A Practical Approach to JAK Inhibitors in IBD 2020

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Binding of Cytokine Receptors by Cytokines Activates JAK Pathways Signaling

1. Cytokine binding to its cell surface receptor leads to receptor polymerization and activation of associated JAKs

2. Activated JAKs phosphorylate the receptors that dock STATs

3. Activated JAKs phosphorylate STATs, which dimerize and move to the nucleus to activate new gene transcription

JAK=Janus kinase; P=phosphate; STAT=signal transducer and activator of transcription.
Consequence of JAK Inhibition on Signaling by Key Immunoregulatory Cytokines

O’Shea J. Immunity 2012
Tofacitinib for Induction of Remission in UC—2 Phase 3 Trials (n=1139)

- Mod-severe UC
- Randomized 4:1 to tofacitinib 10 mg BID or PBO
- Primary endpoint: remission at week 8 (total Mayo ≤2, no subscore>1, rectal bleed 0)
- Results similar regardless of prior anti-TNF
- Rapid improvements
- Infections higher in tofa groups (18-23% vs 15%)

Tofacitinib in Moderate to Severe UC: Clinical Response and Remission at 8 Weeks

Clinical Response

<table>
<thead>
<tr>
<th></th>
<th>OCTAVE 1</th>
<th>OCTAVE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>32.8</td>
<td>29</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID</td>
<td>59.9</td>
<td>55</td>
</tr>
</tbody>
</table>

P<0.001

Clinical Remission

<table>
<thead>
<tr>
<th></th>
<th>OCTAVE 1</th>
<th>OCTAVE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8.2</td>
<td>4</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID, anti-TNF naïve</td>
<td>12.6</td>
<td>22.1</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID, anti-TNF experienced</td>
<td>25.2</td>
<td>12</td>
</tr>
</tbody>
</table>

P<0.01

*Total Mayo score ≤2, no subscore >1, rectal bleeding 0.

OCTAVE Sustain: Clinical Response and Remission at 52 Weeks

![Bar chart showing clinical response and remission results for Placebo (n=198), Tofacitinib 5 mg BID (n=198), and Tofacitinib 10 mg BID (n=197).]

- Clinical response: Placebo 20.2%, Tofacitinib 5 mg BID 51.5%, Tofacitinib 10 mg BID 61.9%
- Remission: Placebo 11%, Tofacitinib 5 mg BID 34.3%, Tofacitinib 10 mg BID 40.6%
- Sustained* mucosal healing: Placebo 6.6%, Tofacitinib 5 mg BID 27.8%, Tofacitinib 10 mg BID 33%
- Sustained steroid-free† remission among remitters at baseline: Placebo 5.1%, Tofacitinib 5 mg BID 35.4%, Tofacitinib 10 mg BID 47.3%

* Sustained endpoints defined as achieving response/remission at both Week 24 and Week 52.
† Steroid-free defined as not requiring corticosteroids for ≥4 weeks prior to each visit.

Tofacitinib Maintenance UC Trial-Safety

• Prescribing info for RA has black boxed warning about serious infections and malignancies

• Adverse events, serious adverse events, serious infection rates similar in all treatment arms

• Overall infections higher, but withdrawal due to AE was lower

• Zoster signal at 10 BID dose

• No deaths

• No intestinal perforations

• Expected changes in lipids, CK

<table>
<thead>
<tr>
<th></th>
<th>PBO BID</th>
<th>Tofa 5 mg BID</th>
<th>Tofa 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs (%)</td>
<td>75.3</td>
<td>72.2</td>
<td>79.6</td>
</tr>
<tr>
<td>Withdrawal due to AE (%)</td>
<td>18.7</td>
<td>9.1</td>
<td>9.7</td>
</tr>
<tr>
<td>SAEs (%)</td>
<td>6.6</td>
<td>5.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Any Infections (%)</td>
<td>24.2</td>
<td>35.9</td>
<td>39.8</td>
</tr>
<tr>
<td>Serious infections (%)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Herpes zoster (%)</td>
<td>0.5</td>
<td>1.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Malignancy excl NMSC (%)</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NMSC (%)</td>
<td>0.5</td>
<td>0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Tofacitinib Potential Safety Issue: Thromboembolism

- FDA-required safety study of tofacitinib in RA patients >50 yrs old with at least one CV risk factor
- Tofa 5 BID vs tofa 10 BID vs anti-TNF
- Based on interim analysis, 10 BID discontinued, changed to 5 BID
- Awaiting final results of this trial
- Boxed warning about DVT/PE added to tofacitinib label
- Indication in UC changed to moderately to severely active UC, failed anti-TNF therapy

<table>
<thead>
<tr>
<th></th>
<th>Tofacitinib 10 mg BID</th>
<th>Anti-TNF</th>
<th>Incidence Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT/PE Incidence (cases per PY)</td>
<td>19/3884 = 0.49/100</td>
<td>3/3982 = 0.07/100</td>
<td>7</td>
</tr>
<tr>
<td>Death Incidence (per PY)</td>
<td>45/3884 = 1.16/100</td>
<td>25/3982 = 0.63/100</td>
<td>1.8</td>
</tr>
</tbody>
</table>

FDA Drug Safety Communication, July 26, 2019
Tofacitinib for Crohn’s Disease—Two Negative Trials

- Two phase 2b studies of moderate-severe Crohn’s (n=280 for induction, 180 for maintenance)
- PBO vs tofacitinib 5, 10, or 15 mg PO BID (highest dose dropped) for 8 weeks
  - Primary endpoint: CDAI<150
- Responders re-randomized to PBO or tofacitinib 5 or 10 mg BID for 26 weeks
  - Forced steroid taper to 10 mg daily for those on steroids
  - Primary endpoint: CDAI<150 or CR100
- Drops in CRP but not FCP in tofacitinib groups were significant in induction
- Both CRP and FCP dropped in tofacitinib groups in maintenance

Filgotinib (Selective JAK1 Inhibitor) Induction Rx for Moderate to Severe Crohn’s (n=174)

- Filgotinib is a selective once-daily oral JAK1 inhibitor
- FITZROY study: randomized to treatment with filgotinib 200 mg QD or placebo for 10 weeks
- All immunosuppressants were discontinued
- Primary endpoint: CDAI <150 at 10 weeks
- Endoscopic response (Reduced SES-CD>50%): 25% vs. 14% (NS)
- Serious AEs: 9% vs. 4%
  - Serious infections: 3% vs. 0%

FITZROY

SES-CD, Endoscopic Response
(Improvement by at least 50%, ITT-NRI, Wk 10)

+ p<0.10

CELEST Study Design

- Adult patients 18-75 years of age
- Moderate to severe Crohn’s disease:
  - CDAI 220-450
  - Average (7-day) daily very soft or liquid stool frequency (SF) > 2.5 and/or abdominal pain (AP) score > 2.0
  - Simplified Endoscopic Score for CD (SES-CD) > 6 (or ≥ 4 in isolated ileal disease), confirmed by a central reader
- Inadequate response or intolerance to an immunosuppressant or tumor necrosis factor antagonist
Upadacitinib (ABT-494)-Selective JAK1 Inhibitor-Induction Rx for Moderate to Severe Crohn’s Disease: CELEST (n=220)

- 96% were refractory to anti-TNF
- Randomized to PBO vs ABT-494 at 3 mg, 6 mg, 12 mg, or 24 mg BID or 24 mg QD x 16 weeks
- Co-primary endpoints
  - Clinical remission (stool frequency ≤ 1.5, abd pain ≤ 1) week 16
  - Endoscopic remission (SES-CD ≤ 4) at week 12/16
- AEs: 76-86% vs. 73% PBO
  - SAEs: 5-28% vs. 5% PBO
  - Serious infections: 0-8% vs. 0% PBO

Sandborn WJ et al, DDW 2017 Late-Breaker (874h)
Co-primary Endpoints: Endoscopic Remission and Clinical Remission (NRI)

Endoscopic Remission: SES-CD ≤ 4 and ≥ 2 point reduction from baseline, with no subscore > 1
Clinical Remission: Very soft/liquid SF ≤ 1.5 and AP score ≤ 1, and both not worse than baseline

Sandborn WJ et al, DDW 2017 Late-Breaker (874h)
Secondary Endpoint: Steroid-free Remission (NRI)

Steroid-Free & CDAI Remission at Week 16

- PBO
- 3 mg BID
- 6 mg BID
- 12 mg BID
- 24 mg BID
- 24 mg QD

*p<0.1; **p<0.05

Sandborn WJ et al, DDW 2017 Late-Breaker (874h)
Modified Clinical Remission and Endoscopic Response 50% at Week 52 in Patients Who Were Responders or Clinical Responders at Week 16

† statistically significant at ≤0.1 level.

Panes J et al, DDW 2018
Upadacitinib for Moderate to Severe UC: U-ACHEIVE

- 250 mod-severe UC
- Randomized to PBO, UPA 7.5, 15, 30, or 45 mg daily
- Primary endpoint: clinical remission per adapted Mayo score at week 8

U-Achieve Primary Endpoint: Clinical Remission per Adapted Mayo Score at Week 8 (NRI). Overall Population

Clinical remission per Adapted Mayo score: stool frequency subscore (SFS) ≤ 1, rectal bleeding subscore (RBS) = 0, and endoscopic subscore ≤ 1.

U-ACHIEVE: Endoscopic outcomes at Week 8 (NRI)

Endoscopic improvement
(endoscopic subscore ≤ 1)

Endoscopic remission
(endoscopic subscore = 0)

UPA: upadacitinib; QD: once daily

UPA: upadacitinib; QD: once daily

* p<0.05; ** p<0.01; *** p<0.001

Sandborn WJ et al, DDW 2019
U-ACHIEVE: Histologic outcomes at Week 8 (NRI)

**Histologic improvement**
(any decrease from baseline in Geboes score)

**Histologic remission**
(Geboes score < 2)

UPA: upadacitinib; QD: once daily

Sandborn WJ et al, DDW 2019

* p<0.1; ** p<0.01; *** p<0.001
U-ACHIEVE: Mucosal healing at Week 8 (NRI)

Endoscopic subscore = 0 AND Geboes score < 2

Endoscopic subscore ≤ 1 AND Geboes score < 2 (post-hoc analysis)

UPA: upadacitinib; QD: once daily

Sandborn WJ et al, DDW 2019
## U-ACHIEVE: Safety Overview

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo N = 46</th>
<th>UPA 7.5 mg QD N = 47</th>
<th>UPA 15 mg QD N = 49</th>
<th>UPA 30 mg QD N = 52</th>
<th>UPA 45 mg QD N = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs</td>
<td>33 (71.7)</td>
<td>29 (61.7)</td>
<td>29 (59.2)</td>
<td>34 (65.4)</td>
<td>35 (62.5)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>7 (15.2)</td>
<td>3 (6.4)</td>
<td>3 (6.1)</td>
<td>3 (5.8)</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>5 (10.9)</td>
<td>0</td>
<td>2 (4.1)</td>
<td>3 (5.8)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>AEs Leading to Discontinuation</td>
<td>4 (8.7)</td>
<td>2 (4.3)</td>
<td>2 (4.1)</td>
<td>4 (7.7)</td>
<td>4 (7.1)</td>
</tr>
</tbody>
</table>

No deaths were reported as of the date of database lock.
## U-ACHIEVE: Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Placebo N = 46</th>
<th>UPA 7.5 mg QD N = 47</th>
<th>UPA 15 mg QD N = 49</th>
<th>UPA 30 mg QD N = 52</th>
<th>UPA 45 mg QD N = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Infections</td>
<td>2 (4.3)</td>
<td>0</td>
<td>1 (2.0)</td>
<td>0</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Opportunistic Infections</td>
<td>1 (2.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Malignancy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1 (2.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic Disorder&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (2.2)</td>
<td>2 (4.3)</td>
<td>0</td>
<td>0</td>
<td>6 (10.7)</td>
</tr>
<tr>
<td>Gastrointestinal Perforations</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (6.5)</td>
<td>1 (2.1)</td>
<td>4 (8.2)</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

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<sup>a</sup> One case of malignant melanoma was reported.

<sup>b</sup> All were reported as liver enzyme abnormalities except for one case of drug-induced liver injury due to isoniazid therapy.
Phase 1b. Colonic Release, Pan-JAK Inhibitor TD-1473 is Efficacious Moderate-Severe UC

- **Aim**
  - TD-1473 is an orally administered and gut-selective pan-Janus kinase (JAK) inhibitor
  - Assess the safety, clinical and molecular effects of TD-1473 in UC after 4 weeks

- **Method**
  - Double-blind, placebo-controlled, multicenter Phase 1b
  - 40 subjects enrolled
    - Placebo n=9
    - 20mg n=10
    - 80mg n=10
    - 270mg n=11

- **Results**
  - Higher rates of clinical response, endoscopic healing, and improvement by ≥ 1 point in rectal bleeding and endoscopy subscores
  - Reduction in CRP + FCAL
  - Well tolerated and minimal risk for systemic immunosuppression

Conclusions

• JAK inhibition represents a potent, fast-acting mechanism of action for reducing inflammation in IBD

• Tofacitinib approved for moderately to severely active UC in patients who have failed anti-TNF therapy

• The selective JAK1 inhibitors appear to have efficacy in moderately to severely active CD, and upadacitinib appears efficacious in UC