Beyond Anti-TNFs… Newer Biologics & Small Molecule Therapies for IBD

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Financial Disclosures

- AbbVie - Speakers Bureau, Advisory Board
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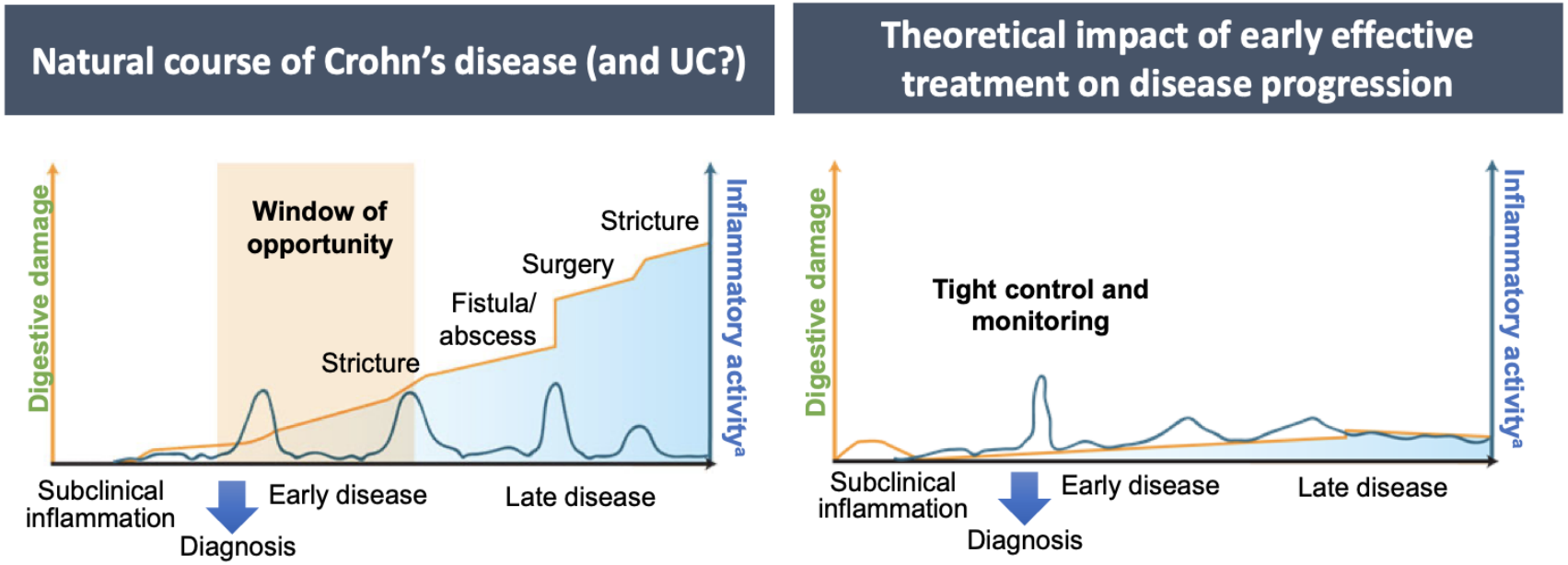
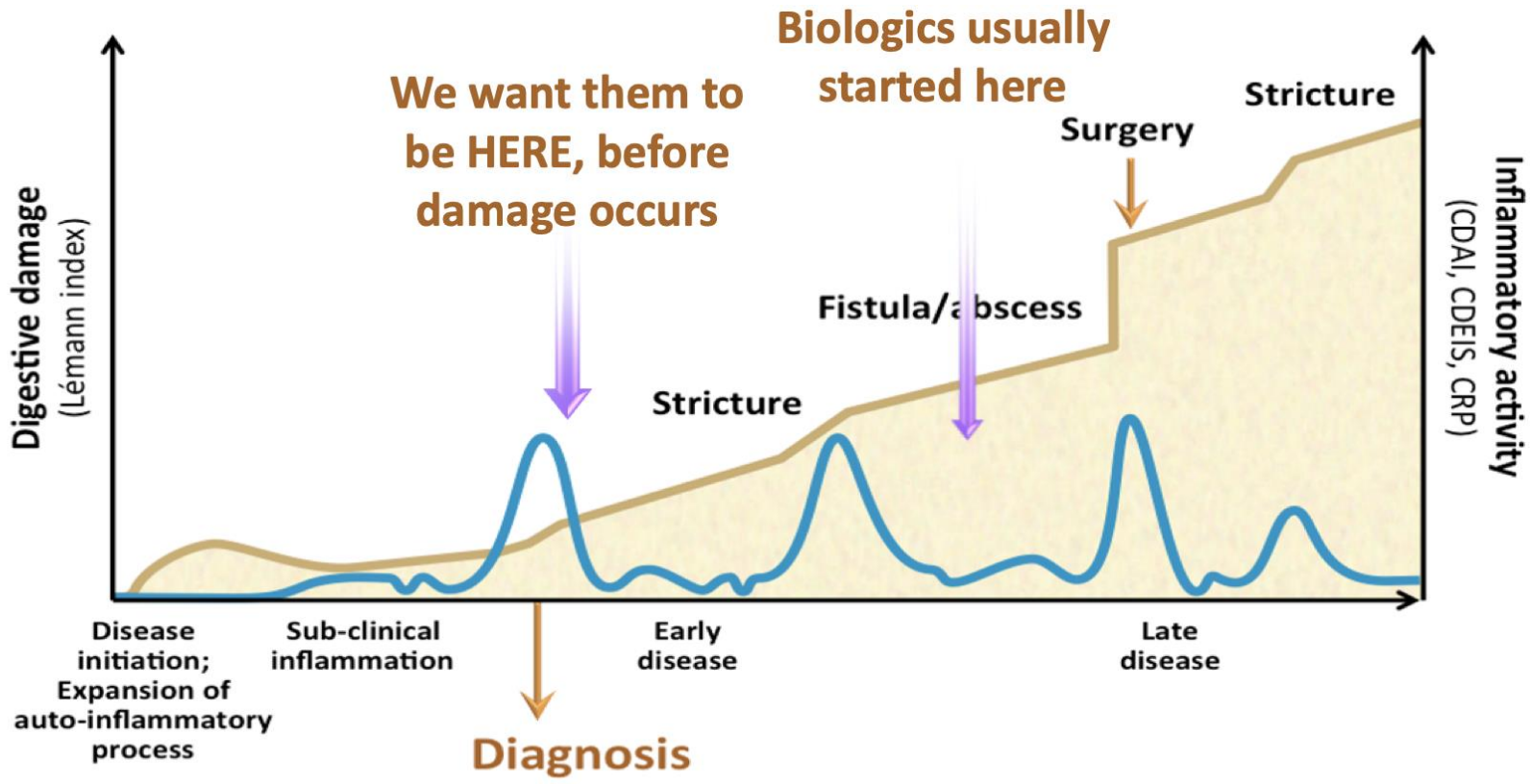
- BMS - Speakers Bureau, Advisory Board

Treating IBD: Why the Urgency?



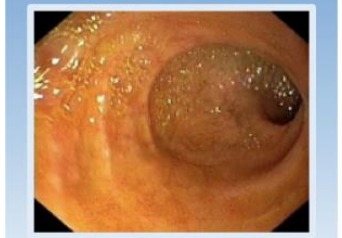
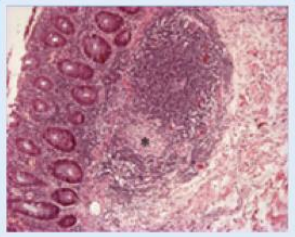
[a]Assessed by CDAI, CDEIS, and/or CRP.
CDAI, Crohn's Disease Activity Index; CDES, Crohn's Disease Endoscopic Index Severity; CRP, C-reactive protein.
Colombel JF et al. *Gastroenterology*. 2017;152:351-361.

When to Start Therapy & Why it's Essential to Get it Right



Pariente B, et al. Inflamm Bowel Dis. 2011;17(6):1415-22

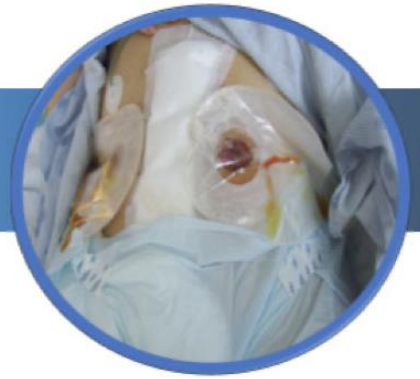
Evolving Definitions in Ulcerative Colitis (UC)

Clinical Remission	Biologic Remission	Endoscopic Remission	Histologic Remission
			
Mayo score 0-1 with no bleeding **PRO** Diarrhea 0 Bleeding 0	**PRO** 0+ Endoscopy 0-1	Mayo endoscopy subscore of 0 (normal) or 1	**Various indices** Robarts Geboes

PRO, patient-reported outcomes.

1. Rogler G et al. *World J Gastroenterol*. 2013;19(43):7552-7560. **2.** Walsh AJ et al. *Nature Rev Gastroenterol Hepatol*. 2016;13:567-579.

Therapy Strategies for UC are driven by RISK of Complicated Disease



Low risk
for colectomy

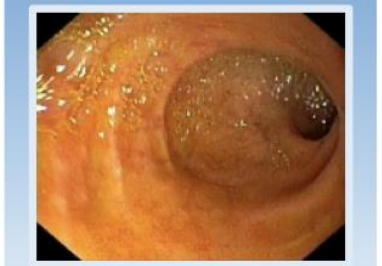
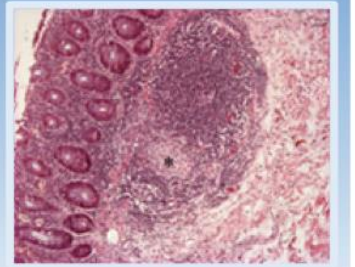
Limited anatomic extent
Mild endoscopic disease

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

Dassopoulos T, Scherl, E, Schwartz R, Kosinski L, Cohen C, and Regueiro M *Gastroenterology*. 2015;149:238-245.

Evolving Definitions in Crohn's Disease (CD)

Clinical Remission	Biologic Remission	Endoscopic Remission	Histologic Remission
			
CDAI < 150 HBI< 5 **PRO** Diarrhea 0 Pain 0	**PRO** + Endoscopy and Cross sectional imaging	**Improvement** CDEIS score <4 SES-CD ≤4 **Healing** Absence of ulcers	**Histologic indices?**

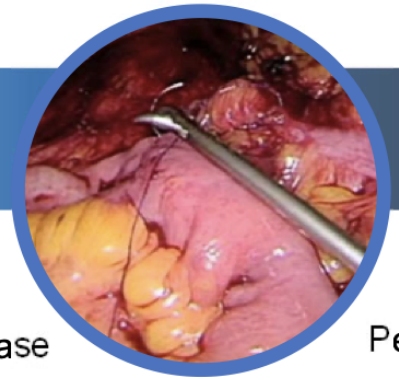
CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; HBI, Harvey-Bradshaw Index; PRO, patient-reported outcomes; SES-CD, Simple Endoscopic Score.

1. Rogler G et al. *World J Gastroenterol*. 2013;19(43):7552-7560. **2.** Walsh AJ et al. *Nature Rev Gastroenterol Hepatol*. 2016;13:567-579.

Therapy Strategies for CD are driven by 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 stricturing 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
Stricturing and/or penetrating pattern

Sandborn WJ. *Gastroenterology*. 2014;147:702-705.

What We Have Learned From Anti-TNFs

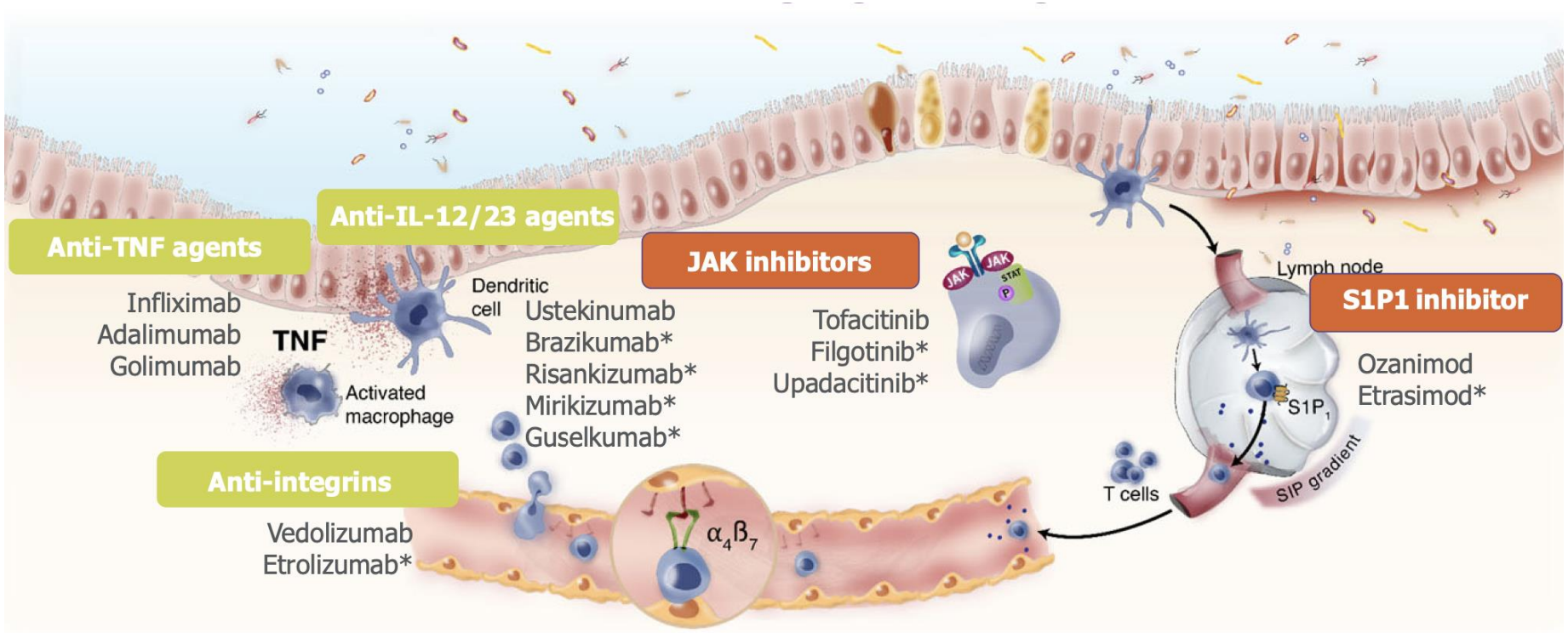
- Cornerstone of therapy for moderate to severe IBD
- Effective for treatment of CD & UC
- High-dose induction, regular maintenance & immunomodulators reduce immunogenicity
- Combination therapy is more efficacious than monotherapy*
- Pro-active drug & disease monitoring with therapy adjustments

- D'Haens G et al. *Lancet*. 2008;371:660-67; Schreiber S et al. *Am J Gastroenterology.* 2010;105:1574-82; Schreiber S et al. *J Crohn's Colitis*. 2013;7:213-21; Colombel JF et al. *N Engl J Med*. 2010;362:1383-95; Lémann M et al. *Gastroenterology*. 2006;130:1054-61; Schreiber S et al. *N Engl J Med*. 2007;357:239-50;
Hanauer S et al. *Lancet*. 2002;359:1541-9; Colombel JF et al. *Gastroenterology*. 2007;132:52-65.

What We Have Learned From Anti-TNFs cont.

- Despite optimization strides:
  - 1/3 will be primary non-responders
  - 1/3 will be 2ndary non-responders due to immunogenicity, pharmacology, or loss of mechanism
  - Leaving ONLY a third in clinical remission after 1 year of therapy
- Risks include infections & neoplasia - especially increased with steroids & thiopurines
- Great need for effective & sate treatment options with alternative mechanisms of action

Current & Emerging Strategies in IBD



Adapted from Coskun M, et al. *Trends Pharmacol Sci*. 2017;38(2):127-142.

New IBD Agents

Small-Molecule

- Tofacitinib (Xeljanz, Pfizer)
- Ozanimod (Zeposia, BMS)
- Upadacitinib (Rinvoq, Abbvie)

Biologics

- Vedolizumab (Entivyo, Takeda)
- Ustekinumab (Stelara, Jansen)
- Risankizumab (Skyrizi, Abbvie)

Tofacitinib- JAK Inhibitor

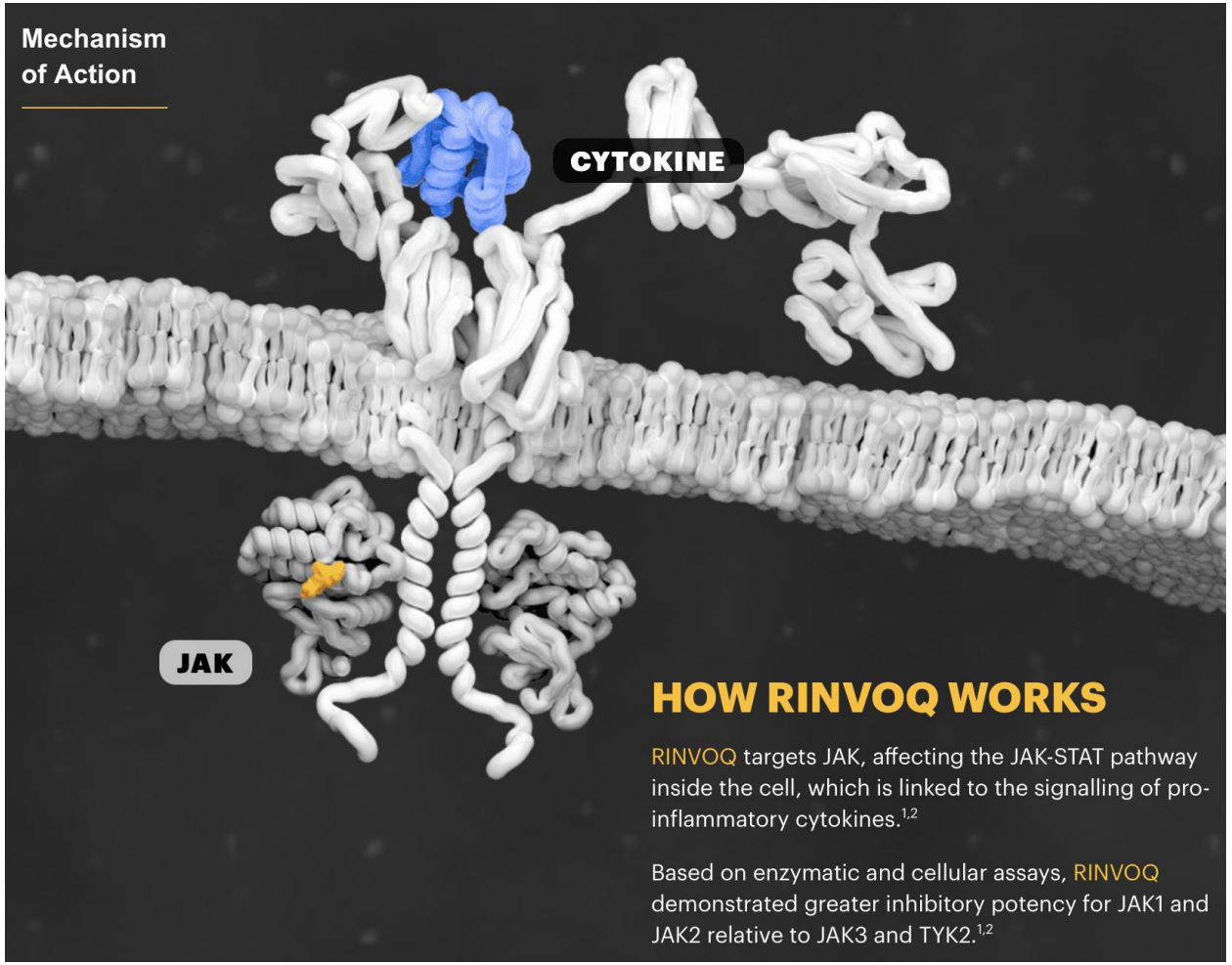
- Oral agent
- Pan-JAK inhibitor (1 & 3; and at higher doses 2)
- moderate to severe UC in adults
- OCTAVE 1 & 2 Induction Trials - OCTAVE Sustain Maintenance Trial
- Induced & maintained clinical remission + mucosal healing
  - w/o response to anti-TNF
- Increased, dose-dependent incidence rate Herpes Zoster
  - 2.1 (5mg bid) vs 6.6 (10mg bid) vs 1.0 (placebo)
  - Risk factors: increasing age, Asian ancestry, prior anti-TNF failure
    - Shingrix (herpes zoster subunit recombinant vaccine) approved for adults 50 y.o or older

Tofacitinib - JAK Inhibitor cont.

- Reduces cholesterol catabolism a/w inflammation
- Pooled analysis dose-dependent, reversible increases in serum lipid levels (total cholesterol, HDL & LDL) inversely correlated with inflammation (CRP)
- Black Box Warning
  - Major Adverse CV Events
    - Observed in RA pts >50 w/at least 1 CV RF treated w/10mg bid; incr. risk in current or past smokers; d/c if h/o MI or stroke
  - Thromboembolic Events
    - Observed in RA patients >50 w/at least 1 CV RF treated w/10mg bid; avoid w/thrombosis risk; d/c & promptly evaluate w/thrombosis sxs
- Feticidal & teratogenic in animals

Upadacitinib– JAK Inhibitor

- Oral agent, once-daily
- Must fail an anti-TNF prior for approval
- Greater inhibitory potency at JAK 1 & 2 relative to JAK 3
  - Leads to disruption of cytokine & growth factor signaling pathways
  - Thereby disrupting the pro-inflammatory signaling cascade
- moderate to severe UC in adults



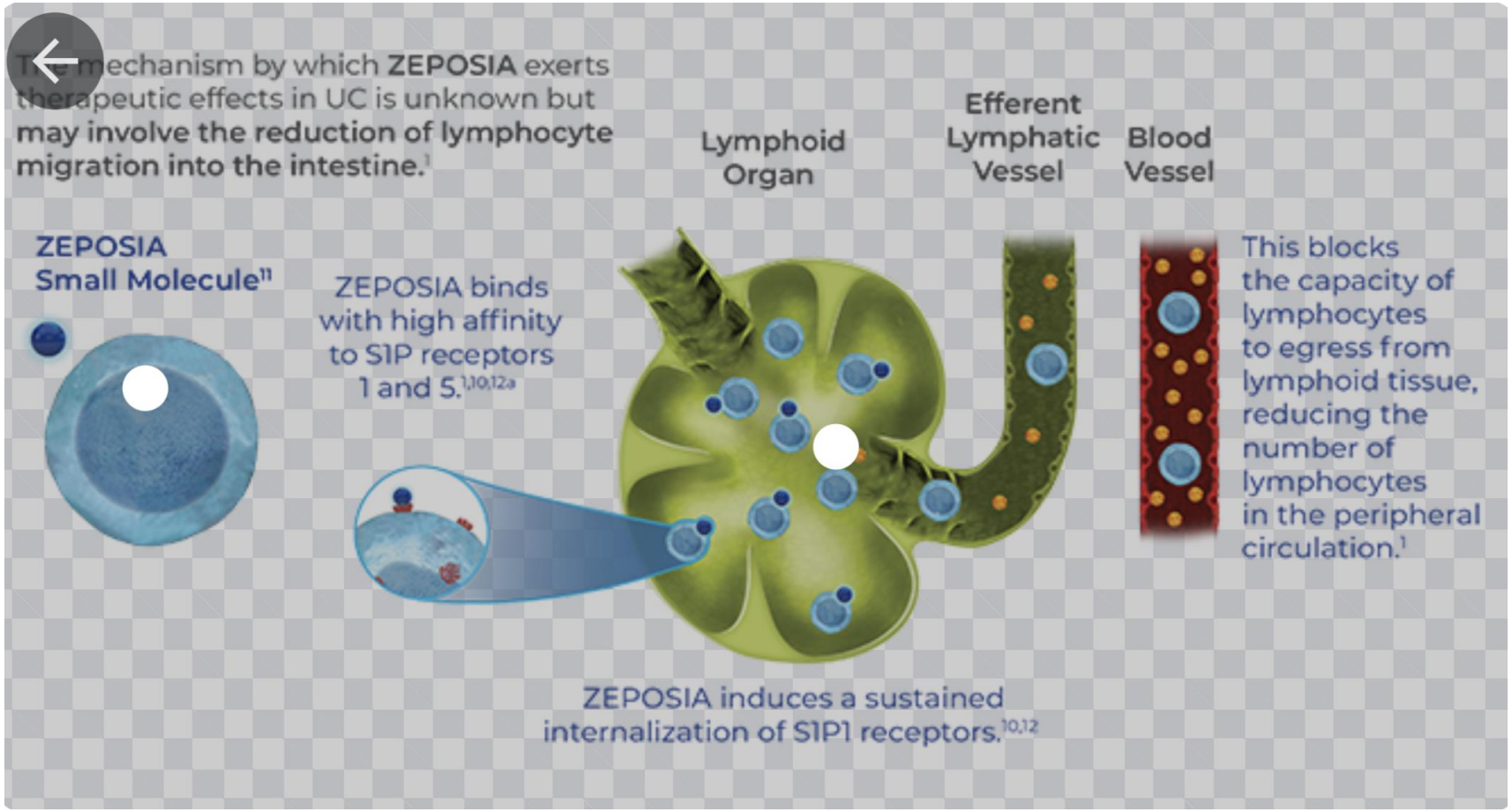
Upadacitinib– JAK Inhibitor cont.

- U-ACHIEVE & U-ACCOMPLISH Induction Trials – U-ACHIEVE Maintenance Trials
  - Relief of rectal bleeding & stool frequency at week 2
  - Durable clinical remission at week 8 and week 52
  - Endoscopic & Histologic-endoscopic mucosal improvement (HEMI) at week 52 (note relationship between HEMI to disease progression & long-term outcomes were not evaluated)
- Black Box Warning
  - Major Adverse CV Events
    - Observed in RA pts >50 w/at least 1 CV RF treated w/10mg bid; incr. risk in current or past smokers; d/c if h/o MI or stroke
  - Thromboembolic Events
    - Observed in RA patients >50 w/at least 1 CV RF treated w/10mg bid; avoid w/thrombosis risk; d/c & promptly evaluate w/thrombosis sxs
- Feticidal & teratogenic in animals

Ozanimod – S1P Inhibitor

- Oral Sphingosine 1-Phospate Receptor Inhibitor
- High binding affinity to S1P receptor subtypes 1 & 5
- moderate to severe UC in adults
- True North Trial – remission rates
  - Induction 18.4% vs placebo 6%
  - Maintenance 37% vs placebo 18.5%
- Treatment a/w bradycardia, AV conduction delays, liver injury, macular edema
- Selectively binds to S1P receptors; reduces lymphocyte egress from lymph nodes & migration into CNS & intestine

Ozanimod – S1P Inhibitor MOA



Ozanimod – S1P Inhibitor cont.

- Contraindications:
- Experienced w/in last 6 months
  - MI, unstable angina, stroke, TIA
  - Decompensated Heart Failure requiring hospitalization, or Class III/IV heart failure or have the presence of Mobitz type II 2nd degree or 3rd degree AVB
  - Sick Sinus Syndrome
  - Sino-atrial block uncles pt w/functioning PM
- Severe untreated Sleep Apnea
- On Monoamine Oxidase (MAO) inhibitor

Vedolizumab – Anti-Integrin

- Alpha 4 Beta 7 integrin
- Biologic Infusion
- Administered:
  - Induction at week 0, 2 & 6
  - Maintenance q 8 weeks
- Approved for moderate to severe UC & CD
- GEMINI-1 showed induces clinical remission & mucosal healing in pts who received anti-TNF & those who did not
- Approved in 2014
- First gut selective agent

Ustekinumab – IL 12/23 Inhibitor

- Binds to & interferes with Interleukin (IL) 12 & 23 cytokines, reducing inflammation & altering immune response
- Administered Induction IV Infusion x 1 dose Maintenance SQ q 8 weeks
- Approved for treatment of moderate to severe UC & CD
- UNIFI Trial
- No Black Box Warnings

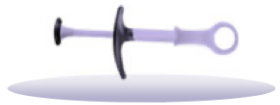
Risankizumab – IL-23 Specific Inhibitor

- Administered
  - Induction 3 IV Infusions; at weeks 0, 4 and 8
  - Maintenance SQ every 8 weeks
    - Administered via on-body injector
- Moderate to Severe CD in adults
- First approved product in CD w/endoscopic response as co-primary endpoint
- ADVANCE & MOTIVATE induction studies; FORTIFY maintenance studies

Positioning Therapies in Moderate to Severe IBD

TNF antagonists

- IV vs SC options
- Rapid onset of action (IV hospitalized patients)
- Best with immunomodulator
- Infection risk
- Lymphoma risk (with immunomodulator)



Lymphocyte trafficking (Vedolizumab)

- IV option (SC?)
- Low rate of immunogenicity
- Onset of action?
- Better results in TNF naïve patients
- Monotherapy or combination therapy?
- "Gut-Selective"
- Long-term safety

Anti-IL12/23(Ustekinumab)
Anti-IL/23 (Risankizumab, Mirikizumab, Guzelkumab)

- Similar induction success as TNFi agents
- Efficacy in TNFi-naïve and -failure patients
- Safety superior to anti-TNF therapies
- Low rate of immunogenicity
- Good use if concomitant psoriasis

JAK inhibitors (Tofacitinib, Upatacitinib)

- Oral
- Rapid onset of action
- Monotherapy, indicated after anti-TNF failure
- Maintenance dosing vs transition?
- Infection risk (zoster)
- MACE
- Lymphoma

S1P Modulator (Ozanimod, Etrasimod)

- Oral
- Rapid onset of action
- Monotherapy
- Dose-Titration
- Cardiac conduction

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
- Fast onset of action
- Efficacy in anti-TNF naïve and failure
- Low immunogenicity
- Psoriasis
- Excellent safety profile
- Will there be higher efficacy with anti-IL23?

S1P

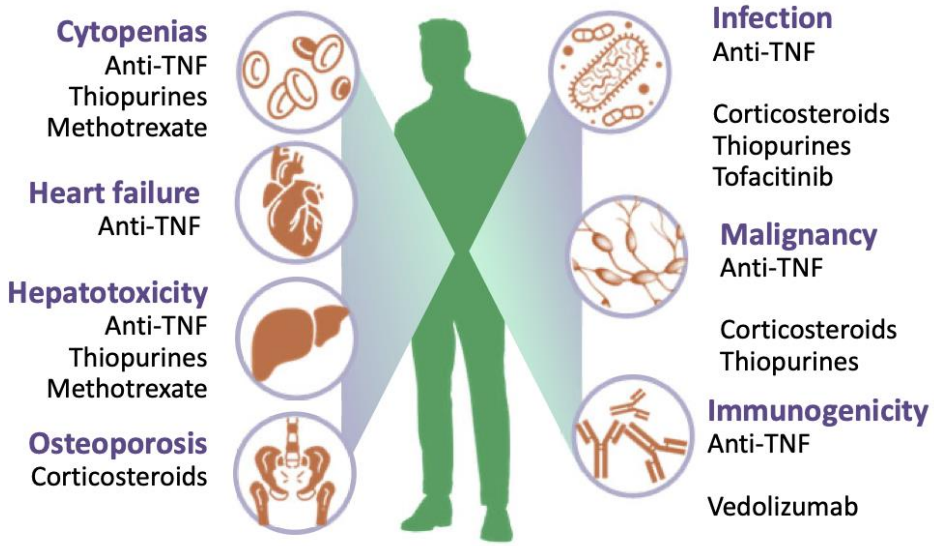
- Oral
- Non-protein-based therapy
- Rapid Onset of Action
- Approved for MS (Ozanimod)
- Lymphocyte suppression
- Elevation of LFTs initially (rare)
- First dose heart rate decrease
- Macular edema in non-selective S1Ps
- **No** first dose observation or ophthalmologic testing required (Ozanimod in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

- IV (soon SQ also)
- Little slower
- Better results in anti-TNF-naive patients
- Low immunogenicity
- Gut-selective with excellent safety profile

- Only for UC, but selective JAKi for CD
- Oral
- Rapid onset of action
- Non-protein-based therapy
- Joints
- Viral infection, e.g. Herpes Zoster
- Blood clots in RA (not UC)
- Improved safety with selective JAKi

Adapted from Click B, Regueiro M. *IBDj* 2019

Key Safety Considerations in IBD



Note: Prescribing information from the following products contain a boxed warning: Anti-TNF agents (serious infections and malignancy), tofacitinib (serious infections and malignancy), methotrexate (bone marrow, lung, and kidney toxicities); and thiopurines (malignancy).

1. Lichtenstein GR et al. *Am J Gastroenterol.* 2009;104:465-483; **2.** Lichtenstein GR, et al. *Am J Gastroenterol*. 2012;107:409-1422;
3. Yadav S et al. *Mayo Clin Proc*. 2015;90(6):738-746.

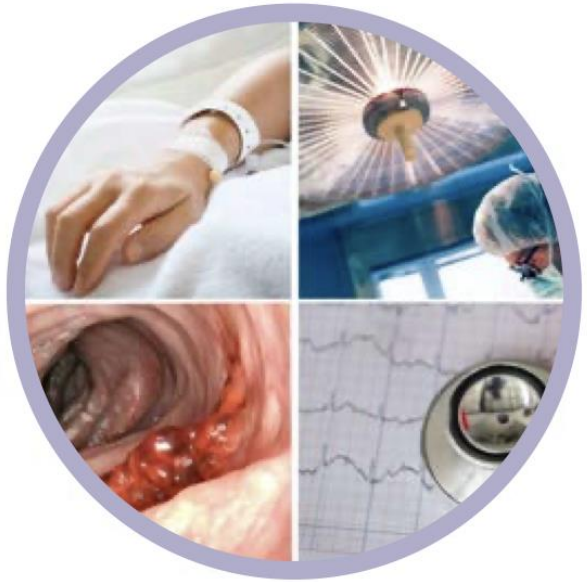
Inadequate Treatment Leads to Serious Complications

Flare and hospitalization

Up to 25% of patients are hospitalized for severe UC[1]

Colorectal cancer

2.4-fold greater risk in patients with UC[5]



Colectomy

≈ 30% of patients require colectomy; significant morbidity, persistent QoL issues[2-4]

Cardiovascular disease

Increased risk of MI, stroke, CV mortality—especially during flares[6]

1. Pola S et al. *Clin Gastroenterol Hepatol.* 2012;10:1315-1325; **2.** Brown C et al. *Springerplus*. 2015;4:573; **3.** Hefti MM et al. *Dis Colon Rectum.* 2009;52:193-197; 4. Ordas I et al. *Lancet.* 2012;380:1606-1619; **5.** Jess T et al. *Clin Gastroenterol Hepatol.* 2012;10:639-645; **6.** Filimon AM et al. *World J Gastroenterol*. 2015;21:9688-9692.

Thank you!

All the new IBD drugs lining up for ‘positioning’ in the next @AmerGastroAssn @AmCollegeGastro guidelines..