Potential COVID-19 Treatments: Janus kinase Inhibitors

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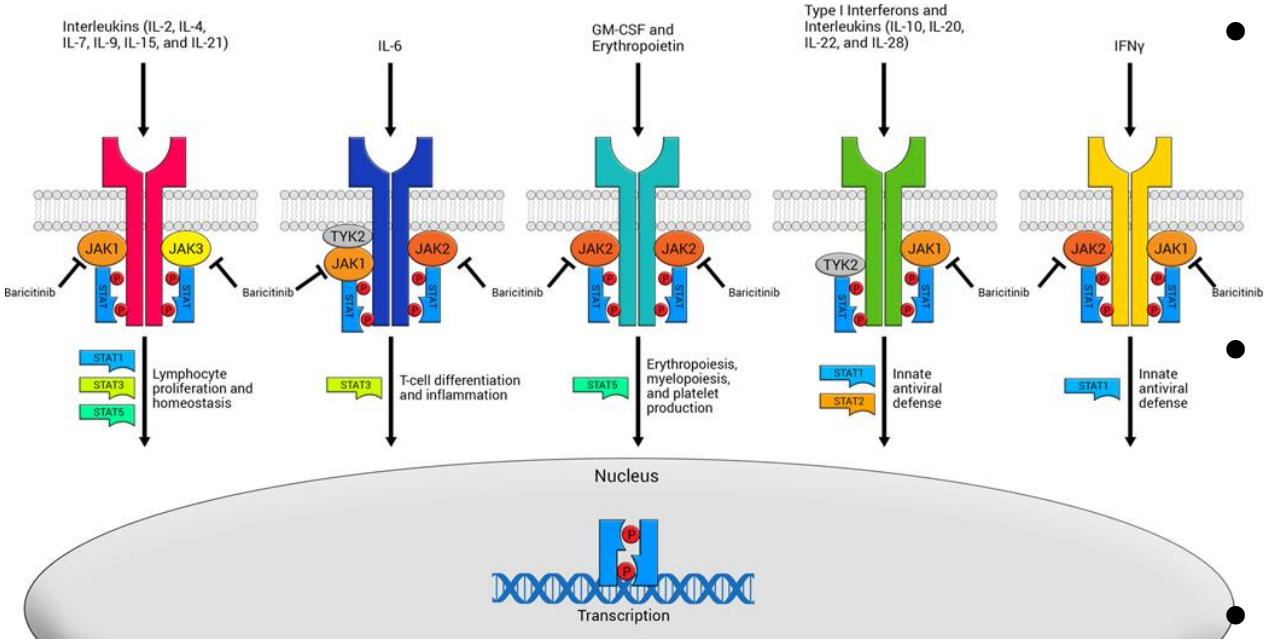
baricitinib (Olumiant®)
Eli-Lilly

- Administered **orally**, currently approved in Canada for the treatment of autoimmune and pro-inflammatory indications including rheumatoid arthritis
  - use in COVID -19 is off-label
  - classified as a hazardous drug that requires special handling
- Mechanism of action (MOA): selective and reversible Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor (JAKi)
- Another JAKi Tofacitinib (Xeljanz®) has also been investigated for use in COVID-19; at this time there is more evidence for baricitinib with upcoming data expected from the RECOVERY Study Group

Hypothesized MOA for JAKi in treating COVID-19



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- JAK/STAT pathway mediates signal transduction from extracellular stimuli including cytokines to the nuclei of cells
- baricitinib exerts its anti-inflammatory effects through reversible JAK inhibition and interruption of signal transduction
- Interleukin-6 transduces signaling via complexes of JAK1, JAK2 and TYK2

Recent Evidence

- **ACTT-2 trial** (baricitinib + remdesivir): published in NEJM Mar 4, 2021; combination shown to be superior to remdesivir alone in time to recovery (total trial population = 1 day faster); patients requiring high-flow and non-invasive ventilation showed a greater benefit in median time to recovery of 10 days vs 18 days with control; patients requiring supplemental oxygen, no oxygen or those on mechanical ventilation or ECMO showed no benefit in time to recovery

- **COV-BARRIER trial** (funded by manufacturer): published in the Lancet Sept 1, 2021; results indicated that baricitinib in addition to standard of care (SOC), e.g. dexamethasone, was associated with reduced mortality in hospitalized adults with COVID-19; safety profile was similar to SOC alone but did not significantly reduce frequency of disease progression overall
- **COV-BARRIER addendum trial** (COV-BARRIER Study Group): pre-print RCT released Oct 12, 2021; included population excluded from COV-Barrier (mechanically ventilated and patients on ECMO); results similar to COV-BARRIER

COV-BARRIER: Primary Trial (n = 1525)

Multinational (12 countries, 101 sites), randomised, placebo controlled, phase 3 trial

- **Inclusion criteria:** hospitalised patients aged 18 years and over, with lab confirmed COVID-19 and either evidence of pneumonia or active/symptomatic COVID-19, and at least one elevated inflammatory marker (CRP, D-dimer, Lactate Dehydrogenase or ferritin); protocol change October 2020 to only patients requiring baseline oxygen support (based on results from ACTT-2)
- **Exclusion criteria:** requiring mechanical ventilation at study entry, actively receiving immunosuppressive therapy, had received convalescent plasma or IVIG for COVID, neutropenia, lymphopenia, ALT/AST 5 x ULN, eGFR less than 30
- **Treatment arms:** Baricitinib 4 mg PO/NG daily (2 mg if GFR 30 – 59) vs. placebo for up to 14 days or until discharge (whichever came first)
  - All patients received standard of care of local practices at the time including: steroids, antivirals or both (note: higher dose steroids >20 mg prednisone equiv. daily, not permitted unless indicated for concurrent condition)
- *VTE prophylaxis required unless major contraindication; 80% of patients also received corticosteroids*

	Baricitinib group (n=764)	Placebo group (n=761)
(Continued from previous column)		
Duration of disease symptoms before enrolment, days		
<7	137/762 (18%)	116/756 (15%)
≥7	625/762 (82%)	640/756 (85%)
Score on NIAID-OS		
4 (hospitalised, not requiring supplemental oxygen)	89/762 (12%)	97/756 (13%)
5 (hospitalised, requiring supplemental oxygen)	490/762 (64%)	472/756 (62%)
6 (hospitalised, receiving non-invasive ventilation or high-flow oxygen)	183/762 (24%)	187/756 (25%)
Concomitant medications of interest		
Remdesivir	140/762 (18%)	147/756 (19%)
Systemic corticosteroids	612/762 (80%)	592/756 (78%)
Dexamethasone	566/612 (92%)	533/592 (90%)
Pre-existing comorbidities of interest		
Obesity	250/764 (33%)	253/761 (33%)
Diabetes (types 1 and 2)	224/764 (29%)	233/761 (31%)
Chronic respiratory disease	34/764 (4%)	36/761 (5%)
Hypertension	365/764 (48%)	366/761 (48%)

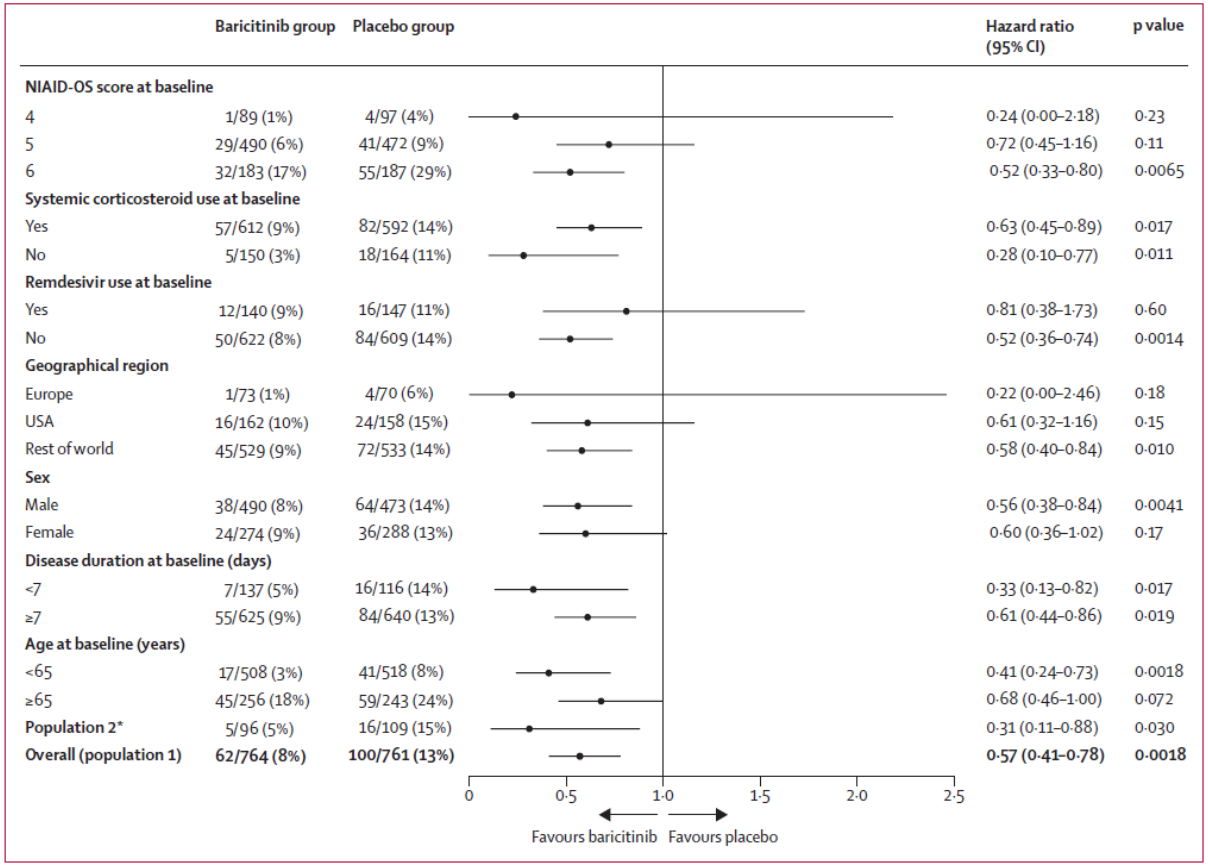
Data are mean (SD) or n/N (%). NIAID-OS=National Institute of Allergy and Infectious Disease Ordinal Scale. *Includes participants from Mexico and Latin America. †Reporting required in the USA only.

Table 1: **Baseline demographics and clinical characteristics**

	Baricitinib group (n=764)	Placebo group (n=761)	Baricitinib vs placebo	
			Point estimate (95% CI)	p value*
Primary outcome				
Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation (including ECMO), or death, by day 28†				
Population 1‡	27·8%	30·5%	OR 0·85 (0·67 to 1·08)	0·18
Population 2§	28·9%	27·1%	OR 1·12 (0·58 to 2·16)	0·73

- Primary intention-to-treat analysis was done in two populations:
  - Population 1 = all randomised patients
  - Population 2 = sub group who at baseline required oxygen but were not receiving systemic corticosteroids for COVID-19

- Pre-specified secondary outcomes up to day 28:
  - All-cause mortality
  - At least 1 point improvement on NIAID-OS
  - Discharge from hospital at day 4, 7, 10 and 14
  - Duration of hospitalization
  - Ventilator free days
  - Time to recovery
  - Overall improvement on NIAID-OS *(National Institute of Allergy and Infectious Disease Ordinal Scale)*
  - Improved oxygen saturation above 94%
  - Adverse events



Primary composite outcome:

- Population 1: NSS difference
- Population 2: NSS difference

→ ***Due to results for primary outcome, none of the secondary endpoints were considered statistically significant after adjusting for multiplicity = p values are nominal****

All-cause mortality at day 28:

- Population 1: absolute risk reduction of 5% in baricitinib group (nominal p = 0.0018)
- Population 2: absolute risk reduction of 10% in baricitinib group (nominal p = 0.03)

* nominal p-value is a calculated observed significance based on a given statistical model. The nominal p-value may become a meaningless number if the assumptions of the statistical model used to compute it does not hold.

COV-BARRIER: Critically ill Addendum Trial

Multinational (18 centres, 4 countries), randomised, placebo controlled, phase 3 trial (n=101)

- **Inclusion criteria:** hospitalised patients aged 18 years and over, with lab confirmed COVID-19 and either evidence of pneumonia or active/symptomatic COVID-19, and at least one elevated inflammatory marker (CRP, D-dimer, Lactate Dehydrogenase or ferritin) and *required invasive mechanical ventilation or ECMO at study entry*
- **Exclusion criteria:** actively receiving immunosuppressive therapy, had received convalescent plasma or IVIG for COVID, neutropenia, lymphopenia, ALT/AST 5 x ULN, eGFR less than 30
- **Treatment arms:** Baricitinib 4 mg PO/NG daily (2 mg if GFR 30 – 59) vs. placebo for up to 14 days or until discharge (whichever came first)
  - All patients received standard of care of local practices at the time including: steroids, antivirals or both (note: higher dose steroids >20 mg prednisone equiv. daily, not permitted unless indicated for concurrent condition)
  - *VTE prophylaxis required for all participants unless major contraindication*

COV-BARRIER: Critically ill Addendum Trial

- Pre-print data; cohort reported as an addendum therefore all endpoints are exploratory
- Pre-specified endpoints = all-cause mortality by day 28 and 60, number of ventilator free days, overall improvement on NIAID-OS* at days 4, 7, 10, 14, and 28, duration of hospitalization and time to recovery to day 28
- Data for all randomised patients included in intention-to-treat analysis (51 participants in baricitinib arm and 51 in placebo arm)
- 86.1% of patients received corticosteroids at baseline
- Of the 52 participants that discontinued treatment, 46 were due to death
- At day 28 mortality was reduced by 46% (relative) in the baricitinib arm (absolute risk reduction 18.8% nominal p = 0.03), NNT = 6
- Adverse event rate was comparable between groups, including VTEs

*NIAID-OS = National Institute of Allergy and Infectious Disease Ordinal Scale

BC CTC Recommendation

- **If tocilizumab is not available** due to ongoing global shortages, **baricitinib is recommended as an alternative** for patients requiring life support due to confirmed COVID-19
  - This includes high-flow oxygen support (e.g., Optiflow) if flow rate greater than 30 L/min and FiO2 greater than 0.4 OR invasive or non-invasive ventilation OR vasopressor or inotropic support.
- baricitinib should be administered within 24 hours of the initiation of life support measures and only when life support is required because of COVID rather than other causes (such as bacterial infection, pulmonary embolism, etc)

- baricitinib should NOT be administered to patients with neutrophils less than 1, lymphocytes less than 0.2, ALT or AST greater than 5 x ULN, or eGFR less than 15 mL/min (or receiving renal replacement therapy)

- Should also be avoided in patients with active immunosuppression due to disease or treatment (e.g. rituximab, IL-6 inhibitors) or recent IVIG treatment for COVID-19

Baricitinib Dosing

- Based on this latest evidence, NH has developed an order set (10-800-5019) to facilitate baricitinib prescribing that aligns with the BCCTC recommendations

  ☐ GFR 60 mL/min or greater: **baricitinib** 4 mg PO or via tube daily X 14 days or until discharge (whichever sooner)
  ☐ GFR 30 to 59 mL/min: **baricitinib** 2 mg PO or via tube daily X 14 days or until discharge (whichever sooner)
  ☐ GFR 15 to 29 mL/min: **baricitinib** 2 mg PO or via tube q2days X 14 days or until discharge (whichever sooner)
  GFR less than 15 or renal replacement: DO NOT GIVE

- Despite no dosing in the trials for GFR less than 30 mL/min, the FDA Emergency Use Authorization Fact Sheet provides dosing recommendation for GFR 15 mL/min and greater (1 mg per day); due to tablet shape and lack of scoring 2mg q2day is preferred over splitting tablets

*There are very limited data on baricitinib in pregnancy (teratogenic effects seen in animal studies at much higher doses than recommended for COVID-19). Risks and benefits of baricitinib should be discussed on a case by case basis with pregnant women with severe COVID-19.

Clinical Considerations

Known Side Effects

- Increased hepatic enzymes (ALT and AST) use caution if ALT or AST 3 to 5 x ULN, thrombocythemia, increased creatinine kinase, secondary infection (frequency and type undefined), thrombosis

Special Precautions

- Pregnancy: limited data available, see previous slide
- Thrombosis: in hospitalized patients with COVID-19, prophylaxis for VTE is recommended unless contraindicated, patients should be monitored for clinical features of VTE while taking baricitinib
- GI perforations: caution in patients at increased risk of GI perforation (e.g. history of diverticulitis)
- Serious adverse effects: black box warning about cardiovascular-related events (stroke, heart attack), cancer, and death related to patients on chronic JAK inhibitor therapy (i.e. tofacitinib)

Ongoing Information/Questions

- NH COVID Therapeutics committee has representation on the BC COVID Therapeutics committee and will continue to update clinicians across the Northern Health Authority as more/new information comes to light

- Information will be circulated via NH COVID Therapeutics committee members, Medical Staff Digest email and physician champion communication network