to show statistical significance. Severe and treatment-related adverse events were comparable across ruxolitinib and placebo groups. In a nonprespecified post hoc analysis of the primary endpoint, when pooling the 15 and 5 mg ruxolitinib arms, the 28-day mortality was 52% versus 70% (OR, 0.47 [95% CI, 0.219–0.996]; one-sided $p = 0.024$) versus placebo. When the analysis was confined to the U.S. population (90% of the study enrollment), there was an improvement in mortality for each ruxolitinib dosing arm: 46.5% (OR, 0.43 [95% CI, 0.188–0.974], $p = 0.022$) for the 15 mg arm, and 47.4% vs 68.2% (OR, 0.39 [95% CI, 0.157–0.948], $p = 0.019$) for the 5 mg arm, versus placebo. Statistical significance cannot be claimed as the p values were one-sided (i.e., significant when $p < 0.025$) and derived from a post hoc analysis without type I error allocated.

The study sponsor prematurely halted enrollment (42% of the original target population of 500 subjects), leaving RUXCOVID-DEVENT significantly underpowered to unequivocally exclude a positive effect of ruxolitinib over the primary endpoint (28-d mortality). Therefore, the study's results leave us reckoning with two realities: First, a substantial body of evidence indicating a significant mortality reduction from JAK inhibitors (five RCTs for baricitinib and one for tofacitinib). This was further confirmed by a recent meta-analysis accompanying the RECOVERY-baricitinib trial publication that included nine RCTs (comprising three ruxolitinib studies, including the RUXCOVID-DEVENT trial), showing that allocation to baricitinib or other JAK inhibitor was associated with a significant 20% reduction in 28-day mortality (13).

Second, a previous negative trial for ruxolitinib in nonventilated COVID-19 patients. The RUXCOVID trial (18) was a placebo-controlled, double-blind, randomized study that evaluated ruxolitinib (5 mg twice per day) versus placebo plus SOC in non-ICU hospitalized patients with COVID-19 and failed to show benefits in the composite primary endpoint of death, respiratory failure, or ICU admission by day 29.

Could the survival benefits from JAK-STAT pathway inhibition be exclusive of baricitinib and tofacitinib? Besides lack of statistical power, another factor to consider is the timing and dosing of the therapeutic intervention. For instance, in the COV-BARRIER-2 trial, the median duration of hospitalization before randomization was 4 days. In contrast, in the RUXCOVID-DEVENT trial, 61% of patients were intubated for greater than 48 hours before randomization, and the median time of initial diagnosis to randomization was 10 and 9 days for ruxolitinib and placebo, respectively. So, inadvertently, by allowing study enrollment up to 3 weeks from SARS-CoV-2 infection, RUXCOVID-DEVANT could have included more patients at an advanced ARDS phase, which is well known to affect outcomes and prognosis. In addition, the negative RUXCOVID-trial (18) employed a ruxolitinib dose of 5 mg twice per day (as approved for initial treatment of steroid-refractive GVHD). In contrast, RCTs for baricitinib and tofacitinib in COVID-19 patients have used dosing regimens of 4 mg daily and 10 mg bid, respectively, a two-fold increase from their respective initial dose recommended for their FDA-approved rheumatologic indications.

The confirmation that another JAK-inhibitor impacts patient survival could have substantial clinical implications worldwide. Mechanistically, the JAK-STAT pathway inhibition offers a broad immunosuppressive effect, albeit transient, due to the short half-life of their agents (half-life: 12, 3, and 6 hr for baricitinib, tofacitinib, and ruxolitinib, respectively). Thus, this short-lived immunomodulatory intervention can be advantageous compared with agents with more restricted cytokine blockage (i.e., IL-6 blockage) and longer half-life (e.g., 11-13 d for tocilizumab). In addition, baricitinib is not recommended for patients with estimated glomerular filtration rate less than 15 mL/min/1.73 m^2 or for patients on hemodialysis, whereas for tofacitinib and ruxolitinib, dosage can be renally adjusted for patients with moderate to severe end-stage renal disease and hemodialysis. The worldwide availability of ruxolitinib for its primary indications, myelofibrosis, and steroid-refractory GVHD could have facilitated global drug access to a potentially life-saving medication in low-resource settings where baricitinib or tofacitinib is not available.

Underpowered clinical trials leave us with a sour taste. In exploring the reasons for enrollment termination by the sponsor in December of 2020, the COVID-19 pandemic shows its resilience against conventional human thinking and exposes the fragmented clinical-trial infrastructure of both national and international systems. The sponsor expected a significant decline of COVID-19 cases following vaccination uptake in December 2020; nonetheless, SARS-CoV-2 subvariants, like alpha, delta, and omicron, have raged

communities and stressed hospital capacity since then. In addition, the FDA announcement on November 19, 2020, issuing Emergency Use Authorization for baricitinib, effectively changed the SOC.

Clinical research study networks, either from governmental funding or public-private partnerships, can link local infrastructure with research organizations in multicenter and international collaborations, implementing adaptive study designs and bringing drug candidates to the field while incorporating changes to the SOC in real time. Depending on the pandemic burden, these study networks, which are pivotal for a coordinated research strategy, could be readily expanded or downsized to meet research needs and should be adaptable to function in diverse healthcare settings (e.g., community, emergency departments, inpatient, or ICUs). During the COVID-19 pandemic, successful examples of effective clinical research study networks partnering with government, industry, and non-profit organizations were the ACTT and Accelerating COVID-19 Therapeutic Interventions and Vaccines initiatives, both sponsored by the NIH. Healthcare challenges such as future COVID-19 surges, seasonal or pandemic influenza, and monkeypox, to mention some examples, will test the lessons learned in this regard. Although maintaining clinical research study networks can be difficult and costly, the missed opportunity and uncertainty left by underpowered and prematurely closed clinical trials can be even more devastating for patients and public health.

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Dr. Gomez disclosed that he was a study site principal investigator for the Adaptive COVID-19 Treatment Trial (ACTT) at his past institution, the University of Utah. National Institutes of Health/National Institute for Allergy and Infectious Diseases was the ACTT network sponsor. Dr. Kalil disclosed he was an investigator for the National Institutes of Health Adaptive COVID-19 Treatment Trial.

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