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PERSPECTIVES

Revisiting Janus Kinase Inhibitors in Hospitalized COVID-19: Evidence for Baricitinib's Superiority and the Absence of a Class Effect

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Abstract: Janus kinase (JAK) inhibitors, developed for autoimmune diseases, have been repurposed as potential therapies for severe COVID-19. Growing evidence indicates that their clinical utility is heterogeneous and cannot be generalized as a class effect. In this Perspective, we focus on the clinical evidence base for JAK inhibitors in COVID-19 and emphasize baricitinib as the the only agent with consistent mortality benefit and highlights the need for agent-specific recommendations and individualized treatment strategies.

Keywords: janus kinase inhibitors, baricitinib, tofacitinib, ruxolitinib, COVID-19, immunomodulation

Janus kinase (JAK) inhibitors have emerged as immunomodulatory agents with potential benefits in the treatment of hospitalized patients with COVID-19. Recent data from multiple randomized controlled trials (RCTs) and large-scale meta-analyses suggest that JAK inhibitors can reduce mortality and improve outcomes in selected patients.[1,2] However, a closer look at agent-specific efficacy, subgroup variations, and long-term safety concerns is essential before broad clinical adoption.

Mechanistically, JAK inhibitors attenuate cytokine-driven hyperinflammation by blocking the JAK–STAT signaling pathway, which regulates multiple pro-inflammatory cytokines such as IL-6, IFN-γ, and GM-CSF that drive the cytokine storm in severe COVID-19.[3,4] Baricitinib uniquely combines JAK1/2 inhibition with the ability to interfere with viral endocytosis,[5,6] potentially explaining its superior efficacy profile. In the RECOVERY trial, baricitinib reduced 28-day mortality to 12% vs 14% in usual care (rate ratio 0.87, 95% CI 0.77–0.99), with fewer patients requiring invasive mechanical ventilation.[7] In the COV-BARRIER trial, baricitinib reduced 28-day mortality from 13% in placebo to 8% (HR 0.57, 95% CI 0.41–0.78).[8] A recent individual patient data meta-analysis of >12,000 patients confirmed these findings, showing a relative reduction in mortality risk of 20% (OR 0.80, 95% CI 0.71–0.89).[1] Its impact on hospital length of stay was modest, with RECOVERY reporting a median of 10 vs 11 days, while evidence for accelerated viral clearance remains limited. This convergence of evidence across RCTs and systematic reviews explains why baricitinib is uniquely recommended by WHO and NIH guidelines, underscoring its central role in the treatment of hospitalized COVID-19 patients.

Tofacitinib primarily targets JAK1/3, resulting in broader immunosuppressive effects, while ruxolitinib, another JAK1/2 inhibitor, has shown limited clinical benefit despite its theoretical rationale.[9–11] These mechanistic distinctions provide a biological basis for the agent-specific differences observed in clinical trials. Tofacitinib yielded mixed results but showed a similar trend toward mortality reduction as observed with baricitinib.[1] In the STOP-COVID trial (NEJM 2021), the composite endpoint of death or respiratory failure occurred in 18.1% of patients receiving tofacitinib vs 29%

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in placebo (risk ratio 0.63, 95% CI 0.41–0.97),[12] but effects on mortality alone were not statistically significant, and no consistent improvement in viral clearance has been demonstrated. Ruxolitinib, despite its theoretical rationale, failed to show benefit. In the RUXCOVID trial, 28-day mortality was 6.7% in ruxolitinib vs 8.4% in placebo (OR 0.80, 95% CI 0.46–1.41), with no difference in time to recovery.[13] Similarly, in the COVID-ARDS trial, 28-day mortality was 51% with ruxolitinib vs 53% with placebo (p=0.76), with no improvement in hospital stay or viral clearance.[14] These findings question its utility in this clinical context.

Beyond differences in agent-specific efficacy, the use of JAK inhibitors in certain populations warrants caution. Subgroup analyses from pooled data and individual trials suggest that immunocompromised patients may be at increased risk of adverse outcomes when treated with these agents. For instance, in one analysis, 28-day mortality among immunosuppressed patients was 20.8% in the JAK inhibitor group compared with 13.3% in controls.[1] Real-world evidence also suggests that the survival benefit of baricitinib may be attenuated in immunocompromised patients. In an Israeli registry study, among patients requiring high levels of oxygen support, treatment with baricitinib or tocilizumab did not significantly improve mortality (62.5% vs 64.1%).[15] Furthermore, in patients receiving tocilizumab without dexamethasone, mortality was notably higher with JAK inhibitor use (44.4% vs 25.0%).[1] These findings emphasize the importance of individualized risk-benefit assessment and careful patient selection.

Long-term safety remains an area of uncertainty, especially given the immunosuppressive nature of JAK inhibitions. Although short-term trials have not shown a significant increase in serious adverse events, concerns persist regarding opportunistic infections, herpes viral reactivations, thromboembolic complications, and potential malignancy risk with extended use.[16,17] Such adverse effects have been well documented in patients receiving JAK inhibitors for chronic inflammatory diseases and warrant attention in the context of COVID-19, particularly for patients with prolonged or repeated courses of therapy.

In conclusion, JAK inhibitors remain a valuable component of COVID-19 treatment, and baricitinib is the only agent with consistent evidence of mortality benefit, while tofacitinib shows limited and mixed effects, and ruxolitinib has failed in major trials. These distinctions highlight that clinical use should be guided by agent-specific evidence rather than class-based assumptions. Looking forward, future studies should refine patient stratification strategies, explore optimal treatment combinations, and clarify long-term outcomes to ensure safe and effective use.

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Disclosure

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