Baricitinib (Olumiant®)

What is it?

- An inhibitor of Janus kinase (JAK) enzymes which are involved in cytokine-mediated inflammatory and immune pathways.
- Hyperinflammation occurring because of COVID-19 may be lessened through JAK inhibitors like baricitinib.

Baricitinib is a Health Canada-approved disease-modifying antirheumatic drug (DMARD) indicated for the treatment of rheumatoid arthritis. It currently does not hold an indication for COVID-19 treatment outside of clinical trials.

Health Canada Indications:	**Moderate to severe rheumatoid arthritis in adults who have responded inadequately to one or more previous DMARD.**

Evidence: Early in the COVID-19 pandemic the ACTT-2 trial suggested that baricitinib 4 mg po daily for 14 days in combination with remdesivir for 10 days was more effective than remdesivir alone for reducing time to recovery in adult patients requiring hospitalization.[2] The majority of ACTT-2 trial participants did not receive corticosteroids as part of their COVID-19 therapy. The subsequent ACTT-4 trial set out to compare the combinations of remdesivir + baricitinib versus remdesivir + dexamethasone for impact on disease progression and/or death in hospitalized adults requiring supplemental oxygen excluding mechanical ventilation. This study was stopped early after meeting pre-specified futility criteria.[3,4]

The **COV-BARRIER study**[5] **(available as a preliminary, non-peer-reviewed pre-print only)** reports on 1525 adults hospitalized with COVID-19 and not receiving mechanical ventilation or ECMO between June 2020 and Jan 2021. Baseline respiratory support: 12% of patients receiving no supplemental oxygen, 63% receiving supplemental oxygen, and 24% non-invasive or high-flow oxygen. Along with standard of care (including 79% of patients receiving dexamethasone) patients were randomized to receive baricitinib 4 mg po daily x up to 14 days or until hospital discharge, or placebo po daily x 14 days. Key results:

COV-BARRIER Preliminary Results

- **No difference in primary outcome, the composite of progression to non-invasive ventilation/high-flow oxygen, invasive mechanical ventilation, or death within 28 days:**
  - 27.8% baricitinib recipients vs 30.5% placebo recipients [OR 0.85 (95% CI 0.67-1.08); p = 0.180]. (Note: calculated by multiple imputation method)
- **Fewer deaths by day 28 (secondary outcome):**
  - 8.1% (62/764) baricitinib recipients vs 13.1% (100/761) placebo recipients died by day 28 [HR 0.57 (95% CI 0.41-0.78); p = 0.0018].
- **Serious adverse events (SAEs):**
  - Occurred in 14.7% (110/750) of baricitinib recipients and 18.0% (135/752) placebo recipients (no statistical comparison provided). Treatment-emergent infections were the most common SAE.

Number needed to treat (NNT): For every 20 hospitalized COVID-19 patients (the majority requiring supplemental or high-flow oxygen or non-invasive ventilation) who receive baricitinib 4 mg po daily x 14 days plus standard of care, one fewer death will occur by day 28 days versus patients receiving placebo and standard of care.

Infectious Diseases Society of America (IDSA): conditionally recommends that adults with severe COVID-19 (i.e., those with SpO2 ≤ 94% on room air, including those on supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation) with elevated inflammatory markers but not on invasive mechanical ventilation receive baricitinib over no baricitinib.[6] They note that baricitinib and tocilizumab or other IL-6 inhibitors should not be co-administered. They also conditionally suggest that baricitinib plus remdesivir be used over remdesivir alone in severe COVID-19 patients for whom corticosteroids are indicated but for whom a contraindication to corticosteroids exists.

Practical Considerations

- Risks and benefits of treatment with baricitinib should be carefully considered in patients with chronic, recurrent, or latent infections (e.g. tuberculosis), and patients at elevated thrombosis risk.
- Baricitinib is dependent on renal excretion and dosage adjustment is required in renal impairment. Administration not recommended if eGFR below 15 mL/min or receiving renal replacement therapy.
- Screen for drug interactions prior to baricitinib initiation. Strong OAT3 inhibitors such as probenecid may result in inhibited baricitinib metabolism and increased exposure.

Prepared by: COVID-19 Clinical Pharmacy Working Group
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