Effect of JAK inhibitor treatment on clinical outcome, lung pathology, and viral load in a mouse model of pathogenic SARS-CoV-2 infection

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October 7, 2020
JAK Inhibitors: Proposed Mechanisms of Action

SARS-CoV-2 entry → Viral replication and spreading → Mild-moderate disease → Severe disease → ARDS

Spinelli et al, Science Immunol, 2020
JAK Inhibitors

• Reversible, competitive inhibitors that binds to the ATP binding site in the catalytic cleft of the kinase domain of JAK

**Tofacitinib**

• Preferentially inhibits JAK1 and JAK3, with some effect on JAK2

• Orally available, FDA approved for treatment of rheumatoid arthritis and IBS in humans

**Baricitinib**

• Potent JAK1 and JAK2 inhibitor, with some activity against JAK3 and TYK2

• Orally available, FDA approved for treatment of rheumatoid arthritis in humans

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<th>Tofacitinib</th>
<th>Baricitinib</th>
<th>Low Dose (Therapeutic Equivalent)</th>
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**Tofacitinib vs. Baricitinib**

- **Tofacitinib**
  - Preferentially inhibits JAK1 and JAK3, with some effect on JAK2
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- **Baricitinib**
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**Dosage Comparison**

- **Low Dose (Therapeutic Equivalent)**: 15 mg/kg PO BID (Tofacitinib) vs. 3 mg/kg PO BID (Baricitinib)
- **Medium Dose**: 50 mg/kg PO BID (Tofacitinib) vs. 30 mg/kg PO BID (Baricitinib)
- **High Dose**: 50 mg/kg PO BID (Tofacitinib) vs. 30 mg/kg PO BID (Baricitinib)
Mouse Adaptation of SARS-CoV-2

Original SARS-CoV-2

Q498Y/P499T SARS-CoV-2-MA

Dinnon et al, Nature 2020
Leist et al, in press

Pathogenic SARS-CoV-MA10
Effect of Tofacitinib Treatment on Clinical Disease

Survival

Body Weight

- 5 = dead/moribund
- 4 = severe hunched posture, minimal spontaneous activity, labored breathing
- 3 = hunched posture, reduced activity
- 2 = scruffy haircoat, mild hunched posture
- 1 = mild scruffy haircoat
- 0 = clinically normal

Vehicle Control

5 mg/kg Tofacitinib

15 mg/kg Tofacitinib

50 mg/kg Tofacitinib

n = 8 mice/group
Effect of Baricitinib Treatment on Clinical Disease

- **Vehicle Control**
- **3 mg/kg Baricitinib**
- **10 mg/kg Baricitinib**
- **30 mg/kg Baricitinib**

**Survival**
- 5 = dead/moribund
- 4 = severe hunched posture, minimal spontaneous activity, labored breathing
- 3 = hunched posture, reduced activity
- 2 = scruffy haircoat, mild hunched posture
- 1 = mild scruffy haircoat
- 0 = clinically normal

**Body Weight**
- Graphs show the percent initial body weight over days post infection for different doses of Baricitinib.

n = 16 mice/group
Effect of JAK Inhibitor Treatment on Lung Pathology

Prophylactic Treatment

ATS Acute Lung Injury Score

Vehicle Control  Tofacitinib  Baricitinib

3 DPI  4 DPI

Diffuse Alveolar Damage Score

Vehicle Control  Tofacitinib  Baricitinib

3 DPI  4 DPI

Therapeutic Treatment

ATS Acute Lung Injury Score

Vehicle Control  Tofacitinib  Baricitinib

3 DPI  5 DPI

Diffuse Alveolar Damage Score

Vehicle Control  Tofacitinib  Baricitinib

3 DPI  5 DPI
Effect of JAK Inhibitor Treatment on Lung Viral Load

**Viral Titers**

**Tofacitinib**

**Viral RNA**

**Baricitinib**

*Open Symbols = Found Dead*
Correlation Between Viral Lung Titers and Clinical Disease & Lung Pathology

- **Clinical Disease**
  - Pearson $r = 0.4328$, $p = 0.0021$
  - Pearson $r = -0.5965$, $p < 0.0001$

- **Lung Pathology**
  - Pearson $r = 0.7366$, $p < 0.0001$
  - Pearson $r = 0.5892$, $p < 0.0001$
Summary of Findings

• Baricitinib treatment exacerbates clinical disease at any dose in a mouse model of pathogenic SARS-CoV-2 infection, while tofacitinib treatment is detrimental primarily at high doses.

• JAK inhibitors at high doses increase SARS-CoV-2-induced lung pathology.

• Baricitinib treatment results in augmented viral replication and impaired viral clearance.

• Worsened clinical disease and increased lung pathology scores correlate with higher lung viral titers.

• Monotherapy with Jak inhibitors in COVID-19 patients may result in enhanced replication of virus, leading to exacerbation or relapse of respiratory disease.
Acknowledgements

**Baxter lab**
- Liz Anderson
- Dr. Audrey Knight
- Jake Dillard
- Sabian Martinez
- Katia Pressey

**Heise lab**
- Dr. Mark Heise
- Dr. Sharon Taft Benz
- Emily Madden
- Jenny Loome
- Dr. Sanjay Sarkar

**Moorman lab**
- Dr. Nat Moorman
- Dr. Wes Sanders

**Baric lab**
- Dr. Ralph Baric
- Dr. Timothy Sheahan
- Ethan Fritch
- Kenny Dinnon
- Dr. Sarah Leist

**Dr. Stephanie Montgomery**
- Dr. Marty Ferris

**Funding:**
- NIH
  - K01 OD026529
  - U19 AI100625
  - U19 AI109680

- UNC
  - Infectious Disease Drug Discovery Program (ID3)
  - Rapidly Emerging Antiviral Drug Development Initiative (READDI)
  - NCTraCS and Emerging Challenges in Biomedical Research COVID Pilot Award
  - SOM Junior Investigator Development Award
  - Department of Pathology and Laboratory Medicine