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MARCH 10–12, 2023
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NAPOLES, FLORIDA

Register online: meetings.gi.org
All attendees will be muted and will remain in Listen Only Mode. Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.

THESE ANSWERS WILL BE REVIEWED.
ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!

There will be NO Virtual Grand Rounds until January 5, 2023.
Have a wonderful holiday season and a happy New Year!

Week 1 – Thursday, January 5, 2023
AI in GI
Faculty: Seth A. Gross, MD, FACG
Moderator: Nasim Parsa, MD
At Noon Eastern and NEW! 8pm Eastern!

Week 2 – Thursday, January 12, 2023
How Can We Close the Screening Disparity Gaps in Our Population?
Faculty: Renee L. Williams, MD, MHPE, FACG
Moderator: Loren G. Rabinowitz, MD
At Noon Eastern and NEW! 8pm Eastern!
Visit gi.org/ACGVGR to Register

ACG 2023
OCTOBER 20-25, 2023
VANCOUVER, CANADA

Be sure your passport is up to date!
Optimal Positioning of Small Molecule Treatment Options in IBD

David T. Rubin, MD, FACP
Joseph B. Kirsner Professor of Medicine
Professor of Pathology
Chief, Section of Gastroenterology, Hepatology and Nutrition
University of Chicago

@IBDMD
RubinLab.uchicago.edu
Learning Objectives

- Understand the need and benefit of novel small molecule therapy in IBD.
- Incorporate JAK inhibitors and S1P receptor modulator therapy in the management of patients with IBD.
- Interpret the safety data for the novel targeted small molecule therapies for patients with IBD.

Medical Treatment Options for IBD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary treatment (PEN/EEN)</td>
<td>CD</td>
<td>CD</td>
</tr>
<tr>
<td>5-ASA</td>
<td>UC</td>
<td>UC</td>
</tr>
<tr>
<td>Steroids (budesonide and prednisone equivalents)</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>CD</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-integrin (natalizumab, vedolizumab)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-p40 (ustekinumab)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-p19 (risankizumab)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-TNF (adalimumab, certolizumab pegol, golimumab, infliximab)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>JAKinibs (tofacitinib, upadacitinib)</td>
<td>UC</td>
<td>UC</td>
</tr>
<tr>
<td>S1P receptor mod (ozanimod)</td>
<td>UC</td>
<td>UC</td>
</tr>
</tbody>
</table>
What is A Small Molecule?

- Small enough to get absorbed through the lining of the small intestine
- Conventional synthetic small molecules (azathioprine, methotrexate, cyclosporine)
- Targeted synthetic small molecules (JAKinibs, S1Ps, others)

Why Do We Need Novel Small Molecule Therapies in IBD?

- Unmet needs in IBD
- Novel mechanisms
- Convenience of delivery (oral)
- Avoids monoclonal antibody challenges
  - Immunogenicity
  - Protein leakage (dose:exposure challenges)
JAK Inhibitors: Tofacitinib, Upadacitinib, Filgotinib

JAKs are involved in lipid metabolism too
# JAK Inhibitors Approved and Under Investigation in IBD

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Studied Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgotinib</td>
<td>JAK 1 selective</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulcerative colitis (FDA Approved 2022)</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>JAK 1 selective</td>
<td>Ulcerative colitis (FDA Approved 2022)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crohn’s disease (NCT02782663)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis (FDA Approved 2019)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atopic Dermatitis (FDA Approved 2022)</td>
</tr>
<tr>
<td>SHR0302</td>
<td>JAK 1 selective</td>
<td>Ulcerative colitis (FDA Approved 2022)</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Non-selective (JAK 1, 2, 3)</td>
<td>Ulcerative colitis (FDA Approved 2018)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis (FDA Approved 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriatic arthritis (FDA Approved 2017)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ankylosing spondylitis (FDA Approved 2021)</td>
</tr>
<tr>
<td>TD-1473</td>
<td>Non-selective (JAK 1, 2, 3)</td>
<td>Ulcerative colitis (Phase 1b)</td>
</tr>
<tr>
<td>BMS-986165</td>
<td>Tyrosine kinase 2 (TKY2) inhibitor</td>
<td>Plaque psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LATTICE UC phase 2 negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LATTICE CD phase 2 ongoing</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>Non-selective (JAK 1, 2)</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COVID (FDA Emergency Authorization May 2022)</td>
</tr>
</tbody>
</table>

## Tofacitinib (JAK1-3 inhibitor) for Patients with Moderate-to-Severe Ulcerative Colitis: Phase 3 OCTAVE Program

**Virtual Grand Rounds**

**Tofacitinib for Induction and Maintenance of Moderately to Severely Active Ulcerative Colitis (OCTAVE 1 and 2)**

![Graph showing patient outcomes](image)

**Primary Endpoint: Remission at Week 8**

<table>
<thead>
<tr>
<th>OCTAVE Induction</th>
<th>10 mg BID vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTAVE Induction 1</td>
<td>18% (P&lt;0.01)</td>
</tr>
<tr>
<td>OCTAVE Induction 2</td>
<td>17% (P&lt;0.001)</td>
</tr>
</tbody>
</table>

~50% of patients in OCTAVE Induction had failed or were intolerant to prior TNF blocker therapy

**Primary Endpoint: Remission at Week 52**

<table>
<thead>
<tr>
<th>OCTAVE Induction 1</th>
<th>10 mg BID vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg BID</td>
<td>41% (P&lt;0.0001)</td>
</tr>
<tr>
<td>5 mg BID</td>
<td>34% (P&lt;0.0001)</td>
</tr>
</tbody>
</table>

Corticosteroid tapering was required upon entrance to maintenance study for patients receiving corticosteroids at baseline

Remission defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0

---

**Virtual Grand Rounds**

**Baseline Albumin Does Not Predict Response to Tofacitinib in Patients with Ulcerative Colitis**

![Diagram showing albumin levels](image)


---

12/19/2022
Virtual Grand Rounds

Tofacitinib Compared with Standard Care for Acute Severe UC (Hospitalized)


- Tofacitinib: two phase 2b studies negative
  - Induction clinical remission week 8: N.S. (placebo 36.7% v tofa 5 BID 43.5% v tofa 10 BID 43.0%)
  - Maintenance Response 100 or remission week 26: N.S. (PBO 38.1% v tofa 5 BID 39.5% v tofa 10 BID 55.8%)
- Real world multi-center experience: positive, favor Crohn’s colitis

What About Tofacitinib in Crohn’s Disease?

- Tofacitinib: two phase 2b studies negative
Virtual Grand Rounds

**Tofacitinib or Vedolizumab in UC Patients After ≥ 1 Biologic Therapy**

Multi-center retrospective study (tofacitinib n=126, vedolizumab n=178)

Corticosteroid-free Clinical Remission (CREM)* at Wk16

- **TOFACITINIB:**
  - No predictors of tofacitinib failure

- **VEDOLIZUMAB:**
  - Predictors of vedolizumab failure:
    - Partial Mayo >6
    - CRP >30 g/L
    - ≥1 Primary Failure to Biologics

\[ \text{aOR} = 0.82 \text{ (0.35-1.91) } P=0.64 \]

**Corticosteroid-free Clinical Remission = Partial Mayo Score ≤2 and no use of steroids at Wk16**


---

**Upadacitinib (selective JAK-1 inhibitor) in Moderate-to-Severe UC Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Program**

Clinical responders with 8-week upadacitinib (45 mg once daily) treatment*

- **Induction study UC1**
  - Upadacitinib 45 mg once daily (N=319)
  - Placebo (N=155)

- **Induction study UC2**
  - Upadacitinib 45 mg once daily (N=341)
  - Placebo (N=174)

- **Maintenance study UC3†**
  - Upadacitinib 15 mg once daily (N=143)
  - Upadacitinib 30 mg once daily (N=154)
  - Placebo once daily (N=149)

Upadacitinib in Induction and Maintenance in Patients with UC

Induction Clinical Remission at Week 8
Clinical remission was defined as stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤1 without friability.

**Overall Population**
- U-ACHIEVE Induction: Placebo 26%, Upadacitinib 45 mg 20%
- Placebo n=154, Upadacitinib 45 mg n=219

**Maintenance Primary Endpoint: Clinical remission at Week 52**
- Placebo: 100%, Upadacitinib 45 mg: 72%


Secondary Endpoints: Endoscopy and histology


Upadacitinib in Induction by Bio-IR Status
(U-ACHIEVE and U-ACCOMPLISH Phase 3 Induction Trials)

Bio-IR: experienced previous biologic failure (inadequate response, loss of response, or intolerance)
Upadacitinib Timing of Response in UC

**Methods**
- U-Achieve and U-Accomplish multicenter, double-blind, PBO-controlled trials with randomization to UPA 45 mg QD or PBO (2:1)

**Results**
- N=998
- Day 7 SFS <1 were more likely to achieve clinical remission at week 8 (OR 2.53, 95% CI 1.59-4.00)

**Conclusion**
- UPA 45 mg QD significantly improved symptoms as early as day 1
- Patients with early improvement were more likely to achieve clinical remission at week 8

**Change in Daily Symptoms UPA 45 mg vs. PBO**


Upadacitinib in Moderate-to-Severe Crohn's Disease

**weeks 12 and 52 (Phase 3)**

Loeff, E, et al. United European Gastroenterol J. 2022;10(S8).

Upadacitinib for Moderate-to-Severe Crohn’s Disease: Phase 3 Secondary Endpoints

1 Endoscopic Remission: SES-CD ≤ 4, at least a 2-point reduction versus baseline and no subscore > 1 in any individual variable, as scored by a central reviewer. 95% CI for response rate is the synthetic result based on Student’s t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. Point estimate and 95% CI for adjusted treatment difference are based on Cochran-Mantel-Haenszel test for adjusted strata for categorical endpoints. Non-responder imputation incorporating multiple imputation was used to handle missing data due to COVID-19. ***P < .001 vs PBO; ** P < .01 vs PBO

Filgotinib (JAK-1 inhibitor) SELECTION Trial: Phase 2b/3 Induction and Maintenance

Primary Endpoint: Clinical Remission at W58

Safety of JAKinibs in IBD

Incidence Rates of Adverse Events in the OCTAVE Clinical Program

Figure created from Sandborn WJ, et al. 20191, Winthrop KL, et al. 20192, Lichtenstein GR, et al. 20193, and Sandborn WJ, et al. 20194. Data as of September 2018 data cut for all AEs unless otherwise indicated. For death, MACE, and GI perforation, data as of November 2017 data cut. All other adverse events, BID=twice daily, CI=confidence interval; DVT=deep vein thrombosis; GI=gastrointestinal; IR=incidence rate; MACE=major adverse cardiovascular event; N=total number of patients; n=number of patients in subpopulation; NMSC=non-melanoma skin cancer; PE=pulmonary embolism; PY=patient-years.

Tofacitinib and Upadacitinib Affect Lipids

**Tofacitinib**
- Total cholesterol, LDL-c and HDL-c all moderately increased from baseline for both 5 and 10 mg maintenance doses
- Lipid ratios predictive of CV risk remained relatively stable during both induction and maintenance

**Upadacitinib**
- Demonstrated to increase lipid levels in patients with rheumatoid arthritis

---

**ORAL Surveillance Study A3921133**

**Methods:**
- Randomized, open-label, non-inferiority safety end-point study of tofacitinib vs anti-TNF
- Subjects: active RA despite MTX, age >50, 1 cardiovascular risk factor
- Randomized tofa 5 mg BID (n=1455), 10 mg BID (n=1456), or TNF inhibitor (n=1451)
- (ALL with MTX)

**Notes:**
- **patients in 10 mg BID arm discontinued treatment in Feb 2019; patients had option to switch to 5 mg BID**

---


**Virtual Grand Rounds**

**Adverse Events with Tofacitinib in Patients with Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Event</th>
<th>Tofacitinib, 5 mg Twice Daily (N=448)</th>
<th>Tofacitinib, 10 mg Twice Daily (N=457)</th>
<th>TNF Inhibitor (N=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event — no. (%)</td>
<td>1333 (31.6)</td>
<td>1354 (31.5)</td>
<td>1358 (31.0)</td>
</tr>
<tr>
<td>Serious adverse event — no. (%)</td>
<td>351 (2.4)</td>
<td>399 (2.8)</td>
<td>396 (2.1)</td>
</tr>
<tr>
<td>Discontinuation of trial due to adverse event — no. (%)</td>
<td>210 (1.4)</td>
<td>304 (2.5)</td>
<td>210 (2.4)</td>
</tr>
<tr>
<td>Temporary discontinution</td>
<td>665 (4.7)</td>
<td>754 (5.0)</td>
<td>774 (5.0)</td>
</tr>
</tbody>
</table>

**Adverse events of special interest**

- **Serious infection — no. (%)** 341 (7.7) 109 (1.6) 119 (8.2)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 1.17 (0.01-1.60) 3.02 (1.17-3.87) Reference
- **Adjudicated opportunistic infection — no. (%)** 39 (7.7) 44 (3.0) 21 (1.4)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 1.31 (1.07-1.69) 2.57 (2.29-3.68) Reference
- **All herpes zoster, varicella and nonvaricella — no. (%)** 110 (2.4) 117 (2.1) 58 (4.0)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 2.28 (2.44-4.41) 3.39 (2.12-4.53) Reference
- **Adjudicated hepatic event — no. (%)** 6 (1.2) 72 (4.9) 35 (2.4)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 1.29 (0.80-2.00) 2.24 (1.40-3.42) Reference
- **Adjudicated NMSC — no. (%)** 41 (8.3) 33 (2.1) 16 (1.3)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 1.90 (1.94-1.97) 2.16 (1.39-3.02) Reference
- **Adjudicated pulmonary embolism — no. (%)** 8 (1.8) 34 (2.3) 3 (0.2)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 2.33 (0.78-7.22) 8.24 (4.95-25.47) Reference
- **Adjudicated DVT — no. (%)** 11 (2.6) 17 (1.2) 7 (0.3)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 1.24 (0.90-1.67) 2.21 (1.80-5.45) Reference
- **Adjudicated IIs — no. (%)** 17 (2.1) 29 (2.3) 10 (0.7)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 1.56 (0.92-2.66) 1.54 (1.28-1.84) Reference
- **Adjudicated death from any cause — no. (%)** 26 (5.8) 39 (2.7) 17 (1.2)
- **Hazard ratio vs. TNF inhibitor (95% CI)** 1.49 (0.81-2.74) 2.37 (1.44-4.18) Reference

**Incidence Rates of MACE**

- **Tofacitinib, 10 mg Twice Daily**
  - Incidence Rate: 1.2
  - Hazard Ratio: 1.0 (Reference)

- **Combined Tofacitinib Doses**
  - Incidence Rate: 1.2
  - Hazard Ratio: 1.0 (Reference)

- **TNF Inhibitor**
  - Incidence Rate: 1.2
  - Hazard Ratio: 1.0 (Reference)

**Impact of ORAL Surveillance Study on Regulatory Labels for JAKinibs**

- **Position JAKinibs after anti-TNF**
- **Screen for risk of VTE and MACE**
- **Dose reduce when possible**
  - NOTE: that with tofacitinib and upadacitinib in UC, patients with “refractory” disease do better with higher dose in maintenance (Tofa 10 BID, Upa 30 QD)
Mechanistic Considerations for JAKinibs and VTE or MACE

- Unclear!
  - Tox studies did not see any markers.
  - No signal in the UC/RA/PsA pivotal trials or real world studies
  - IBD (especially colonic) is associated with increased VTE and MACE. Expected that if JAKinib was pro-thrombotic there would be a strong signal

- The role of JAK-STAT signaling in clotting cascades or cellular interactions related to that is not well characterized.

- IL-6 is associated with atherosclerotic heart disease, and JAKinib inhibits IL-6

**Incidence Rates of DVT and PE**

<table>
<thead>
<tr>
<th>Incidence Rates of Adverse Events of Special Interest in the Maintenance and Overall Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Cohort</td>
</tr>
<tr>
<td>Placebo (n=198)</td>
</tr>
<tr>
<td>psCIF</td>
</tr>
<tr>
<td>Serious infection event</td>
</tr>
<tr>
<td>Herpes Zoster (HZ)</td>
</tr>
<tr>
<td>Opportunistic infection*</td>
</tr>
<tr>
<td>Opportunistic infection (excluding HZ)*</td>
</tr>
<tr>
<td>Malignancy (excluding NMSC)*</td>
</tr>
<tr>
<td>NMSC*</td>
</tr>
<tr>
<td>MACE*</td>
</tr>
<tr>
<td>GI perforation*</td>
</tr>
</tbody>
</table>

NOTE: With the exception of malignancy (excluding NMSC), NMSC, and MACE, IRs presented in the table exclude events that occurred >28 days after the last dose of the study drug.

CI, confidence interval; IR, incidence rate; patients with >=1 event per year per 100 patient-years; OLE, open-label, long-term extension study; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular event; GI, gastrointestinal; *Adjudicated data do not include data from Study A3921063

**Rare Incidence of Venous Thromboembolic Events in Patients With UC on Tofacitinib**

Tofacitinib: Incidence Rates for Selected Adverse Events of Special Interest Across Studies and Indications

Table 3: IRA (95% CI) for AEs of special interest

<table>
<thead>
<tr>
<th>IRA (95% CI)</th>
<th>IRA (95% CI)</th>
<th>IRA (95% CI)</th>
<th>IRA (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRA (95% CI)</td>
<td>IRA (95% CI)</td>
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</tr>
<tr>
<td>IRA (95% CI)</td>
<td>IRA (95% CI)</td>
<td>IRA (95% CI)</td>
<td>IRA (95% CI)</td>
</tr>
</tbody>
</table>


Tofacitinib Real-World Safety and Efficacy in Ulcerative Colitis Comparable to Registration Trials

<table>
<thead>
<tr>
<th>Abstract Reference</th>
<th>Study design</th>
<th>N</th>
<th>Prior TNF</th>
<th>Clinical remission*</th>
<th>Endoscopic remission</th>
<th>Histological remission</th>
<th>Discontinued</th>
<th>Colectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Retrospective observational Chicago</td>
<td>91</td>
<td>97%</td>
<td>-</td>
<td>64% (9/14)</td>
<td>36% (5/14)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Prospective observation Belgium</td>
<td>40</td>
<td>98%</td>
<td>33%</td>
<td>28%</td>
<td>25%</td>
<td>63%</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>Systematic review 11 articles/8 abstracts</td>
<td>2,013</td>
<td>36%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Systematic review 7 observational studies</td>
<td>715</td>
<td>28%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>35%</td>
<td>13%</td>
</tr>
</tbody>
</table>

*Clinical remission rates between week 16 and 26

Serious infections occurred in 4%, abnormal lipids 12%, zoster infection in 3% and thromboembolic events in 0.3%

Tofacitinib NOT Associated with Increased Risk of VTE when Compared to Anti-TNF Agents in Patients with IBD

Methods
- Retrospective cohort study in a large U.S. claims database
- Identified patients with IBD by ICD-codes
- Primary outcomes were ICD-codes for VTE and cardiovascular (CV)-events
- Fitted propensity score (PS)-weighted Cox proportional hazard models

Thromboembolic & CV Outcomes in Patients with IBD Newly Initiated on Tofacitinib and anti-TNF Agents

Methods
- Retrospective cohort study in a large U.S. claims database
- Identified patients with IBD by ICD-codes
- Primary outcomes were ICD-codes for VTE and cardiovascular (CV)-events
- Fitted propensity score (PS)-weighted Cox proportional hazard models

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Upadacitinib: Treatment-Emergent Adverse Events

PBO
(N=176)

UPA 45 mg QD
(N=350)

Any AE
58.5%
62.6%

Severe AE
8.5%
8.9%

Serious AE
6.8%
6.9%

AE possibly related to study drug*
21.6%
31.1%

AE relating to discontinuation of study drug
5.7%
4.3%

AE related to COVID-19
0.6%
0.9%

Deaths
0%
0%

Percent of Adverse Events

Loftus, EV, et al. United European Gastroenterol J. 2022;10(s8).
Virtual Grand Rounds

Upadacitinib: Adverse Events of Special Interest
Ulcerative Colitis Program

<table>
<thead>
<tr>
<th>Adverse event, Events (E/100 PY)</th>
<th>PBO N=223; PY=107.0</th>
<th>UPA 15 mg QD N=221; PY=148.2</th>
<th>UPA 30 mg QD N=229; PY=166.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infection</td>
<td>9 (6.4)</td>
<td>9 (6.1)</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>Opportunistic infection excl Tuberculosis and Herpes zoster</td>
<td>0</td>
<td>1 (0.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>5 (4.7)</td>
<td>6 (4.0)</td>
<td>12 (7.2)</td>
</tr>
<tr>
<td>Anemia†</td>
<td>13 (12.2)</td>
<td>15 (10.1)</td>
<td>11 (6.6)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>10 (9.3)</td>
<td>4 (2.7)</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (0.9)</td>
<td>3 (2.0)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Creatine phosphokinase elevation</td>
<td>3 (2.8)</td>
<td>5 (3.4)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Hepatic disorder‡</td>
<td>3 (2.8)</td>
<td>11 (7.4)</td>
<td>17 (10.2)</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>2 (1.9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adjudicated gastrointestinal perforation</td>
<td>1 (0.9)</td>
<td>1 (0.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Adjudicated thromboembolic event*</td>
<td>0</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Malignancies (all types)‡</td>
<td>0</td>
<td>1 (0.7)</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>

No tuberculosis, adjudicated cardiovascular, or non-melanoma skin cancer events were observed in any treatment group.

† Anemia (which includes other preferred terms, in addition to the preferred term “anaemia”), herpes zoster, neutropenia and lymphopenia were based on CMQ search. ‡ Hepatic disorder included transaminase elevations that were mild or moderate, asymptomatic, nonserious and uncommonly led to treatment discontinuation. *Hepatic vein thrombosis concurrent with an event of exacerbation of CD. ‡ Metastatic ovarian cancer in a patient the upadacitinib 15 mg group, and colon cancer and invasive lobular breast cancer in one patient each in the upadacitinib 30 mg QD group.

Virtual Grand Rounds

Practical Approach to Tofacitinib and Upadacitinib

- Moderately to severely active UC, After anti-TNF, monotherapy
- Baseline labs including lipid panel, screen for VTE risk (personal/family history, obesity, immobility)
- Dosing:
  - Tofa: 10 mg BID for 8-16 weeks, then 10 or 5 mg BID in maintenance
    - Consider dose reduction (to 5 mg BID) in maintenance if deep remission
  - Upa: 45 mg QD for 8 (-16) weeks, then 30 or 15 mg QD in maintenance
- Vaccinate for herpes zoster, can be after starting therapy-use attenuated vaccine (now FDA approved for ≥18 yo)
- Assess efficacy early: 2 weeks symptom assessment; 4-6 weeks FCP, repeat lipid panel

<table>
<thead>
<tr>
<th>Lab</th>
<th>At initiation</th>
<th>4-8 weeks</th>
<th>Every 3-6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lipids</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

How To Screen People for Risk of DVT: The Caprini Score


S1P Receptor Modulators: Ozanimod, Etrasimod
• Under physiological conditions, about 2% of the total lymphocyte pool in the human body is located in the circulation.¹

• S1P regulates lymphocyte migration from lymphoid tissue to sites of inflammation.²

• Cells involved in immune surveillance (e.g., monocytes and NK cells) are not negatively affected and continue to circulate.³

1. Lymphocytes exit lymphoid tissue
   • Migrate to sites of inflammation in response to signalling cues
   • Enter tissue and perpetuate inflammation

S1P Receptor Modulator Mechanism of Action

Possible direct effects on gut tissue and inflammation

Lymphocytes providing immune surveillance
   • Lymphocytes trafficking through lymphoid tissue
   • Activated lymphocytes
   • Antigen-presenting cell
   • S1P
   • S1P receptor
   • NK = natural killer.

Brain vasculature
   • Endothelial permeability (S1P1)
   • Transcellular transport (S1P1 and/or S1P3)
   • Hearing and balance (S1P1 and/or S1P3)

Lungs
   • Leaksage (S1P1 and/or S1P3)
   • Inflammation (S1P1 and/or S1P2 and/or S1P3)
   • Airway hyper-responsiveness (multiple S1P receptors)

Heart
   • Heart rate (S1P3)
   • Myocyte survival (S1P2 and/or S1P3)
   • Inflammation (S1P1 and/or S1P3)
   • Vascular resistance (S1P2 and/or S1P3)

Kidneys
   • Vascular leakage (S1P1)
   • Inflammation (S1P1)

Lymph nodes
   • Lymphocyte sequestration (S1P1)
   • Dendritic cell sequestration (S1P3)

Sphingosine-1-Phosphate Receptors: S1P₁-₅ (Ozanimod is S1P₁, P₅; Etrasimod is S1P₁, P₄, P₅)

Virtual Grand Rounds

Differentiation of S1P Modulators

<table>
<thead>
<tr>
<th>Differentiating Parameter</th>
<th>Ozanimod1-3</th>
<th>Etrasimod4-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor selectivity</td>
<td>S1P1, S1P5</td>
<td>S1P1, S1P4, S1P5</td>
</tr>
<tr>
<td>Lymphocyte suppression in healthy volunteers</td>
<td>1 mg: ~65% 2 mg: 69%</td>
<td>1 mg: 50% 2 mg: 40%</td>
</tr>
<tr>
<td>Lymphocyte suppression in disease (MS, UC, CD)</td>
<td>1 mg: 50% 2 mg: 40%</td>
<td>1 mg: 50% 2 mg: 40%</td>
</tr>
<tr>
<td>CYP450 interactions</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Liver enzyme elevations</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>21 hours; metabolite 11 days</td>
<td>~33 hours</td>
</tr>
<tr>
<td>Fast lymphocyte recovery time</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>First-dose HR reduction</td>
<td>Yes</td>
<td>Yes (modest)</td>
</tr>
<tr>
<td>Dose titration required</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>First-dose monitoring</td>
<td>No</td>
<td>?</td>
</tr>
</tbody>
</table>

**Ozanimod:**
- Reduces lymphocytes: Level normalizes within 3 days to 3 months of cessation (healthy and MS populations)\(^1,2\)
- Half-life: ~20 hours (metabolite ~11 days)\(^1,2\)
- Has first-dose heart rate reduction; mitigated with dose escalation\(^3\)

**Etrasimod:**
- Reduces lymphocytes: Level normalizes within 7 days of cessation\(^4\)
- Half-life: ~33 hours\(^3\)
- Has modest first-dose HR reduction; titration does not alter cardiovascular effects\(^5\)


---

Virtual Grand Rounds

Ozanimod Phase 1 Data (Healthy Volunteers): Lymphocyte Reduction

**Mean % lymphocyte change from baseline\(^1\)**

- **At Day 3,** ozanimod showed ~15% reduction
- **Half life:** ~10-13 days\(^2\)

**Mean % lymphocyte change from baseline\(^1\)**

- **93%** patients return to normal lymphocyte range within 3 months (US PI\(^2\))
- **Half life:** ~10-13 days\(^2\)

Virtual Grand Rounds

Ozanimod in Moderate-to-Severe UC
Phase 3, Randomized, Double-Blind, Placebo-Controlled True North Study

Cohort 1: N=645
Randomized 2:1
Placebo (n=216)
Ozanimod 1 mg (n=429)

Cohort 2: N=367
Open-label
Ozanimod 1 mg (n=367)

Responders
Placebo (n=69)
Ozanimod/placebo (n=227)
Ozanimod/ozanimod (n=230)

Nonresponders
Disease relapse
Completed maintenance

Open-label extension: ozanimod 1 mg

Study population:
- Male or female, 18–75 years of age
- Moderate-to-severe UC (total Mayo score 6–12, endoscopic subscore ≥2, rectal bleeding subscore ≥1, stool frequency subscore ≥1)
- Stable oral aminosalicylates, prednisone (≤20 mg/day), or budesonide MMX prior to screening and continuing through Induction


Virtual Grand Rounds

Ozanimod (S1P1,P5) for Induction and Maintenance of Moderately to Severely Active UC: TRUE NORTH Study

Week 10

Clinical Remission
Clinical Response
Endoscopic Improvement
Mucosal Healing

Week 52

Clinical Remission
Clinical Response
Endoscopic Improvement
Corticosteroid-free Remission
Mucosal Healing
Durable Remission

Virtual Grand Rounds

Ozanimod for Induction of UC by Prior TNF Inhibitor Use at Week 10


Ozanimod in the Treatment of Ulcerative Colitis: Initial Real-World Data from A Large Tertiary Center

Etrasimod (S1P1,P4,P5) for Moderate-to-Severe UC Phase 2
Week 12

A

 Improvement from baseline in the modified Mayo Clinic score

\[ \Delta = 0.99 (0.30 \text{ to } 1.68; P = .009) \]

\[ \Delta = 0.43 (-0.24 \text{ to } +1.11; P = .15) \]

Placebo (n = 54)  
Etrasimod 1 mg (n = 52)  
Etrasimod 2 mg (n = 50)

B

Patients achieving endoscopic improvement

\[ \Delta = 24.4\% (9.8\% \text{ to } 39.0\%; P = .003) \]

\[ \Delta = 4.1\% (-9.1\% \text{ to } +17.2\%; P = .31) \]

Placebo (n = 54)  
Etrasimod 1 mg (n = 52)  
Etrasimod 2 mg (n = 50)

Methods

- ELEVATE UC 12 & 52: Phase 3 randomized, double-blinded, placebo-controlled trials evaluating etrasimod 2 mg daily in adults with UC
- Study population: Moderate-severe UC (16-80 years, Baseline Modified Mayo Score 4-9)
Etrasimod is Effective in Induction and Maintenance in UC

ELEVATE UC 12 & 52: Results

**Results ELEVATE UC 12:**
- N=354 randomized (Etrasimod 2mg N=238, Placebo N=116)
- N=316 completed week 12

**Results ELEVATE UC 52:**
- N = 433 (Etrasimod 2mg N=289, Placebo N=144)
- N = 207 completed week 52

**Figure 1:** Primary and Key Secondary Efficacy Endpoints at Week 12
- Baseline MMS 5-9 (n=334)
- Clinical Remission
- Endoscopic Improvement
- Symptomatic Remission
- Physician Global Assessment
- Overall Response

**Figure 2:** Primary Endpoint Clinical Remission at week 12 and 52
- Baseline MMS 5-9 (n=409)

**Figure 3:** Key Secondary Endpoints at week 12 and 52
- Clinical Remission
- Symptomatic Remission
- Physician Global Assessment
- Overall Response

---

Safety of S1P Receptor Modulators in IBD
### Safety of Ozanimod in Moderate-to-Severe UC

#### Induction Period (Week 10) vs. Maintenance Period (Week 52)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=216)</th>
<th>Ozanimod (n=429)</th>
<th>Placebo (n=227)</th>
<th>Ozanimod (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any treatment-emergent adverse event (TEAE)</strong></td>
<td>82 (38.0)</td>
<td>172 (40.1)</td>
<td>83 (36.6)</td>
<td>113 (49.1)</td>
</tr>
<tr>
<td><strong>Common TEAEs (≥23% in any group)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (5.6)</td>
<td>18 (4.2)</td>
<td>4 (1.8)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (1.4)</td>
<td>15 (3.5)</td>
<td>4 (1.8)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (1.9)</td>
<td>14 (3.3)</td>
<td>1 (0.4)</td>
<td>8 (3.5)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>0</td>
<td>11 (2.6)</td>
<td>1 (0.4)</td>
<td>11 (4.8)</td>
</tr>
<tr>
<td>Gamma glutamyl transferase increased</td>
<td>0</td>
<td>5 (1.2)</td>
<td>1 (0.4)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td><strong>Serious TEAEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC exacerbation</td>
<td>7 (3.2)</td>
<td>17 (4.0)</td>
<td>18 (7.9)</td>
<td>12 (5.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>4 (0.9)</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Appendicitis/Complicated appendicitis</td>
<td>0</td>
<td>1 (0.2)</td>
<td>3 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Serious TEAEs</strong></td>
<td>3 (1.4)</td>
<td>10 (2.3)</td>
<td>6 (2.6)</td>
<td>7 (3.0)</td>
</tr>
</tbody>
</table>

#### Serious TEAEs

- UC exacerbation: 7 (3.2) vs. 17 (4.0) vs. 18 (7.9) vs. 12 (5.2)
- Anemia: 0 vs. 4 (0.9) vs. 0 vs. 1 (0.4)
- Appendicitis/Complicated appendicitis: 0 vs. 1 (0.2) vs. 3 (1.2) vs. 0

#### TEAEs leading to treatment discontinuation

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=227)</th>
<th>Ozanimod (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any treatment-emergent adverse event (TEAE)</strong></td>
<td>83 (36.6)</td>
<td>113 (49.1)</td>
</tr>
<tr>
<td><strong>Common TEAEs (≥3% in any group)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (3.6)</td>
<td>17 (7.4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14 (6.2)</td>
<td>24 (10.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (2.2)</td>
<td>12 (5.2)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>1 (0.4)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Gamma glutamyl transferase increased</td>
<td>1 (0.4)</td>
<td>6 (2.6)</td>
</tr>
</tbody>
</table>

---

*Ocurring in ≥2 patients in any group.


---

### Etrasimod Safety in Moderate-to-Severe UC

#### Placebo (n = 54) vs. Etrasimod 1 mg (n = 52) vs. Etrasimod 2 mg (n = 50)

<table>
<thead>
<tr>
<th>Patient with any TEAE, n (%):</th>
<th>Placebo (n = 54)</th>
<th>Etrasimod 1 mg (n = 52)</th>
<th>Etrasimod 2 mg (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any TEAE, n (%)</td>
<td>27 (50.0)</td>
<td>31 (59.6)</td>
<td>28 (56.0)</td>
</tr>
<tr>
<td>Number of TEAEs, n</td>
<td>64</td>
<td>66</td>
<td>78</td>
</tr>
<tr>
<td>Patients with TEAEs leading to death, n</td>
<td>1 (2.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients discontinued due to ≥1 TEAE, n (% of events)</td>
<td>0</td>
<td>3 (5.8)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Patients with serious TEAEs, n (% of events)</td>
<td>6 (11.1%)</td>
<td>11 (21.2%)</td>
<td>9 (18.0%)</td>
</tr>
<tr>
<td>TEAE relation to study drug, n (% of events)</td>
<td>25 (45.6%)</td>
<td>30 (57.7%)</td>
<td>26 (52.0%)</td>
</tr>
<tr>
<td>Related:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related TEAEs of special interest, n (%):</td>
<td>3 (5.8)</td>
<td>4 (7.7)</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Atioventricular block, second degree (type I):</td>
<td>0</td>
<td>0</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Heart rate lowering:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAEs reported by ≥2 patients in any treatment group, n (%):</td>
<td>0</td>
<td>3 (5.8)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>UC—worsening:</td>
<td>4 (7.4)</td>
<td>6 (11.5)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection:</td>
<td>2 (3.7)</td>
<td>4 (7.7)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Nasopharyngitis:</td>
<td>4 (7.4)</td>
<td>2 (3.9)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Anemia:</td>
<td>2 (3.7)</td>
<td>4 (7.7)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Urinary tract infection:</td>
<td>0</td>
<td>2 (3.9)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain:</td>
<td>2 (3.7)</td>
<td>2 (3.9)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.9)</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (5.8)</td>
<td>4 (7.7)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Fecal calprotectin increased</td>
<td>2 (3.7)</td>
<td>5 (9.6)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (3.7)</td>
<td>1 (1.9)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased:</td>
<td>0</td>
<td>1 (1.9)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>γ-Glutamyl transferase increased:</td>
<td>0</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (9.3)</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Anal fissure:</td>
<td>2 (3.7)</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkalemia:</td>
<td>0</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count increased:</td>
<td>0</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

---

Etrasimod Safety in Moderate-to-Severe UC

<table>
<thead>
<tr>
<th>Patients with any TEAE, n (%)</th>
<th>Placebo (n = 54)</th>
<th>Etrasimod 1 mg (n = 52)</th>
<th>Etrasimod 2 mg (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of TEAEs, n</td>
<td>64</td>
<td>66</td>
<td>78</td>
</tr>
<tr>
<td>Patients with TEAEs leading to death, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients discontinued due to ≥1 TEAE, n (%) (number of events)</td>
<td>0 (1/5)</td>
<td>3 (6/15)</td>
<td>4 (8/30)</td>
</tr>
<tr>
<td>TEAE related to study drug, n (%) (no. of events)</td>
<td>6 (11,1%)</td>
<td>3 (5,8%)</td>
<td>0</td>
</tr>
<tr>
<td>Not related</td>
<td>27 (50,0)</td>
<td>31 (59,6)</td>
<td>28 (56,0)</td>
</tr>
</tbody>
</table>

Number of TEAEs, n 164 166 178

Patients with TEAEs leading to death, n 0 0 0

Patients discontinued due to ≥1 TEAE, n (%) (number of events) 0 3 (6/15) 4 (8/30)

TEAE related to study drug, n (%) (no. of events) 6 (11,1%) 3 (5,8%) 0

Number of TEAEs leading to death, n 0 0 0

Patients discontinued due to ≥1 TEAE, n (%) (number of events) 0 3 (6/15) 4 (8/30)

TEAE related to study drug, n (%) (no. of events) 6 (11,1%) 3 (5,8%) 0

Treatment-related TEAEs of special interest, n (%) a

Anticoagulant, second degree (type 2) 0 0 0

Heart rate lowering 0 0 0

TEAEs reported by ≥2 patients in any treatment group, n (%) b

UC—worsening 4 (7,4) 5 (8,6) 4 (4,0)

Upper respiratory tract infection 2 (3,7) 4 (7,7) 2 (4,0)

Nasopharyngitis 4 (7,4) 2 (3,8) 1 (2,0)

Anemia c 2 (3,7) 2 (3,8) 3 (6,0)

Urinary tract infection 0 2 (3,8) 2 (4,0)

Abdominal pain 2 (3,7) 2 (3,8) 0

Headache 1 (1,9) 0 1 (2,0)

Nausea 2 (3,7) 3 (5,8) 0

Fecal calprotectin increased 2 (3,7) 1 (1,9) 0

Arthralgia 2 (3,7) 1 (1,9) 1 (2,0)

Blood creatine phosphokinase increased 0 1 (1,9) 2 (4,0)

γ-Glutamyl transferase increased 0 1 (1,9) 2 (4,0)

Sinusitis 0 1 (1,9) 0

Fever 1 (1,9) 0 2 (4,0)

Anal fissure 2 (3,7) 0 0

Hyperlipasemia 0 0 1 (2,0)

Neutrophil count increased 5

Hemoglobin

Liver enzymes


Practical Approach to Ozanimod

- Moderately to severely active UC, monotherapy
- Baseline labs, ECG, eye exam (only in patients with diabetes or uveitis)
- Dosing:
  - 0.23 mg BID for 1-4 days, then 0.46 mg for day 5-7, 0.92 mg on day 8 and after
- Vaccinate for varicella zoster, 4-6 weeks prior to starting therapy
- Assess efficacy early: 2 weeks symptom assessment; 4-6 weeks FCP, repeat lipid panel

<table>
<thead>
<tr>
<th>Lab</th>
<th>At initiation</th>
<th>4-8 weeks</th>
<th>Every 3-6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Novel Considerations for Small Molecules

- Intermittent (pulse) therapy?
- Induction, followed by different strategy for maintenance
- Combination therapy
- What else?


Case Examples
Case Example: 32 yo Medical Resident with Resistant UC

- 32 yo medical resident with left-sided ulcerative colitis at age 9
- Previous therapy with mesalamine, infliximab, adalimumab, vedolizumab, ustekinumab, tofacitinib
- Presented with urge incontinence 2/month and 6-8 stools per day with bleeding (SCCAI=9)
- Current meds: golimumab and budesonide foam
- Started on upadacitinib 45 mg daily (stopped golimumab and budesonide)
- Improved symptoms within 2 weeks

<table>
<thead>
<tr>
<th>Baseline Labs</th>
<th>CRP (mg/L)</th>
<th>FCP (ug/g)</th>
<th>Cholesterol (mg/dL)</th>
<th>HDL Cholesterol (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
<th>LDL Cholesterol (mg/dL)</th>
<th>Hemoglobin</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>680</td>
<td>167</td>
<td>63</td>
<td>61</td>
<td>92</td>
<td>14.9 g</td>
<td>4.6 g/dL</td>
</tr>
<tr>
<td>Week 4 Labs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12 Labs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Continued to feel well
- Seen for follow-up labs and in clinical remission
- Repeat flexible sigmoidoscopy performed
Case: Endoscopic Improvement on Upadacitinib at 13wks

- BEFORE
- AFTER

Case: Undergraduate Student with Ulcerative Proctitis

- 20 yo undergraduate student diagnosed with UP diagnosed 9 months prior
- Previous therapy with mesalamine suppositories and enemas, steroid suppositories, and oral mesalamine
- Presented with urgency, rectal bleeding, 4 BM/day, no incontinence (SCCAI=7)
- Current meds: oral mesalamine and steroid suppositories
- Started on ozanimod 1 mg daily (stopped mesalamine and steroid supp)
- Improved symptoms within 12 weeks, biochemical makers

<table>
<thead>
<tr>
<th></th>
<th>CRP (mg/L)</th>
<th>FCP (mcg/g)</th>
<th>Absolute lymphocytes Interface External (cells/μL)</th>
<th>Lymphocytes Interface External (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Labs</td>
<td>1.4</td>
<td>1100</td>
<td>1800</td>
<td>27.6</td>
</tr>
<tr>
<td>Week 6 Labs</td>
<td>31.1</td>
<td>1145</td>
<td>776</td>
<td>19.9</td>
</tr>
<tr>
<td>Week 20</td>
<td>&lt;1.0</td>
<td>38</td>
<td>900</td>
<td>18</td>
</tr>
</tbody>
</table>
## Summary of Small Molecules in IBD 2022

**Clinical Scenario**

<table>
<thead>
<tr>
<th>JAK1-3 Inhibitor</th>
<th>JAK1 Inhibitor</th>
<th>S1P Receptor Modulator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tofacitinib</strong></td>
<td><strong>Upadacitinib</strong></td>
<td><strong>Filgotinib</strong></td>
</tr>
<tr>
<td>(IR: 10 mg BID, 5 mg BID)</td>
<td>(45 mg PO QD for 8 weeks, then 15 mg or 30 mg QD)</td>
<td>(200 mg daily)</td>
</tr>
<tr>
<td><strong>Ozanimod</strong> (titration in week 1, then 1 mg daily)</td>
<td><strong>Etrasimod</strong> (2mg daily)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New UC, failing 5-ASA</th>
<th>Moderate to severe UC, failing anti-TNF</th>
<th>Low albumin</th>
<th>Concomitant MS and UC</th>
<th>Peripheral arthropathy</th>
<th>Axial spondyloarthropathy</th>
<th>Inpatient acute severe UC</th>
<th>History of heart disease</th>
<th>History of eye disease, specifically uveitis or DM-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>maybe</td>
<td>Not if atherosclerotic</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Questions?**

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ACG Hepatology Circle
ACG Functional GI Health and Nutrition Circle
ACG Women in GI Circle

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