Participating in the Webinar

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, 2021 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, 2022 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!

Week 1, 2022
Management of Pancreatic Pseudocysts
Mohit Girotra, MD
January 6, 2022 at Noon Eastern

Week 2, 2022
Chronic Constipation: More Than Just Bowel Movements
Kyle Staller, MD, MPH
January 13, 2022 at Noon Eastern

Visit gi.org/ACGVGR to Register
Positioning IBD Advanced Therapies: Today & Tomorrow

Miguel Regueiro, MD, FACG, AGAF

Chair, Department of Gastroenterology, Hepatology, & Nutrition

Vice Chair, Digestive Diseases and Surgery Institute

The Pier C. and Renee A. Borra Family Endowed Chair in Gastroenterology and Hepatology

Professor of Medicine, Lerner College of Medicine

Cleveland Clinic
The IBD Therapy Landscape: personalizing the choice of biologic or small molecule

- Longest history
- IV and SQ options
- Rapid onset of action
- Best with IM (SONIC)
  - Immunogenicity
  - Joints/perianal disease
  - Infection risk
  - Lymphoma risk (with IM)
- IV then SQ
- Efficacy in anti-TNF naïve and failure
  - Low immunogenicity
  - Psoriasis
  - Excellent safety profile
  - Will there be higher efficacy with anti-IL23?

S1P

- Oral
- Non-protein-based therapy
- Rapid Onset of Action
- Approved for MS (Ozanimod)
  - Lymphocyte suppression
  - Elevation of LFTs initially (rare)
  - First dose heart rate decrease
  - Macular edema in non-selective S1Ps
  - No first dose observation or ophthalmologic testing required (Ozanimod in MS)

Adapted from Click B, Regueiro M. IBDj 2019

Treating IBD: Why the Urgency?

Natural course of Crohn's disease (and UC?)

Theoretical impact of early effective treatment on disease progression

*Assessed by CDAI, CDEIS, and/or CRP.
CDAI, Crohn's Disease Activity Index; CDEIS, Crohn’s Disease Endoscopic Index Severity; CRP, C-reactive protein.
When to start biologics – we need to get it right in induction!

We want them to be HERE, before damage occurs


Evolving Definitions of Remission in UC

PRO, patient-reported outcomes.
Treatment Strategies for UC Are Driven By Patient Risk of Complicated Disease

**Low risk** for colectomy
- Limited anatomic extent
- Mild endoscopic disease

**High risk** for colectomy
- Age < 40 years
- Extensive colitis
- Deep ulcers
- Corticosteroid dependent
- History of hospitalization
- High CRP and ESR
- C difficile infection
- CMV infection


---

Risk of Colectomy in UC Dictates (first line) Therapy

**AGA Clinical Pathway for Initial Treatment of UC**

**Low colectomy risk patient** ($50\%$)
- Oral 5-ASA and/or
- Rectal 5-ASA and/or
  - Oral budesonide or prednisone and/or
  - Rectal steroids

Remission
- Maintenance with oral 5-ASA and/or rectal 5-ASA
- Taper steroid over 60 days

No remission
- Short course of steroids with initiation of thiopurine or
  - Anti-TNF with or without thiopurines
  - Vedolizumab with or without immunomodulator
  - Ustekinumab

**High colectomy risk outpatient** ($50\%$)

Remission
- Anti-TNF ± thiopurine
  - Thiopurine (optimize 6-TGN concentrations)
  - Vedolizumab ± immunomodulator
  - Tofacitinib
  - Proctocolectomy

No remission
- Thiopurine and taper steroids over 60 days
- Anti-TNF with or without thiopurine
- Vedolizumab with or without thiopurine or methotrexate

---

1. Adapted from AGA Clinical Pathway.
Positioning Therapies in the Low-Risk UC Patient

Oral 5-ASA agents\(^1,2\)
- Mainstay of therapy in mild to moderate UC
- Therapy should be optimized (dose, formulation, route and good adherence) should be optimized before moving to immunosuppressants
- Favorable risk-benefit profile

Rectal 5-ASAs/corticosteroids
- Suppositories preferred in proctitis\(^3\)
- Enema preferred in left-sided colitis in order to reach splenic flexure\(^3\)
- Combination therapy with oral 5-ASA recommended in left-sided or extensive disease
- Rectal steroids are option as add-on therapy in proctitis or left-sided disease

Oral corticosteroids\(^1,2\)
- Rapid induction\(^1,2\)
- Budesonide has fewer systemic effects than conventional steroids; consider as alternative first-line option for induction
- Repetitive or prolonged courses should be avoided

---

Positioning Therapies in the High-Risk UC Patient

TNF antagonists\(^1\)
- Rapid induction
- Significant maintenance benefit, but immunogenicity and loss of response is common

Vedolizumab\(^1,2\)
- Slower onset of action
- Significant benefit in maintenance
- Better results in anti-TNF-naïve patients
- LOVE trials evaluating vedolizumab in early and late UC

Tofacitinib\(^1,3\)
- Rapid induction
- Effective in both anti-TNF-naïve and experienced patients
- Infection risk may be problematic in combination therapy\(^1\)
- Avoid in patients at risk for thrombosis

Ustekinumab
- IV then SQ maintenance
- Fast onset of action
- Efficacy in anti-TNF-naïve and failure patients
- Excellent safety profile
- Low immunogenicity
- Good use if concomitant psoriasis

---

# Systematic Review with Network Meta-Analysis: First-Line Induction Pharmacotherapy for Moderate to Severe Ulcerative Colitis (caution applying systematic reviews to practice)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
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<tbody>
<tr>
<td>Infliximab vs placebo</td>
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<td>Jiang 2015</td>
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<td>ULTRA 2011</td>
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<td>Golimumab vs placebo</td>
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<tr>
<td>PURSUIT Phase 2</td>
<td>Golimumab 13</td>
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<td>Tofacitinib vs placebo</td>
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<td>OCTAVE 1 2016</td>
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<td>1039</td>
<td>2.35 (1.11, 4.99)</td>
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</tbody>
</table>

Effect size was positive for all treatments (compared to control)

Strongest for vedolizumab and infliximab


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## Monitoring in UC

**Stratify according to risk of relapse**

### Low risk
- Remission > 1 year
- Stable maintenance therapy
- Endoscopic healing
- Histologic healing
- Smoking habit
- Good adherence to therapy
- Age >50 years

- Clinic visit 6-12 months
- Calprotectin 3-6 months
- CRP 3-6 months (if elevated during flare)
- Endoscopy if symptoms or abnormal biomarkers

### High risk
- Flare within 1 year
- Recent change in maintenance therapy
- Persistent endoscopic lesions
- Persistent neutrophil infiltration in biopsy
- Recent smoking cessation
- Low adherence to therapy
- Age <50 years

- Clinic visit 3-4 months
- Calprotectin 2-3 months
- CRP 2-3 months (if elevated during flare)
- Endoscopy if symptoms or abnormal biomarkers

Evolving Definitions of Remission in CD

Clinical Remission
- CDAI < 150
- HBI< 5
- PRO
  - Diarrhea 0
  - Pain 0

Biologic Remission
- PRO + Endoscopy and Cross sectional imaging

Endoscopic Remission
- Improvement
  - CDEIS score <4
  - SES-CD ≤4
- Healing
  - Absence of ulcers

Histologic Remission
- Histologic indices?

CDAI, Crohn’s Disease Activity Index; CDEIS, Crohn’s Disease Endoscopic Index of Severity; HBI, Harvey-Bradshaw Index; PRO, patient-reported outcomes; SES-CD, Simple Endoscopic Score.


Treatment Strategies for CD Are Driven By Patient Risk of Complicated Disease

Low risk for rapid progression
- >30 years old at initial diagnosis
- Limited anatomic involvement
- No perianal and/or severe rectal disease
- Superficial ulcers
- No prior surgical resection
- No strictureing and/or penetrating pattern

High risk for rapid progression
- ≤30 years old at initial diagnosis
- Extensive anatomic involvement
- Perianal and/or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Strictureing and/or penetrating pattern

Sandborn WJ. Gastroenterology. 2014;147:703-705
Stratifying Treatment Based on Crohn’s Disease Severity Risk

AGA Clinical Pathway for Initial Treatment of Crohn’s Disease

**Low-risk* patient (<20%)**
- Ileum and/or proximal colon, none to minimal symptoms
  - Budesonide 9 mg/day with or without AZA
  - Tapering course of prednisone with or without AZA
- Diffuse or left colon, none to minimal symptoms
  - Tapering course of prednisone with or without AZA

**Moderate/high-risk* patient (>80%)**
- Options
  - Anti-TNF monotherapy over no therapy or thiopurine monotherapy
  - Anti-TNF + thiopurine over thiopurine monotherapy or anti-TNF monotherapy
  - Methotrexate for patients who do not tolerate purine analog in combination with anti-TNF
  - Vedolizumab
  - Ustekinumab

*AZA=azathioprine.

*Risk based on age at initial diagnosis (> 30 years vs < 30 years); anatomic involvement (limited vs extensive); presence or absence of perianal and/or severe rectal disease; ulcers (superficial vs deep); history of prior resection, and stricturing and/or penetrating behavior.


Positioning Therapies in the Low-Risk CD Patient

**Thiopurines**
- Not effective in inducing short-term remission
- Effective in steroid-sparing and maintaining steroid-induced remission

**Oral corticosteroids**
- Rapid induction, used primarily as a “bridge” during disease flares to achieve symptom control until immunomodulators and/or biologics achieve mucosal healing
- CIR-budesonide induces remission and minimizes systemic exposure, but is less effective than conventional oral corticosteroids
- Repetitive or prolonged courses should be avoided

Positioning Therapies in the High-Risk CD Patient

**TNF antagonists**
- Rapid induction
- Significant maintenance benefit, but immunogenicity and loss of response is common
- Only biologic with proven efficacy in fistulizing disease

**Vedolizumab**
- Option for induction, with or without immunomodulator
- Slower onset of action relative to anti-TNF inhibitors
- Favorable safety profile observed to date

**Ustekinumab**
- Option for patients who have failed corticosteroids, immunomodulators, or anti-TNF inhibitors
- Favorable safety profile

**Thiopurines**
- Combination with anti-TNF inhibitors recommended, with careful assessment of risk-benefit in individual patients

**Systematic Review with Network Meta-Analysis:**

**First-Line Induction Pharmacotherapy for Moderate to Severe Crohn’s Disease (caution applying systematic reviews to practice)**

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<td>Subtotal (95% CI)</td>
<td>160</td>
<td>400</td>
<td>78</td>
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</table>

Effect size was positive for all treatments except CTZ (compared to control). Strongest for infliximab and adalimumab
Systematic Review: 2nd Line Agents for Crohn’s Disease after IFX

Singh S et al, Aliment Pharmacol Ther 2018;48:394-409

Effect size was positive for ADA and UST, not Vedo (compared to control).

Monitoring in IBD

Low long-term risk
- Complete clinical remission
- Biomarker normalization at 12-16 weeks
- Monitor symptoms and biomarkers every 3-6 months
- Endoscopy and/or cross-sectional imaging
- Adapt therapy and further monitoring according to risk

High long-term risk
- Complete clinical remission
- Biomarker normalization at 12-16 weeks
- No
- After 6 months

The Evolution of the Safety Pyramid

Safety (and Access) Influences Positioning

- **Prevention is the best way to avoid complications**: vaccinations, baseline screening, careful history, and incorporate IBD checklists in your practice

- **If an event occurs, ask questions**: is it related to IBD or the medication? e.g. anti-TNF & psoriasis=YES, anti-TNF & PSC in UC=NO

- **anti-TNFs**: common infections greatest risk, e.g. bacterial pneumonia. Rarer but also associated are opportunistic infections, e.g. fungal, mycobacterial, viral. Less common but associated, lymphoma

- **JAK inhibitors** (Tofa): lipid increase, viral infections (zoster), NMSC, Venous Thromboembolism in RA (UC?)

- **Anti IL12/23**: although no “black box”, vigilance for infections

- **Vedolizumab**: transient LFT elevation, arthralgias, non-infectious pharyngitis, C diff?

- **Age matters**: over 60 years consider monotherapy biologic and weigh the risks/benefits of biologics

Click B, Regueiro M. IBDj 2019
Where will selective JAKi, anti-IL23, and S1P be positioned?

1. Selective JAKi, anti-IL23, and S1Ps appear to have similar efficacy (without head-to-head data) to other biologics/small molecules to date
2. Better efficacy in bio-naïve patients
3. Positioning of selective JAKi and S1P will be based on safety (and cost, access to new meds)
4. The safety of anti-IL23 appears similar to anti-IL12/23, and equally positioned based on safety.

Safety (and Access) Influences Positioning

• Prevention is the best way to avoid complications: vaccinations, baseline screening, careful history, and incorporate IBD checklists in your practice
• If an event occurs, ask questions: is it related to IBD or the medication? e.g. anti-TNF & psoriasis=YES, anti-TNF & PSC in UC=NO
• anti-TNFs: common infections greatest risk, e.g. bacterial pneumonia. Rarer but also associated are opportunistic infections, e.g. fungal, mycobacterial, viral. Less common but associated, lymphoma
• JAK inhibitors (Tofa): lipid increase, viral infections (zoster), NMSC, Venous Thromboembolism in RA (UC?), cardiovascular risk, malignancy, less AEs with selective JAKi
• Anti IL12/23: although no “black box”, vigilance for infections, equal safety with anti-IL23
• Vedolizumab: transient LFT elevation, arthralgias, non-infectious pharyngitis, C diff?
• S1P: increased LFTs, first dose heart rate reduction, lymphopenia, macular edema (non-selective S1Ps in uveitis, diabetes)
The Original Safety pyramid for IBD meds

(Click, Regueiro IBD) 2019

Safest

Vedo

UST

Anti-TNFs mono

Thiopurine or TOFA

Thiopurine/anti-TNFs combo

STEROIDS

Inadequate Treatment is an Adverse Event

The Modified Safety pyramid of current IBD meds

Queiroz, Regueiro Curr Opinion Gastro 2019

Safest

VEDO=UST

Anti-TNFs mono

Thiopurine or TOFA

Thiopurine/anti-TNFs combo

STEROIDS

Inadequate Treatment is an Adverse Event

American College of Gastroenterology
The New Safety Pyramid of Today*

1. Safest
2. VEDO=UST
3. Anti-TNF = TOFA
4. Thiopurine
5. Thiopurine/anti-TNFs combo

STEROIDS

Inadequate Treatment is an Adverse Event

*These are my opinions, not based on head-to-head data

---

The Safety Pyramid of Tomorrow*

1. Safest
2. VEDO=UST
3. Anti-TNF = TOFA
4. Thiopurine
5. Thiopurine/anti-TNFs combo

STEROIDS

Inadequate Treatment is an Adverse Event

S1P? sJAKi? antII23?

*These are my opinions, not based on head-to-head data
The Safety pyramid of Tomorrow  
(my opinion, no data)

Safest

With more data?

VEDO=UST  
antiIL23

S1P, sJAKi

Anti-TNFs = TOFA

Thiopurine

Thiopurine/anti-TNFs combo

STEROIDS

Inadequate Treatment is an Adverse Event

---

**Biologics & Small Molecules for IBD “Which One Today?” – Miguel's Practice**

*many insurances require anti-TNF first (FDA note: Tofa only after anti-TNF)*

- **UC severe** (hospitalized or “pending” hospitalization)
  - 1st Infliximab (up to 10mg/kg) with AZA (MTX young males) 2nd Tofa (more data needed for inpt)
- **UC: outpatient moderate** (not “impending” hospitalization)
  - > 60 years or comorbid cancer/infection: 1st Vedolizumab or UST monotherapy
  - < 60 years without comorbidity: 1st Vedolizumab or UST, 2nd Tofacitinib or antiTNF/IMM
- **CD: one segment of bowel without fistula** (*with fistula or extensive = IFX/IMM*)
  - > 60 years or comorbid cancer/infection: Vedolizumab or Ustekinumab monotherapy
  - < 60 years without comorbidity: *still* 1st Vedolizumab or Ustekinumab, 2nd antiTNF/IMM
- **Loss of response to an anti-TNF (if antiTNF was first):**
  - Secondary LOR (immunogenicity): **LOR to SQ** - switch to IFX/UST/Tofa(UC) > Vedo.
  - **LOR to IFX** – switch to Tofa (UC) or UST > Vedo (note: I do not switch from IV to SQ anti-TNF)
  - Primary LOR (no antibodies, good levels): switch out of class to Tofa(UC) or UST > Vedo
- **Extraintestinal manifestations**
  - Secondary to bowel inflammation (peripheral arthritis, iritis, EN): any that heal inflammation
  - Pyoderma gangrenosum, Uveitis, Central Arthritis: anti-TNF/MTX (Ustekinumab? or Tofa?)
- **Pregnancy** – any monoclonal Ab is ok, I treat straight through pregnancy: **stop** MTX > 3 mos and Tofa > 1 mos prior to conception

---

American College of Gastroenterology
Many insurances require anti-TNF first. Where will sJAKi, S1Ps, anti-IL23 be placed?

**UC severe** (hospitalized or “pending” hospitalization)
- 1st Infliximab (up to 10mg/kg) with AZA (MTX young males) 2nd Tofa (more data needed for inpt) **selective JAKi?**, **probably not S1Ps at this point – more data needed**

**UC: outpatient moderate** (not “impending” hospitalization)
- > 60 years or comorbid cancer/infection: 1st Vedolizumab or UST monotherapy, **Selective JAKi, S1P, antiIL23?**
- < 60 years without comorbidity: 1st Vedolizumab or UST or **sJAKi or S1P or antiIL23**, 2nd Tofacitinib or antiTNF/IMM

**CD: one segment of bowel without fistula** *(with fistula or extensive = IFX/IMM)*
- > 60 years or comorbid cancer/infection: Vedolizumab or Ustekinumab monotherapy or **antiIL23 or sJAKi?**
- < 60 years without comorbidity: still 1st Vedolizumab or Ustekinumab, 2nd antiTNF/IMM or **antiIL23 or sJAKi**

**Loss of response to an anti-TNF (if antiTNF was first):**
- Secondary LOR (immunogenicity): **LOR to SQ** - switch to IFX/UST/Tofa(UC) > Vedo or.... **sJAKi or antiIL23 or S1P (UC)**
- **LOR to IFX** - switch to Tofa (UC) or UST > Vedo (note: I do not switch from IV to SQ anti-TNF) or... **sJAKi or antiIL23 or S1P (UC)**
- Primary LOR (no antibodies, good levels): switch out of class to Tofa(UC) or UST > Vedo, **sJAKi or antiIL23 or S1P**

**Pregnancy** – any monoclonal Ab is ok *(antiIL23)*, I treat straight through pregnancy: **stop** MTX > 3 mos and Tofa > 1 mos prior to conception, **Not S1P or sJAKi yet, need more date**

**Questions?**

**Speaker:**
Miguel D. Regueiro, MD, FACG

**Moderator:**
Jami Kinnucan, MD