Background:

- Tofacitinib (Xeljanz®), like baricitinib (Olumiant®), is a Janus kinase inhibitor which blocks the inflammatory process involving cytokine interleukin-6. It is approved for treatment of rheumatoid arthritis, psoriatic arthritis, inflammatory bowel diseases and other similar conditions.  
- Due to its anti-inflammatory mechanism of action, tofacitinib, along with baricitinib, have been studied as a potential COVID-19 treatment. However, unlike baricitinib, tofacitinib does not have an EUA for this indication.  
- Safety concerns: tofacitinib and baricitinib carry similar black box warnings, including for thrombotic events. The largest trial to date was in tofacitinib, however, where in comparison to TNF blockers in RA patients, tofacitinib group had an increase in thrombotic events, including cardiovascular, and death. The FDA is requiring new additional warnings and narrowing of indication for tofacitinib, as well as other JAK inhibitors, as similarly large trials have not been conducted for the other agents.

Role in Tocilizumab (Actemra®) Shortage and NIH Guideline Recommendations:

- Due to recent COVID-19 surge and increased demand for tocilizumab, all presentations of this agent are currently in short supply.  
- As both tocilizumab and baricitinib are recommended by the NIH for the treatment of recently hospitalized patients with rapidly increasing oxygen needs, including oxygen delivery through a high-flow device or noninvasive ventilation, baricitinib is an appropriate substitute for tocilizumab in this patient population. 
  - NIH recommends tofacitinib as a substitute for baricitinib, if baricitinib is unavailable (IIb).  
  - Tofacitinib Dosing  
    - Tofacitinib 10mg PO twice daily for up to 14 days or until hospital discharge  
    - Tofacitinib 5mg PO BID if eGFR <60 mL/min/1.73m²

Data Summary for Tofacitinib Use in COVID-19:  

- Randomized Controlled Trials
  - To date, there is only one randomized controlled trial (STOP-COVID; in Brazil) which showed tofacitinib was effective in reducing death or respiratory failure as a primary end point. However, secondary end point of mortality benefit did not show statistical difference with tofacitinib use.  
  - Note: compared to pivotal baricitinib trial, this trial allowed for the use of glucocorticoids

- Systematic Review and Meta-Analysis  
  - No current systematic reviews or meta-analyses specific to tofacitinib in the treatment of COVID-19. [Note: there are 3 JAK inhibitor meta-analysis, 2 of which include the previously mentioned STOP-COVID trial. These are small (3 and 4 studies), differ in studies included and are highly heterogeneous. Study authors acknowledge the limitations of the meta-analysis and caution their interpretation. They are of limited use to clarify the specific place of tofacitinib in the treatment of COVID-19.]

- Observational Cohorts (Prospective and Retrospective)
  - A retrospective observational study in Mississippi has shown that tofacitinib in addition to dexamethasone in comparison to dexamethasone alone reduced odds of death at discharge.  
  - A second retrospective observational study based in Russia concluded that tofacitinib reduced mortality and rate of admission to ICU compared to standard of care alone.

Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SAMPLE SIZE (estimated)</th>
<th>STUDY DESIGN/STATUS</th>
<th>INCLUSION</th>
<th>TREATMENT VS COMPARATOR</th>
<th>PRIMARY OUTCOME</th>
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<tbody>
<tr>
<td>CT19841301</td>
<td>NCT02234022</td>
<td>Phase 2, randomized, double-blind Recruiting</td>
<td>Hospitalized Adults ≥18 years w/ confirmed infection by PCR, evidence of pneumonia by imaging, and requiring ≥3L O2 or ≥2L O2 and hscC reactive protein (hsCRP) &gt; =70 mg/L</td>
<td>Tofacitinib 10mg PO twice daily until return to clinical baseline (defined by supplementary CO2 requirement), then 5mg PO BID for total treatment duration of 14 days vs placebo</td>
<td>Unrescue severity determined by proportion of subjects alive and not needing mechanical ventilation, high flow oxygen, or ECMO by day 14</td>
</tr>
<tr>
<td>CT19841301</td>
<td>NCT04380601</td>
<td>Phase 2, multicenter randomized open-label Not yet recruiting</td>
<td>Hospitalized adults 18-85 yrs w/ confirmed infection by PCR, evidence of pneumonia by CT scan, P/F ratio &gt;150 mmHg, and from admission from less than 24 hours</td>
<td>Tofacitinib 10mg PO twice daily + Hydroxychloroquine 200mg three times daily for 14 days vs Hydroxychloroquine 200mg three times daily for 14 days</td>
<td>Prevention of severe respiratory failure requiring mechanical ventilation in 14 days determined by rate of patients needing mechanical ventilation to maintain PaO2/FiO2 &gt; 150 mmHg</td>
</tr>
<tr>
<td>CT19841301</td>
<td>NCT04332082</td>
<td>Phase 2, open label prospective cohort study Not yet recruiting</td>
<td>Hospitalized adults 18-85 yrs w/ confirmed infection by PCR, evidence of pneumonia by CT scan, and from admission less than 24 hours</td>
<td>Tofacitinib 10mg twice daily within 24 hours from hospital admission for 14 days</td>
<td>Need for mechanical ventilation at 14 days determined by rate of patients needing mechanical ventilation to maintain PaO2/FiO2 &gt; 150 mmHg or SPO2 &gt; 94%</td>
</tr>
</tbody>
</table>

Summary/Recommendations:

- NIH recommends tofacitinib as a substitute for baricitinib when the latter is unavailable, however data is very limited for the former agent. A single randomized controlled trial failed to show mortality benefit, but did show reduction in death OR respiratory failure. However, compared to baricitinib pivotal trial, tofacitinib trial allowed for the use of glucocorticoids.  
- Recent study results showing increased thrombotic and cardiovascular events, including death, in RA patients treated with tofacitinib, are of concern. Because similarly large trials are unavailable for other JAK inhibitors, the FDA is requiring increased warnings and narrowing of indication for all products in this class, including baricitinib. Increase in thrombotic events were not seen in tofacitinib COVID-19 trials. Shorter duration of treatment for COVID-19 and the usual use of anticoagulants in this patient population are noteworthy.  
- At this time, there is insufficient evidence to support the use of tofacitinib as a treatment option for COVID-19 outside of clinical trials. Use in COVID-19 is NOT recommended by the Sutter Health COVID-19 Clinical Advisory Group. While there is a paucity of data, given recent guideline support, it is not unreasonable to consider tofacitinib in patients who meet baricitinib and tocilizumab criteria and restrictions previously outlined in Sutter Health Guidance, if both agents become completely unavailable.
**Study Design**

1:1 Randomization to oral tofacitinib 10mg or placebo twice daily in addition to standard care for up to 14 days or until hospital discharge, whichever was earlier. Reduced dose of 5mg tofacitinib twice daily was administered in patients with estimated eGFR <50 mL/min/1.73m², moderate hepatic impairment, and with concomitant use or strong CYP3A4 inhibitor or combination of moderate CYP3A4 inhibitor and strong CYP2C19 inhibitor.

**Exclusion**
- Older than 18 years
- Laboratory-confirmed novel coronavirus (SARS-CoV-2) infection as determined by PCR or other commercially available or public health assay prior to Day 1.
- Evidence of COVID-19 pneumonia assessed by radiographic imaging (CXR or chest CT).

**Included**
- Laboratory-confirmed novel coronavirus (SARS-CoV-2) infection as determined by PCR or other commercially available or public health assay prior to Day 1.
- Evidence of COVID-19 pneumonia assessed by radiographic imaging (CXR or chest CT).

**Primary outcome: statistically significant difference**
- Death or respiratory failure through day 28: 18.1% vs 29.0% (risk ratio, 0.63; 95% confidence interval [CI], 0.41 to 0.97; P=0.04)

**Secondary outcome: No statistically significant difference**
- No difference: death from any cause through day 28 occurred in 2.8% of patients in the tofacitinib group and in 5.5% of those in the placebo group (hazard ratio, 0.49; 95% CI, 0.15 to 1.63) (Fig. S4).
- No difference: As compared with placebo, the proportional odds of having a worse score on the eight-level ordinal scale with tofacitinib was 0.60 (95% CI, 0.36 to 1.00) at day 14 and 0.54 (95% CI, 0.27 to 1.06) at day 28.

**Adverse events:**
- Similar number of any adverse event between tofacitinib and placebo group (26.1% vs 22.5%).
- No significant difference in serious adverse events were observed, although numerically higher in tofacitinib treated patients compared to placebo and usual care (14.1% vs 12.0%).
- Adverse events other than death that led to the discontinuation of the trial regimen occurred in 11.3% of the patients in the tofacitinib group and in 3.5% of those in the placebo group. The most common such events were an increase in aminotransferase levels (4.2% vs 0.7%) and lymphopenia (2.8% vs 1.4%).

**Patient selection (tofacitinib vs placebo):**
- Mean age (55 vs 57 years), male (50% vs 49%), white (81.9% vs 84.8%), DM (23.6% vs 23.4%), mean BMI 29.4 vs 29.7, dyslipidemia (20.8% vs 13.8%)
- Median time from symptom onset 10 days
- Score of 4 on ordinal scale (hospitalized but not receiving supplemental oxygen): 23.6% vs 25.5%
- Score of 5 on ordinal scale (hospitalized and receiving supplemental oxygen through low-flow devices): 63.2% vs 62.1%
- Score of 6 on ordinal scale (hospitalized and receiving supplemental oxygen through high-flow devices): 13.2% vs 12.4%
- At baseline, roughly 80% of patients received glucocorticoids in both groups. High numbers received prophylactic anticoagulation as well (78.5 vs 77.2%). Approximately 13% of patients received oseltamivir.

**Conclusions**
- Tofacitinib was effective in reducing death or respiratory failure through day 28 compared to placebo.
- No difference between tofacitinib and placebo in death from any cause through day 28.
- No statistically significant difference in median duration of hospital stay and ICU stay between tofacitinib and placebo.

**Limitations:**
- Small sample size
- Inflammatory markers were not reported
- Not applicable to patients with more severe disease, ie with need for mechanical ventilation
- Patients treated approximately 10 days from symptom onset; unclear benefit from therapy earlier on in disease course

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Guimaraes, ST (STOP COVID) January 2021, n = 289

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, placebo-controlled multicenter Phase 2 trial of 289 hospitalized patients with COVID-19 between July 2020 and November 2020 across 20 hospitals in Brazil.</td>
<td>Primary outcome: statistically significant difference</td>
<td>Tofacitinib was effective in reducing death or respiratory failure through day 28 compared to placebo.</td>
<td></td>
</tr>
<tr>
<td>1:1 Randomization to oral tofacitinib 10mg or placebo twice daily in addition to standard care for up to 14 days or until hospital discharge, whichever was earlier. Reduced dose of 5mg tofacitinib twice daily was administered in patients with estimated eGFR &lt;50 mL/min/1.73m², moderate hepatic impairment, and with concomitant use or strong CYP3A4 inhibitor or combination of moderate CYP3A4 inhibitor and strong CYP2C19 inhibitor.</td>
<td>Secondary outcome: No statistically significant difference</td>
<td>No difference between tofacitinib and placebo in death from any cause through day 28.</td>
<td></td>
</tr>
<tr>
<td>Evidence of COVID-19 pneumonia assessed by radiographic imaging (CXR or chest CT).</td>
<td>Adverse events:</td>
<td>No statistically significant difference in median duration of hospital stay and ICU stay between tofacitinib and placebo.</td>
<td></td>
</tr>
<tr>
<td>Hospitalized and receiving standard care for COVID-19.</td>
<td></td>
<td>Limitations:</td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion</strong>:</td>
<td><strong>Patient selection (tofacitinib vs placebo):</strong></td>
<td>Small sample size</td>
<td></td>
</tr>
<tr>
<td>Require non-invasive ventilation, invasive mechanical ventilation, or ECMO on Day 1.</td>
<td>Mean age (55 vs 57 years), male (50% vs 49%), white (81.9% vs 84.8%), DM (23.6% vs 23.4%), mean BMI 29.4 vs 29.7, dyslipidemia (20.8% vs 13.8%)</td>
<td>Inflammatory markers were not reported</td>
<td></td>
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<tr>
<td>History of or known current thrombosis.</td>
<td>Median time from symptom onset 10 days</td>
<td>Not applicable to patients with more severe disease, ie with need for mechanical ventilation</td>
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</tr>
<tr>
<td>Personal or first-degree family history of blood clotting disorders.</td>
<td>Score of 4 on ordinal scale (hospitalized but not receiving supplemental oxygen): 23.6% vs 25.5%</td>
<td>Patients treated approximately 10 days from symptom onset; unclear benefit from therapy earlier on in disease course</td>
<td></td>
</tr>
<tr>
<td>Immuno compromised, with known immunodeficiencies, or taking potent immunosuppressive agents</td>
<td>Score of 5 on ordinal scale (hospitalized and receiving supplemental oxygen through low-flow devices): 63.2% vs 62.1%</td>
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<td></td>
</tr>
<tr>
<td>Any current malignancy or lymphoproliferative disorders that requires active treatment</td>
<td>Score of 6 on ordinal scale (hospitalized and receiving supplemental oxygen through high-flow devices): 13.2% vs 12.4%</td>
<td></td>
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<tr>
<td>Severe hepatic impairment, defined as Child- Pugh class C.</td>
<td>At baseline, roughly 80% of patients received glucocorticoids in both groups. High numbers received prophylactic anticoagulation as well (78.5 vs 77.2%). Approximately 13% of patients received oseltamivir.</td>
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| Hayek, Jun 2021*<br>n = 269  
Single-center, retrospective, observational study of 269 hospitalized COVID-19 patients at Delta Regional Medical Center in Mississippi discharged between March 1 and September 30, 2020 | Tofacitinib orally 10mg twice daily for 5 to 14 days in addition to dexamethasone 10mg IV for 5 to 10 days in comparison to dexamethasone alone  
Patients in both groups received antiviral therapy (hydroxychloroquine, azithromycin, and zinc; the combination was changed to remdesivir as it became available), anticoagulant, and dexamethasone treatment depending on indications and contraindications  
Included  
- all admitted patients for COVID-19–induced hypoxemia or severe inflammation as noted by CRP greater than 50 mg/dL or ferritin greater than 500 ng/mL received the full regimen uniformly immediately on admission, whether patients required supplemental nasal oxygen, high-flow oxygen, or intubation  
Exclusion  
- had no hypoxemia and no evidence of inflammation | Primary outcome: in-hospital mortality  
- 70% reduction in odds of dying among tofacitinib group compared to dexamethasone only group (after adjusting for age and clinical parameters)  
  (adjusted odds ratio: 0.30; 95% CI: 0.12 to 0.76; P=.01).  
- Clinical parameters: diabetes, obesity, hypertension, GFR, lymphocyte, ferritin, D-dimer, CRP  
Adverse events:  
- Similar rates of positive blood cultures in both groups  
- Hyperglycemia in dexamethasone group often requiring insulin coverage  
Patient selection (tofacitinib - dexamethasone vs dexamethasone alone):  
- Mean age (61.3, 66.7), male (55% vs 62%), obesity (63.8% vs 48.9%), hypertension (50.0% vs 51.2%), diabetes (23.2% vs 13.7%, p = 0.047), African American (84.8% vs 82.4%)  
- Initial D-dimer >1 (54.4% vs 76.7%, p <0.001) | Tofacitinib in addition to dexamethasone reduced odds of death at discharge compared to dexamethasone therapy alone  
Limitations:  
- Small sample size  
- Retrospective study  
- Antiviral therapy changed in patient population as guidelines shifted during the time period studied  
- Changing tofacitinib regimen duration from 5 days to up to 14 days early on in the time period observed |
| Maslennikov, Aug 2021*<br>n = 62  
Retrospective, observational study of 62 hospitalized COVID-19 patients at a Russian hospital between April and July 2020 | Tofacitinib orally on the first day at a dose of 10mg twice daily, then for four days at 5mg twice daily, versus the control group who did not receive anti-cytokine therapy  
Patients in both groups received antiviral, antibacterial, anticoagulant, and dexamethasone treatment depending on indications and contraindications  
Included  
- age over 18 years | Primary outcome: survival or death  
- Improved survival rate in patients who received tofacitinib compared to those who did not receive anti-cytokine treatment (84.4% vs 60.0%; p = 0.009)  
- Patients who received tofacitinib died later than patients who did not receive it (36 [27–40] days vs. 20 [15–26] days; p = 0.035).  
Secondary outcome:  
- Statistically significant decrease in CRP after 7-10 days in both groups (even in control group that did not receive anti-cytokine treatment), however the decrease was significantly greater in treatment group versus control group  
- Statistically significant lower incidence of admission to ICU (15.6% vs 50.05%, p = 0.004)  
- Statistically significant increase in proportion of patients who required mechanical ventilation in control group compared to treatment group (0 vs 26.7%, p=0.002)  
- No statistically significant difference in proportion of patients who no longer needed supplemental oxygen 7-10 days after administration of tofacitinib | Tofacitinib reduced mortality and rate of admission to the ICU compared to standard of care, which included glucocorticoids  
Limitations:  
- Small sample size  
- Retrospective study  
- Unclear timing of administration in regard to symptom onset  
- Excluded CRP levels of above 150mg/L  
- Decrease in inflammatory markers can be contributed to glucocorticoid use |
<table>
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<tr>
<td></td>
<td>laboratory-confirmed COVID-19 (a positive result of polymerase chain reaction) or suspected COVID-19 (based on the complex of clinical, imagine and epidemiological data)</td>
<td>No difference in total length of hospital stay or total duration of disease in days</td>
<td>Patient selection (tofacitinib vs usual care):</td>
</tr>
<tr>
<td></td>
<td>absence of pregnancy</td>
<td>Adverse events:</td>
<td>Mean age (64, 68), male (59% vs 53%), BMI 29.2 vs 31.0</td>
</tr>
<tr>
<td></td>
<td>CRP level above 60 mg/L</td>
<td>– No statistically different occurrence of pulmonary embolism, acute kidney injury, and liver enzyme elevation between treatment and control group</td>
<td>Initial CRP 1-3 days before beginning of tofacitinib use or equivalent days in control group: 95 vs 110 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>– No cytopenias and extrapulmonary infections in either groups</td>
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<td></td>
<td>on other anti-cytokine drugs</td>
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<tr>
<td></td>
<td>CRP levels of above 150 mg/L</td>
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**References**