New Therapies in IBD: A Practical User's Guide

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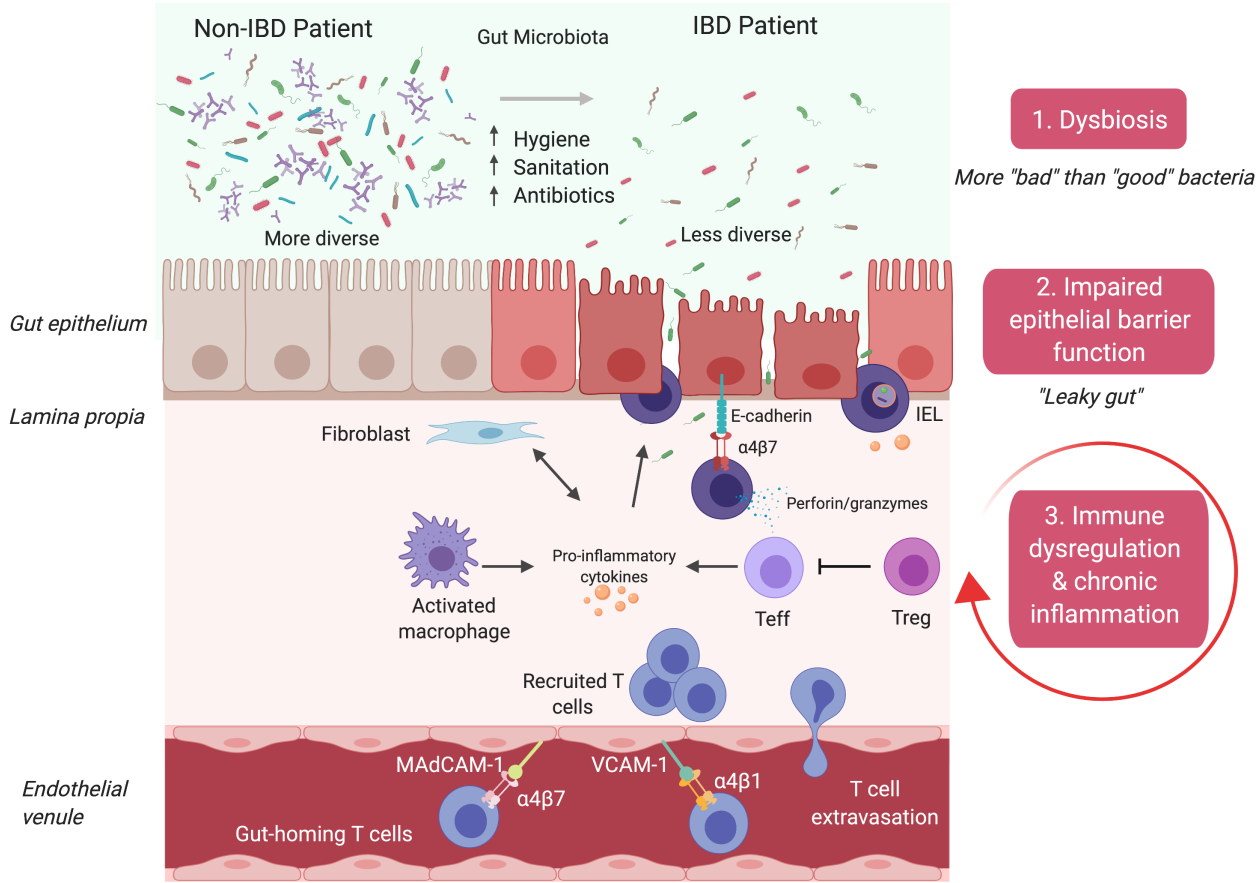
Drs. Miguel Regueiro, David Rubin, Ryan Ungaro

Learning objectives:

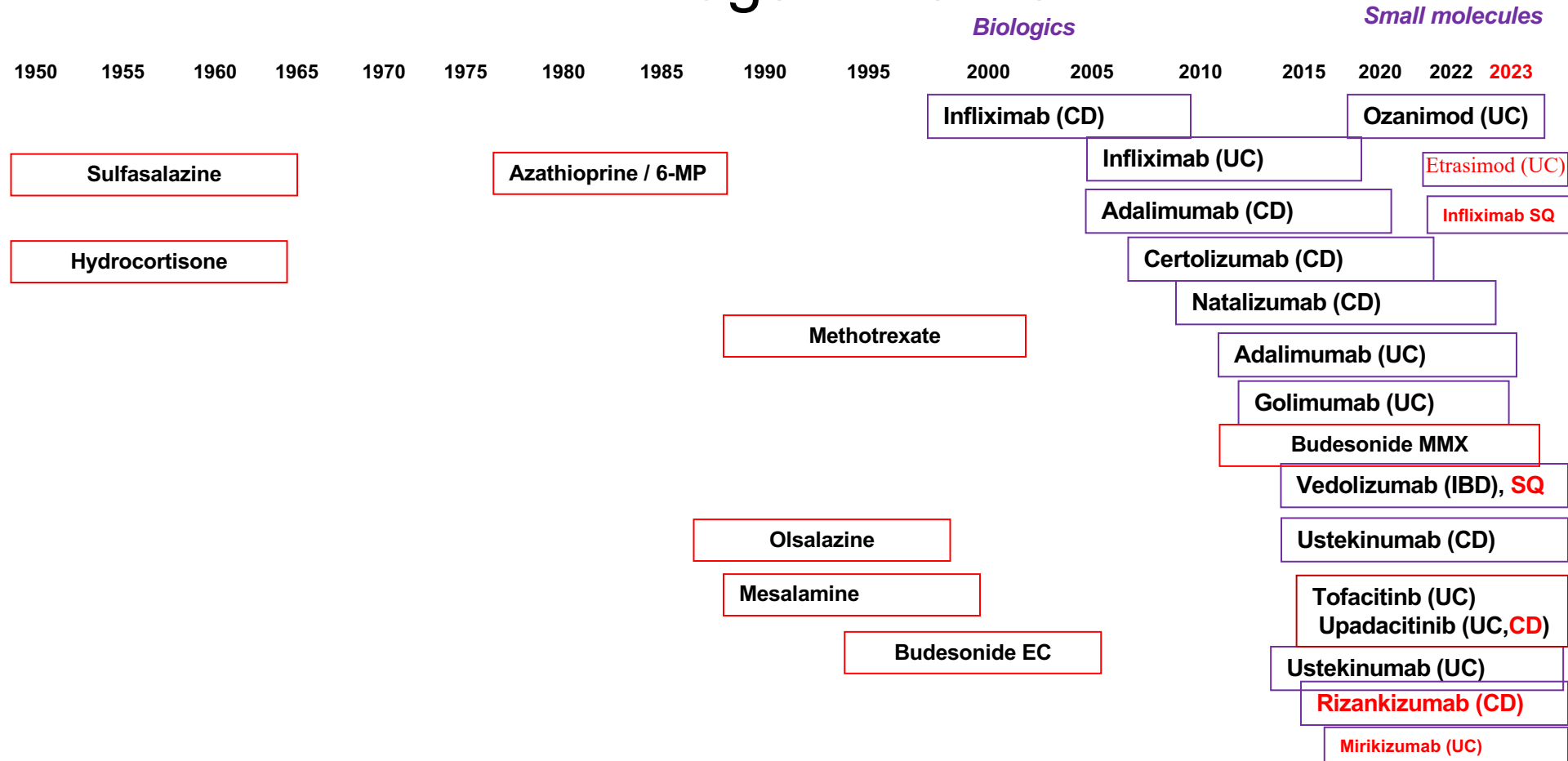
- Be able to identify current biological and small molecule agents available to treat IBD patients
- Understand mechanism of action, sequencing of therapies, and risk associated with therapies
- Be familiar with patient education resources and importance of vaccinations
- Understand the treat to target approach in utilizing therapies: patient reported outcomes, mucosal healing, fecal calprotectin and imaging

Pathogenesis of IBD is Multifactorial



Modified from Round and Palm, *Sci Immunol.* 2018 Feb 9;3(20). pii: eaao1603. doi: 10.1126/sciimmunol.aao1603 and Genentech Inc. 2018

IBD Drugs Timeline



FDA-Approved Targeted Therapies for IBD

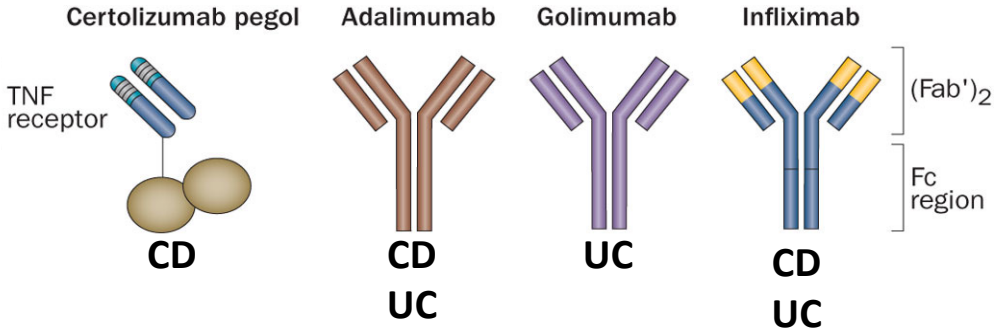
Class	CD	UC
TNF inhibitor	Adalimumab[1] Certolizumab[2] Infliximab[3]	Adalimumab[1] Golimumab[8] Infliximab[3]
IL-12/IL-23 inhibitor	Ustekinumab[4] Risankizumab[5] Mirikizumab	Ustekinumab[4]
Integrin inhibitors	Natalizumab[6] Vedolizumab[7]	Vedolizumab[7]
JAK inhibitors	Upadicitinib	Tofacitinib[9] Upadicitinib[10]
S1P receptor modulators	—	Ozanimod[11] Etrasimod

1. Humira (adalimumab) Prescribing Information. https://www.rxabbvie.com/pdf/humira.pdf. 2. Cimzia (certolizumab pegol) Prescribing Information. https://www.cimzia. /themes/custom/cimzia/docs/CIMZIA_full_prescribing_information.pdf. 3. Remicade (infliximab) Prescribing Information. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf. 4. Stelara (ustekinumab) Prescribing Information. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf. 5. Skyrizi (risakizumab-rzaa) Prescribing Information. https://www.rxabbvie.com/pdf/skyrizi_pi.pdf. 6. Tysabri (natalizumab) Prescribing Information. https://www.tysabrihcp.com/content/dam/commercial/tysabri/hcp/en_us/pdf/tysabri_prescribing_information.pdf. 7. Entyvio (vedolizumab) Prescribing Information. https://general.takedapharm.com/ENTYVIOPI. 8. Simponi (golimumab) Prescribing Information. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SIMPONI-pi.pdf. 9. Xeljanz (tofacitinib) Prescribing Information. http://labeling.pfizer.com/ShowLabeling.aspx?id=959. 10.Rinvoq (upadacitinib) Prescribing Information. https://www.rxabbvie.com/pdf/rinvoq_pi.pdf. 11. Zeposia (ozanimod) Prescribing Information. https://packageinserts.bms.com/pi/pi_zeposia.pdf.

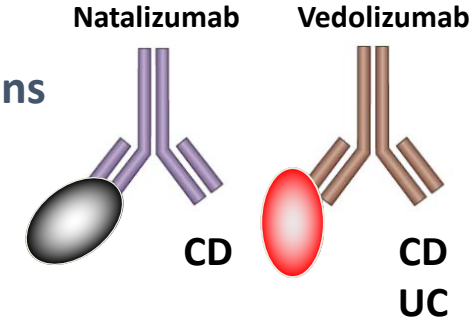
2023 Biologic Therapies for IBD

Small Molecules
Jak inhib- tofacitinib,
Upadacitinib, Filgotinib
S1P1 R – ozanimod
etrasimod

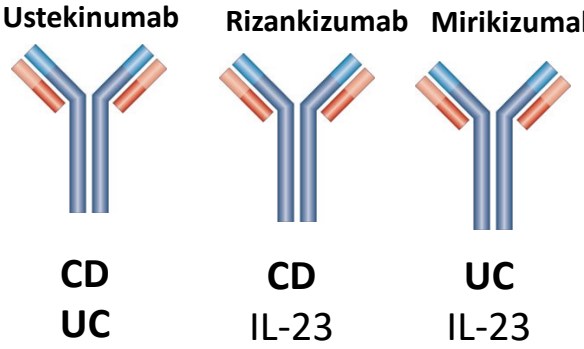
Anti-TNF agents +-AZA/MTX



Anti-integrins

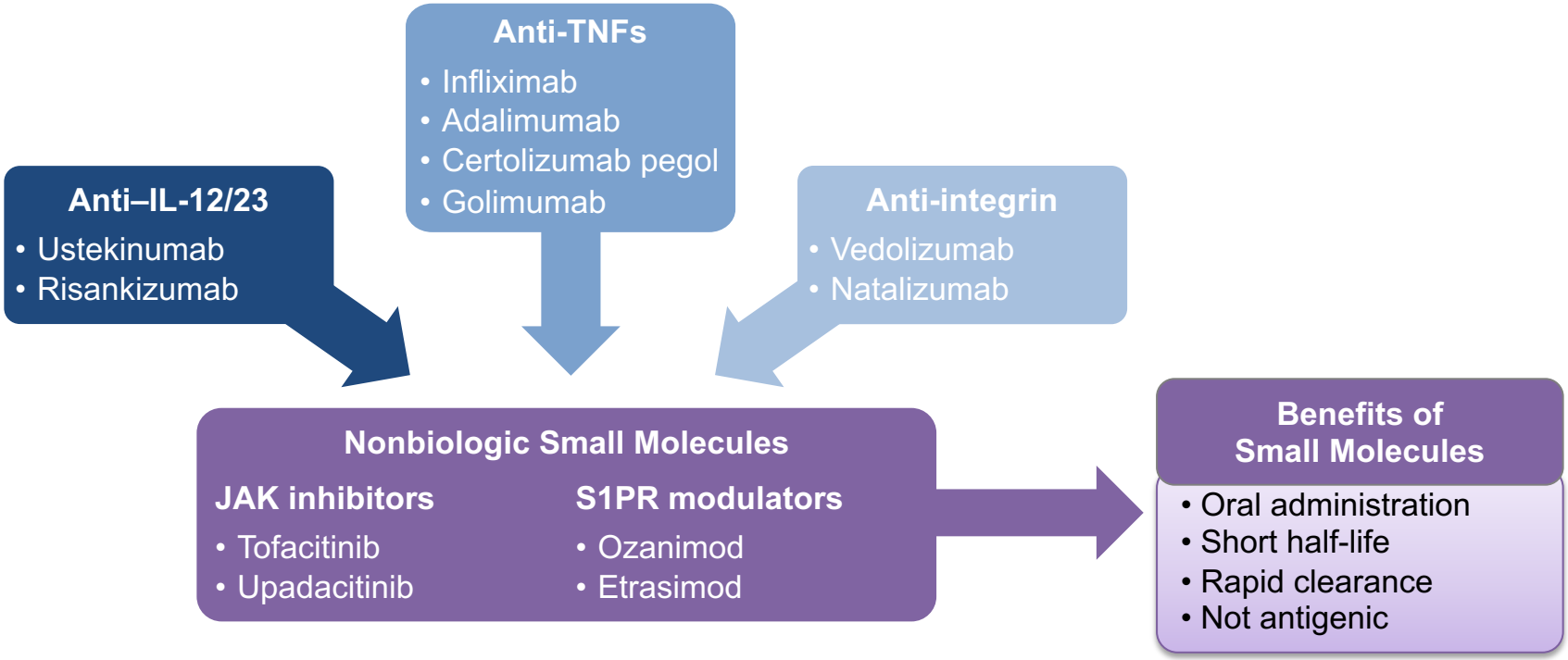


Anti-IL12/23



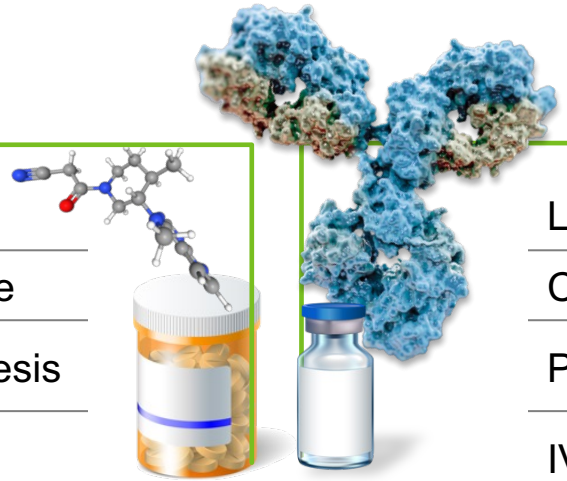
Modified from van Schouwenburg PA, et al. *Nat Rev Rhematol*. 2013;9(3):164-72.

Evolution of Therapeutic Targets for IBD: Monoclonal Antibodies and Small Molecules[1-3]



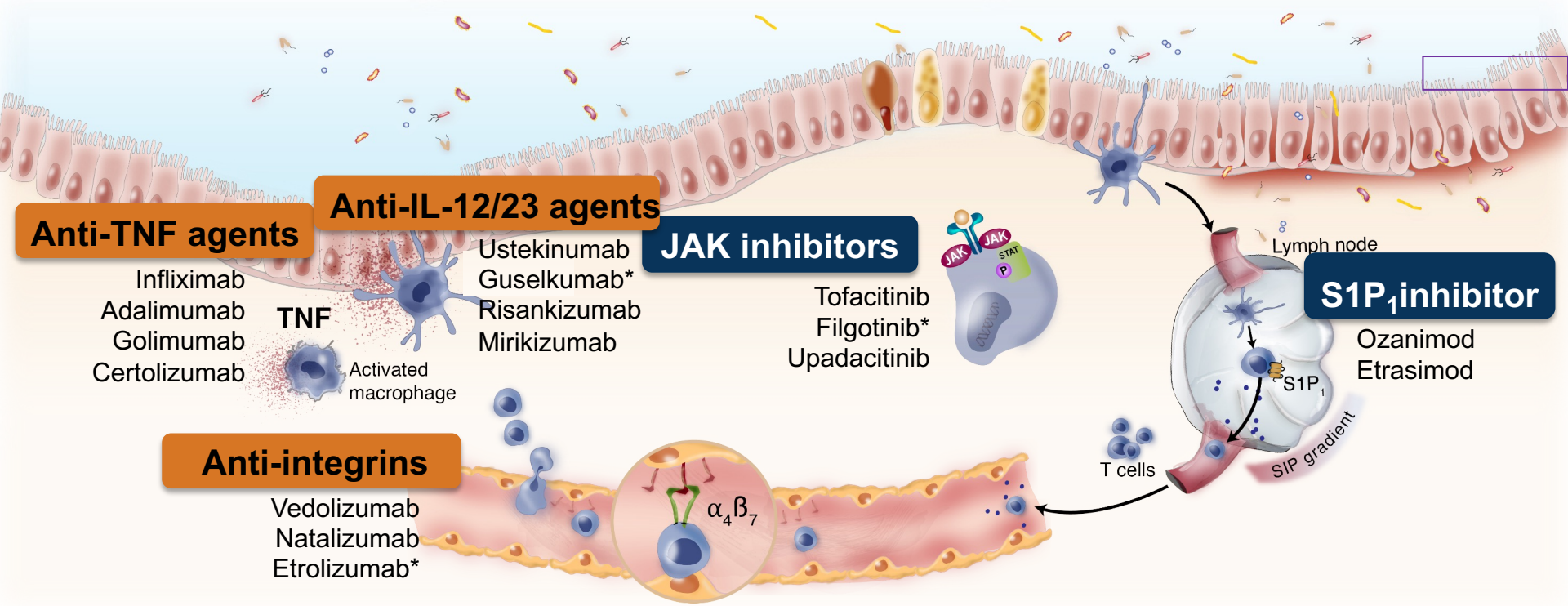
1. Fukuda T et al. *Intest Res*. 2019;17:36-44. 2. Gajendan M et al. *Dis Mon*. 2019;65:100851. 3. Hemperly A et al. *Inflamm Bowel Dis*. 2018;24:2527-2542.

Small Molecules versus Biologics

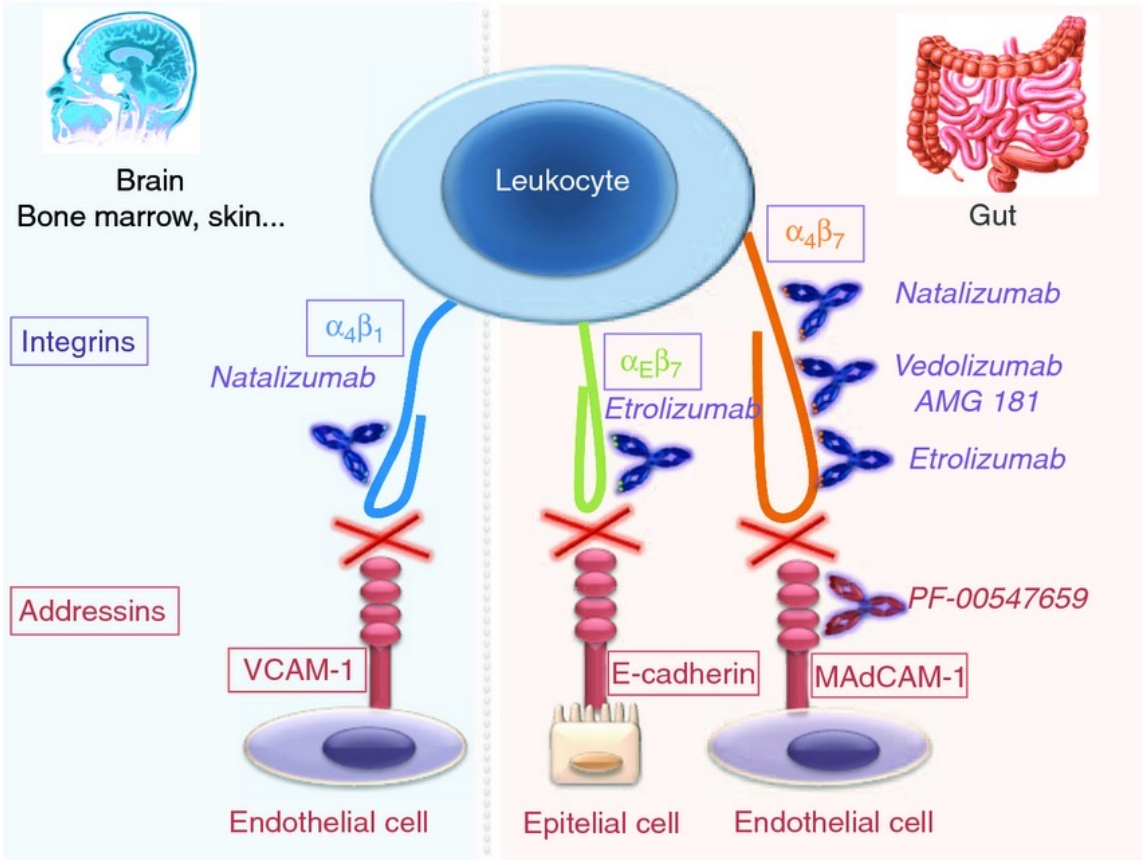


Small molecules	Biologics
Small (single molecule)	Large (mixture)
Simple, well-defined structure	Complex heterogeneous structure
Produced by chemical synthesis	Produced in a living cell culture
Oral	IV to SC
Non-immunogenic	Immunogenic

Current and Emerging Strategies for IBD



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

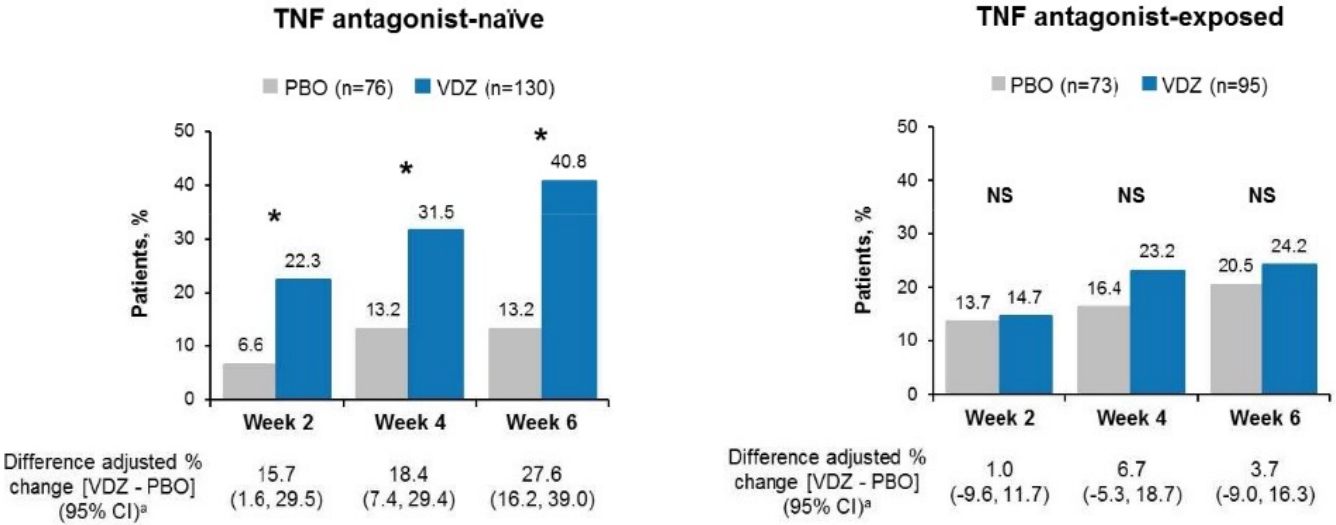


VCAM = vascular cell adhesion protein 1.

Lobaton T, et al. *Aliment Pharamcol Ther.* 2014;39:579-594.

Vedolizumab's Efficacy Decreased in Anti-TNF-Exposed Patients with UC

Post-Hoc Analysis of GEMINI 1 Trial
Proportion of Patients Who Achieved Stool Frequency Subscore ≤1 and Rectal Bleeding Subscore =0

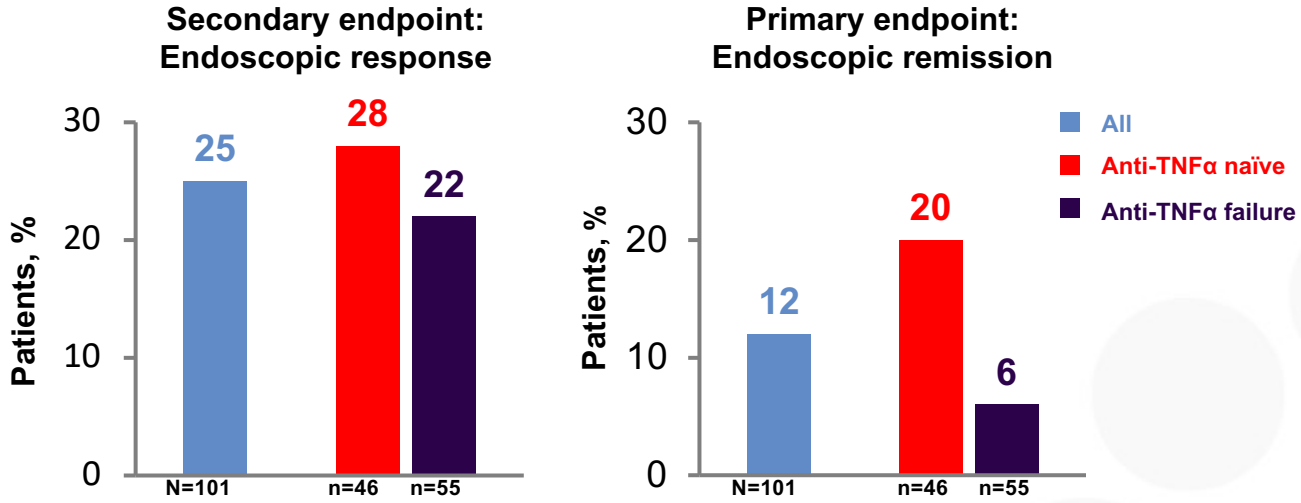


[a]% Diff from PBO=adjusted mean % change from baseline for VDZ – adjusted mean % change from baseline for PBO;
*Lower limits of 95% CI >0 indicate statistical significance at a nominal significance level of 0.05 and are shown in bold.
CI = confidence interval; diff = nominal difference; PBO = placebo; RBS = rectal bleeding subscore; SFS = stool frequency subscore; VDZ = vedolizumab; NS = not significant.

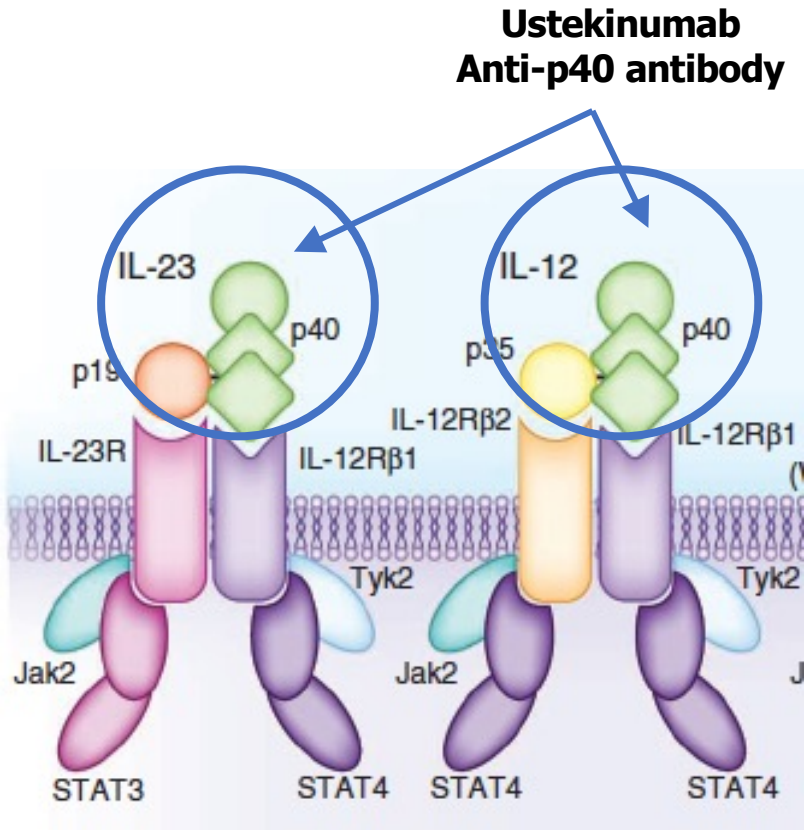
Feagan B, et al. *Clin Gastroenterol Hepatol*. 2019;17(1):130-138.e7.

VERSIFY: Endoscopic Response and Remission with VDZ Were Greater in Anti-TNF-Naïve Patients with CD

- Endoscopic response rates were greater than endoscopic remission rates
- Both followed a similar pattern, with higher rates in anti-TNF-naïve patients



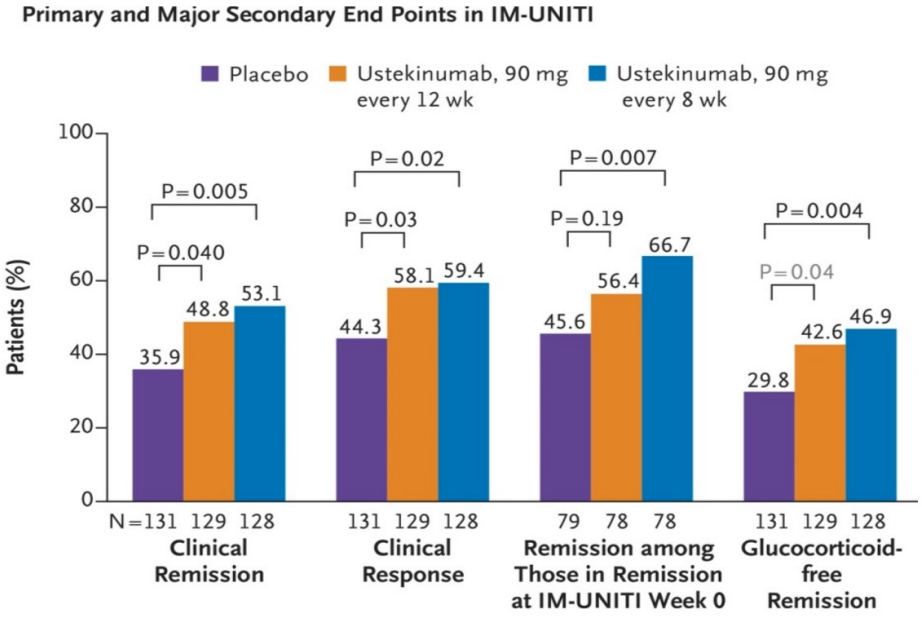
Endoscopic response: SES-CD ≥50% reduction from baseline; endoscopic remission: SES-CD ≤4.
SES-CD = Simple Endoscopic Score for CD.
Danese S, et al. *J Crohn's Colitis*. 2018;12(Suppl 1):S016-S017.

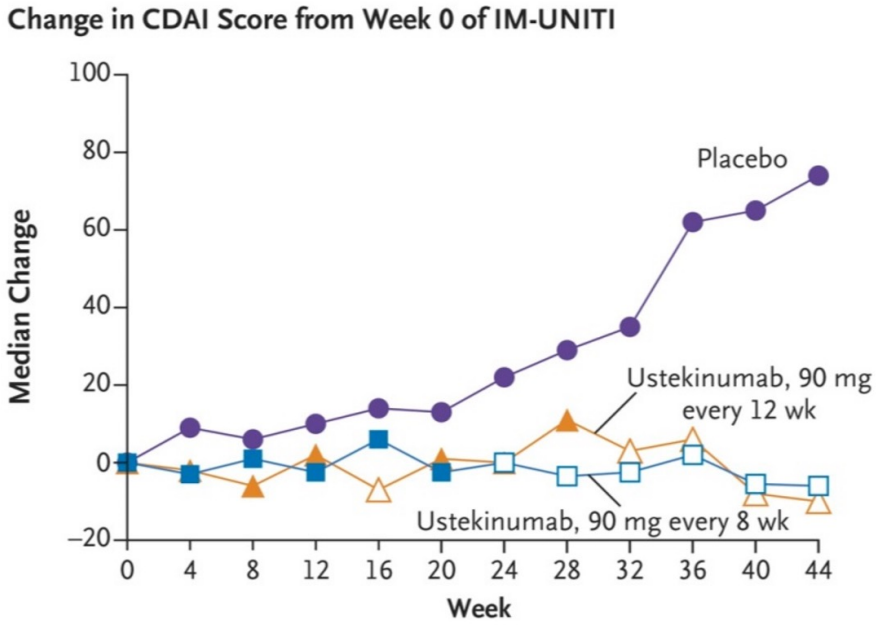


Tyk = tyrosine kinase; STAT = signal transducers and activators of transcription.
Adapted from: Teng MW, et al. *Nat Med*. 2015 Jul;21(7):719-29.

Ustekinumab for Crohn's Disease

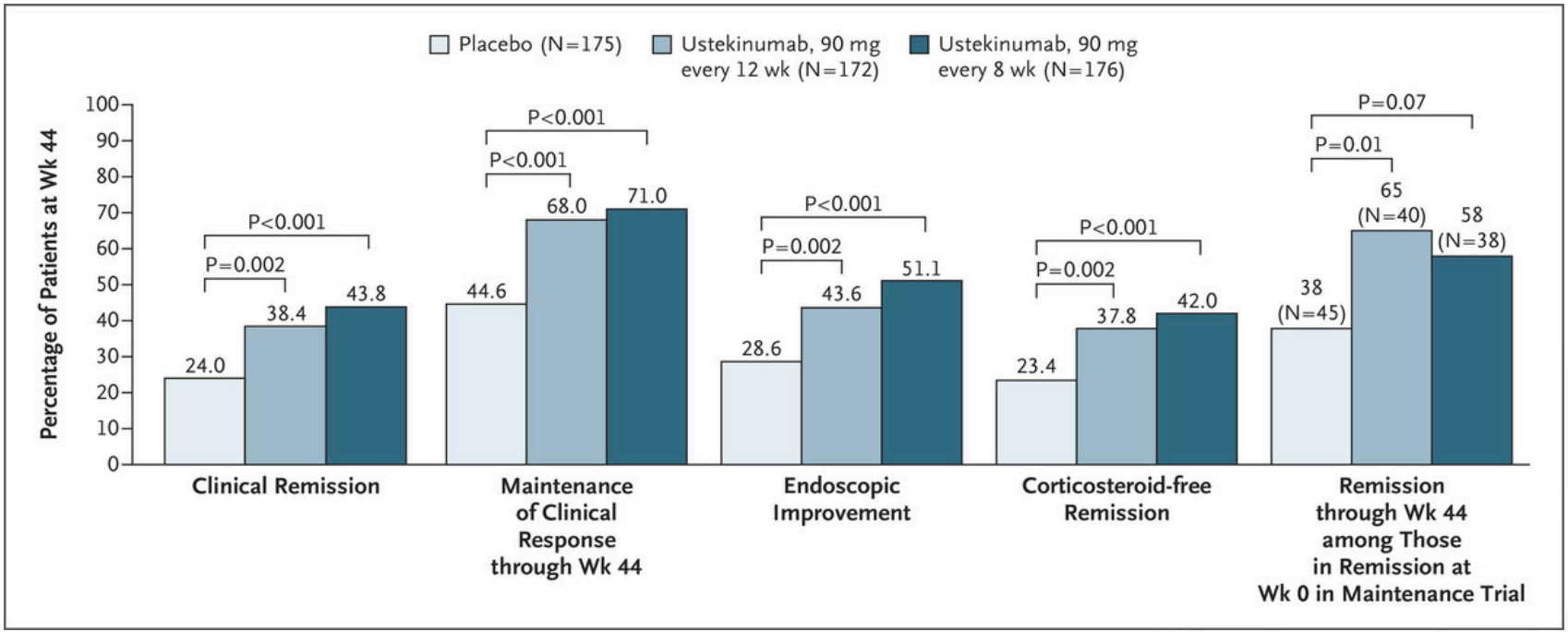
- UNITI maintenance: Week 44





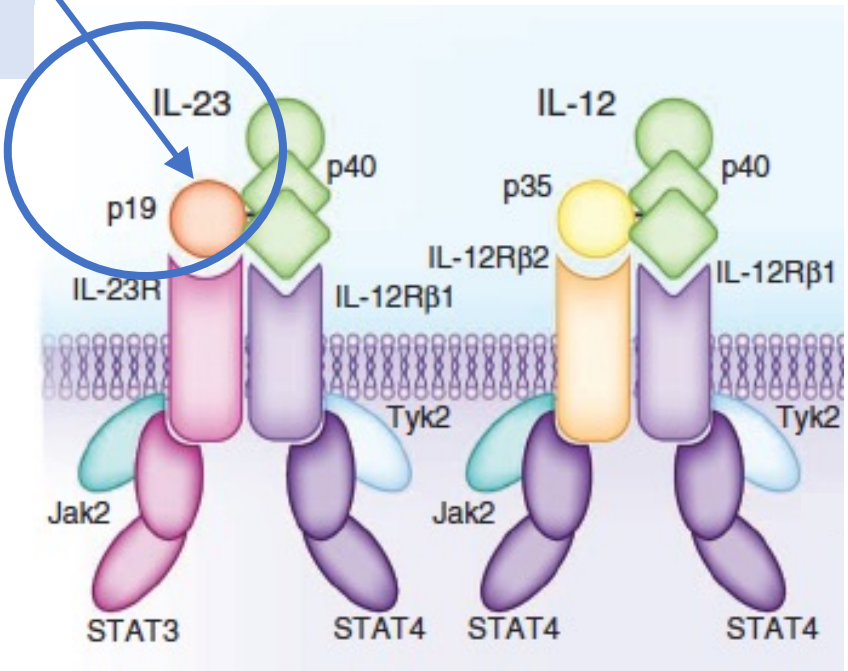
Feagan BG, et al. *N Engl J Med*. 2016;375(20):1946-1960.

Ustekinumab for Ulcerative Colitis



Sands BE, et al. *N Engl J Med*. 2019;381(13):1201-1214.

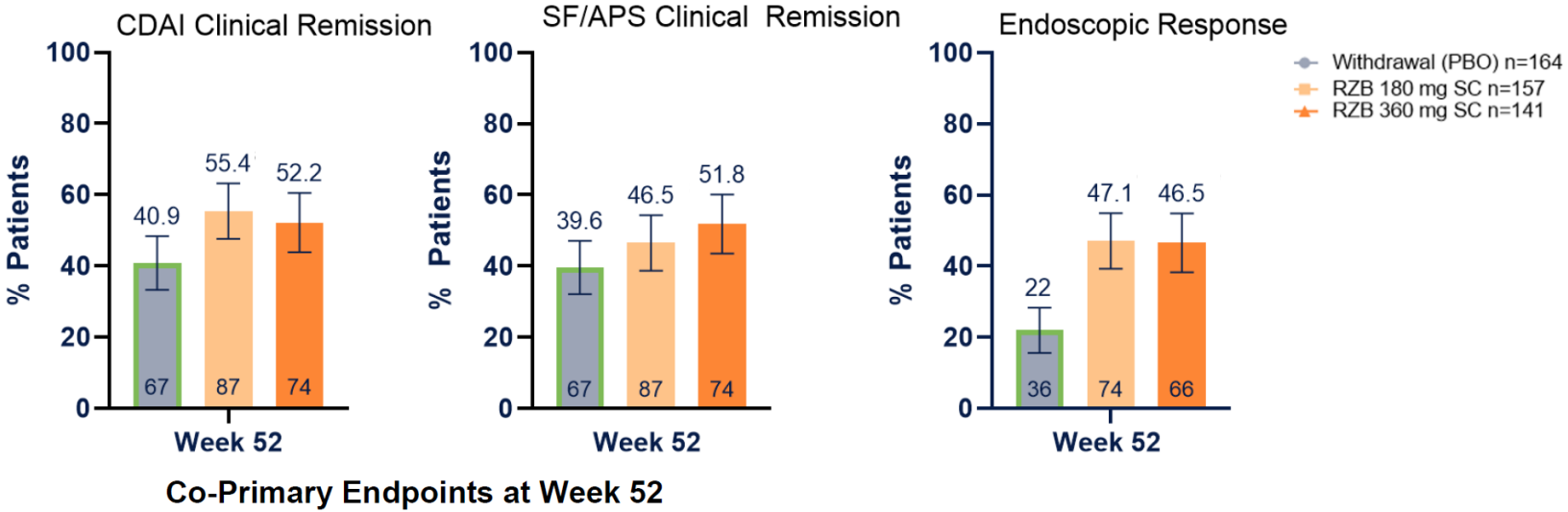
Anti-p19 Antibody
Brazikumab*
Risankizumab
Mirikizumab
Guselkumab*



Adapted from: Teng MW, et al. *Nat Med*. 2015 Jul;21(7):719-29.

Risankizumab: FORTIFY (Maintenance)

Responders: 52-week follow-up



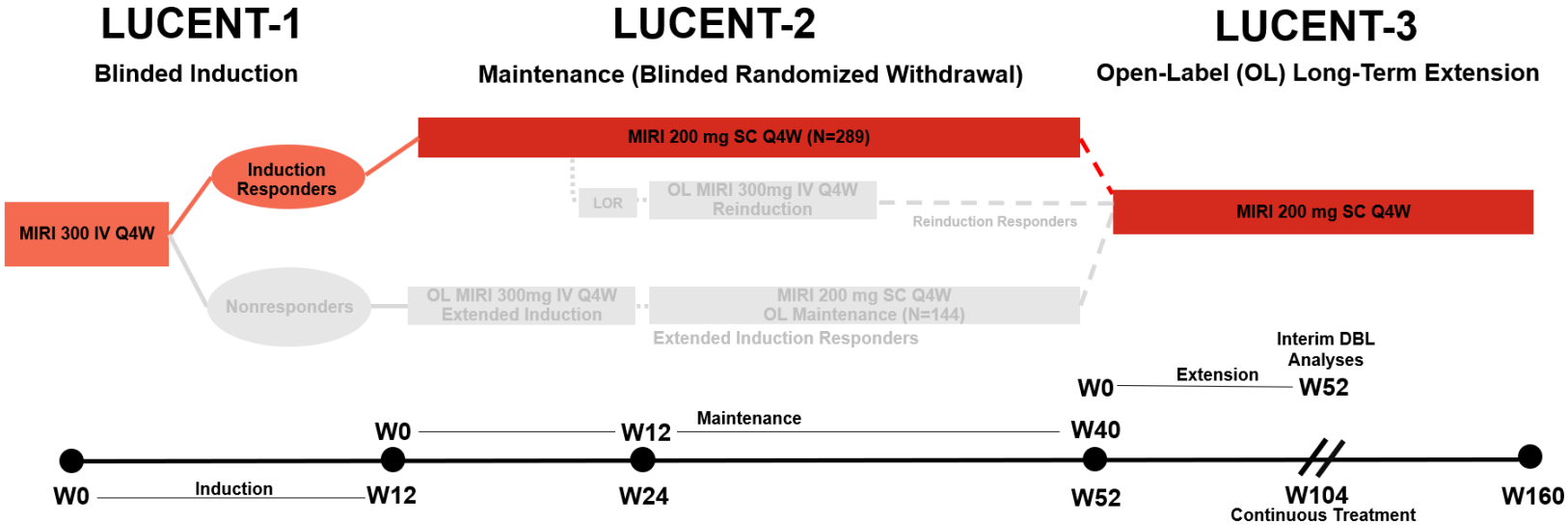
Co-Primary Endpoints at Week 52

No safety signals identified vs placebo

SF = stool frequency; APS = Abdominal Pain Score; RZB = risankizumab.

Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046.

Study Design



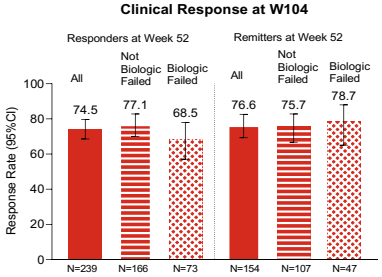
Abbreviations: DBL, data base lock; IV, intravenous; LOR, loss of response; MIRI, mirikizumab; Q4W, every 4 weeks; SC, subcutaneous; W, week.

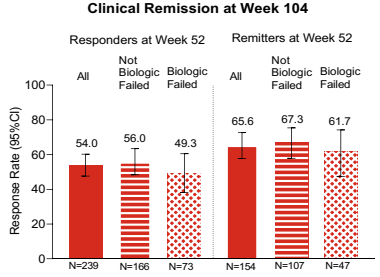
Induction Responders: LUCENT-1 induction W12 mirikizumab responders who stayed on blinded mirikizumab in LUCENT-2 maintenance and continued to LUCENT-3; main analysis cohort. (The investigator could move patients forward into LUCENT-3 even if not meeting responder definition at W40 of the maintenance study LUCENT-2 if they thought the patient would benefit; thus, the induction responder population number is different from the maintenance responder population number.) **Days on study are cumulative**: LUCENT-2 W40 = 52 weeks of continuous treatment; LUCENT-3 W52 = 104 weeks of continuous treatment. **Response:** achieving ≥2-point and ≥30% decrease in the Modified Mayo Score from induction baseline with rectal bleeding score = 0 or 1, or ≥1-point decrease from baseline.

Clinical Trials.gov: NCT03518086, NCT03524092, NCT03519945

LUCENT-3 Response and Remission Rates at 104 Weeks of Continuous Treatment in LUCENT-2 Responders and Remitters by Biologic Failed and Not Failed Treatment Status, NRI

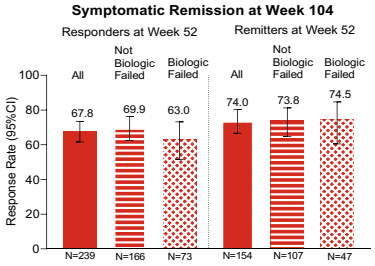
Clinical Response: ≥2-point and ≥30% decrease in MMS from baseline; RB=0 or 1 or,
RB ≥1-point decrease from baseline

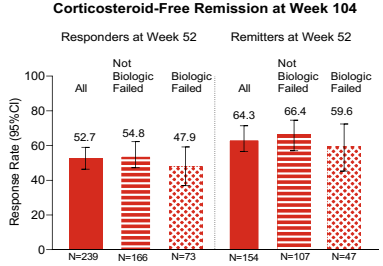




Clinical Remission: SF=0 or 1, with ≥1-point decrease in MMS from baseline; RB=0; and ES=0 or 1 (excluding friability)

Symptomatic Remission: SF=0 or 1, with ≥1-point decrease in MMS from baseline; RB=0



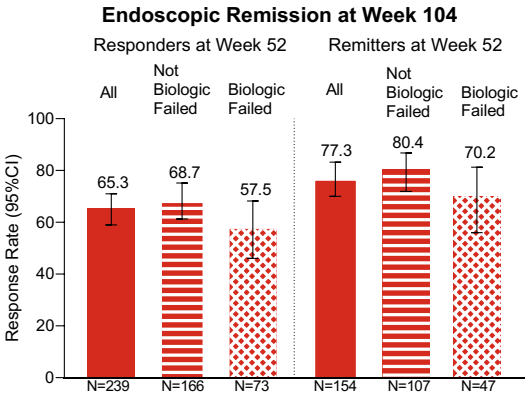


Corticosteroid-free Remission: Clinical remission at LUCENT-3 W52 with no corticosteroid use for ≥12 weeks

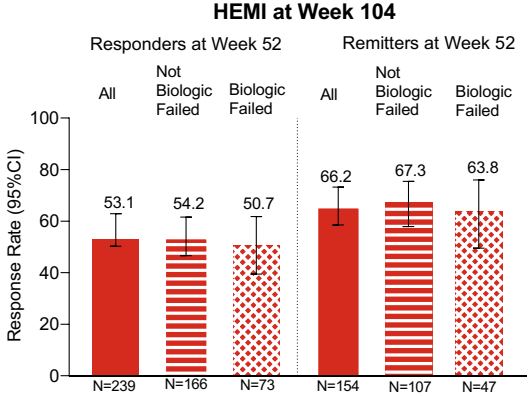
Abbreviations: ES, endoscopic subscore; MMS, modified Mayo score; RB, rectal bleeding score; SF, stool frequency.

Maintenance Responders: Induction responders who were then LUCENT-2 W40 (W52 continuous mirikizumab treatment) clinical responders. **Maintenance Remitters:** Induction responders who were then LUCENT-2 W40 (W52 continuous mirikizumab treatment) clinical remitters. **Not Biologic Failed**: Not biologic failed patients at LUCENT-1 induction baseline; patients not meeting Biologic Failed definition who had failed a conventional therapy such as immunomodulators or corticosteroids. **Biologic Failed**: Biologic failed patients at LUCENT-1 induction baseline; prior inadequate response, loss of response, or intolerance to biologic therapy or Janus kinase inhibitors (tofacitinib).

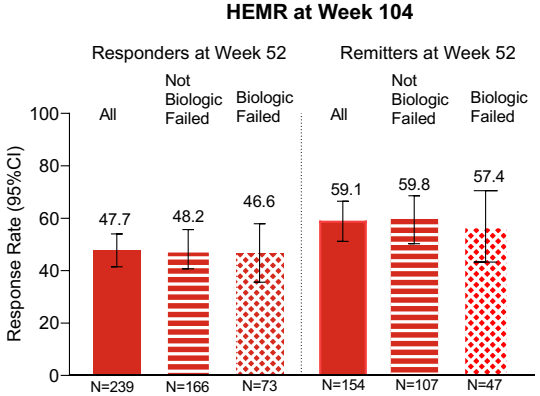
LUCENT-3 Response and Remission Rates at 104 Weeks of Continuous Treatment in LUCENT-2 Responders and Remitters by Biologic Failed and Not Failed Treatment Status, NRI (Continued)



Endoscopic Remission: Endoscopic Subscore (ES)=0 or 1 (excluding friability); score ranges 0 to 4; a lower score indicates less mucosal damage

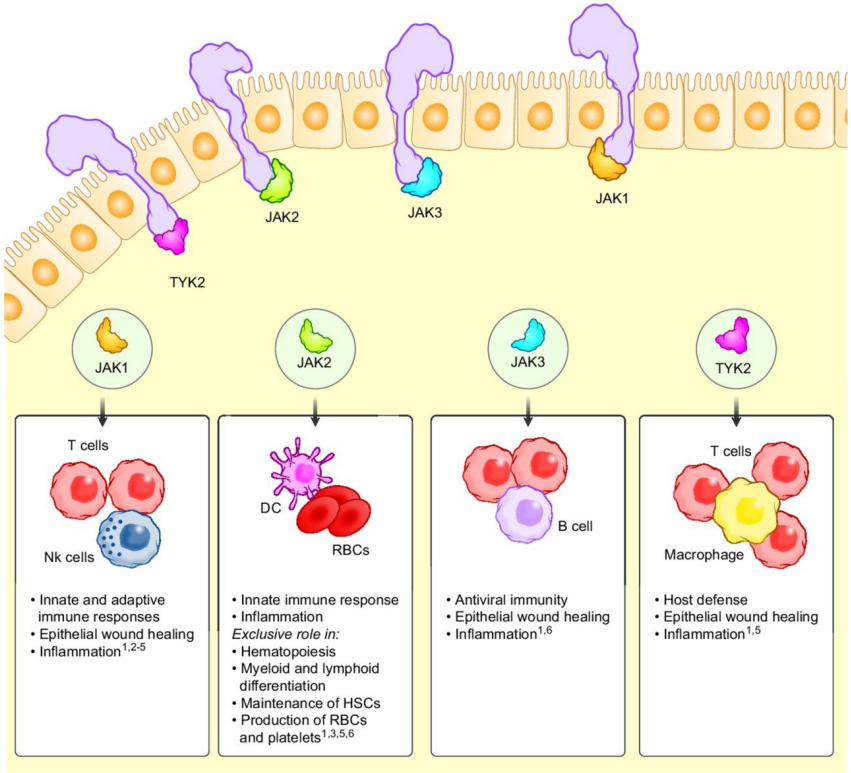


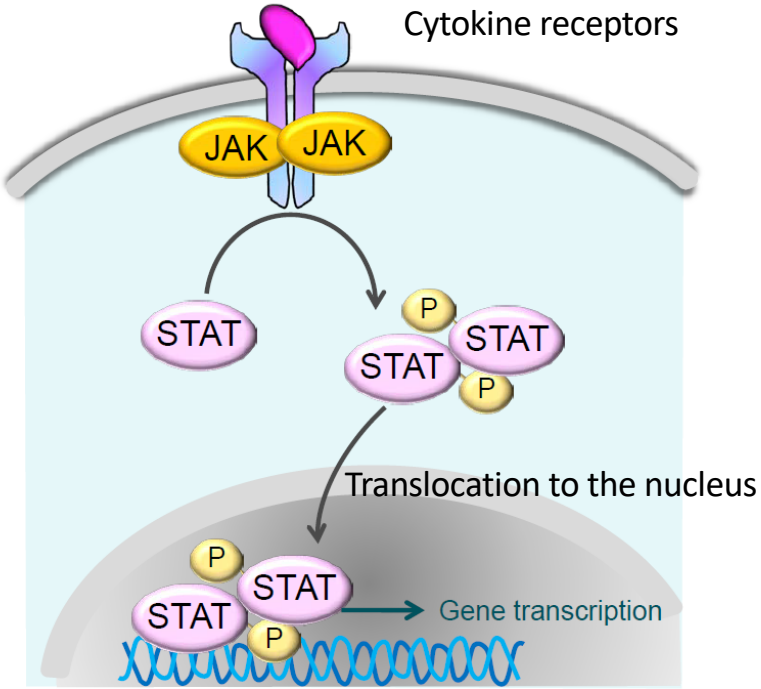
HEMI: histologic-endoscopic mucosal improvement, Geboes≤3.1 + ES=0 or 1 (excluding friability)



HEMR: histologic-endoscopic mucosal remission, Geboes≤2B.0 + ES=0 or 1 (excluding friability)

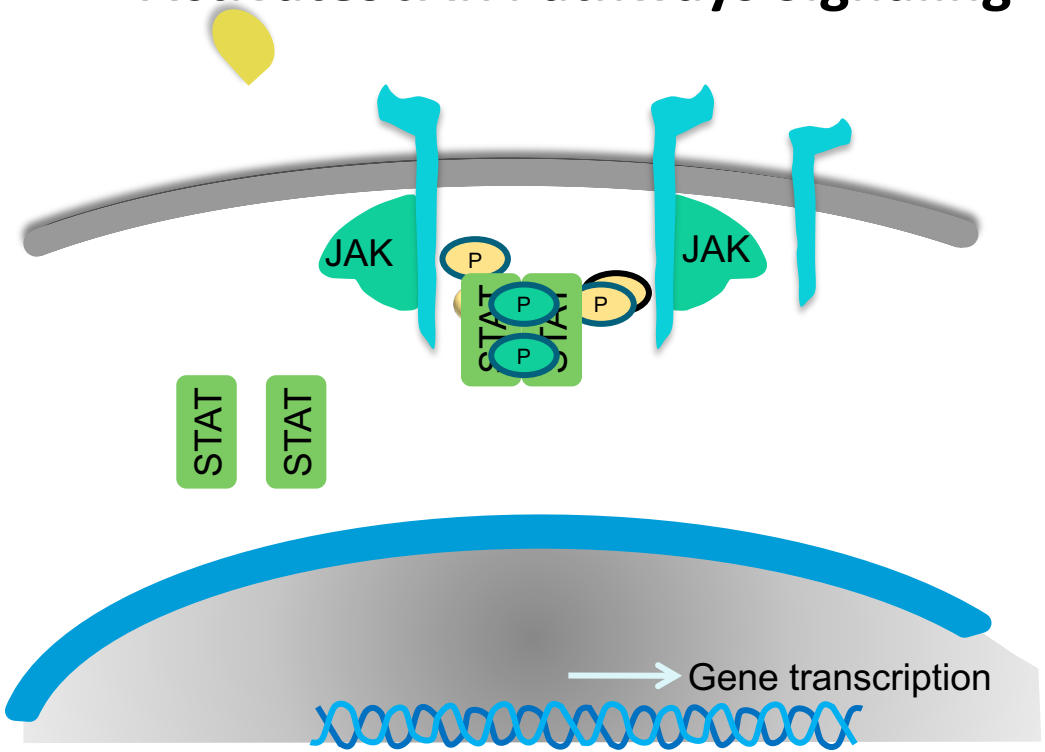
JAK pathways: Tofa Jak1,3 and UPA Jak1





Adapted from Shuai K et al. Nat Rev Immunol 2003; Danese S et al. Gut 2019

Binding of Cytokine Receptors by Cytokines Activates JAK Pathways Signaling



Shuai K, et al. *Nat Rev Immunol.* 2003;3:900-911.

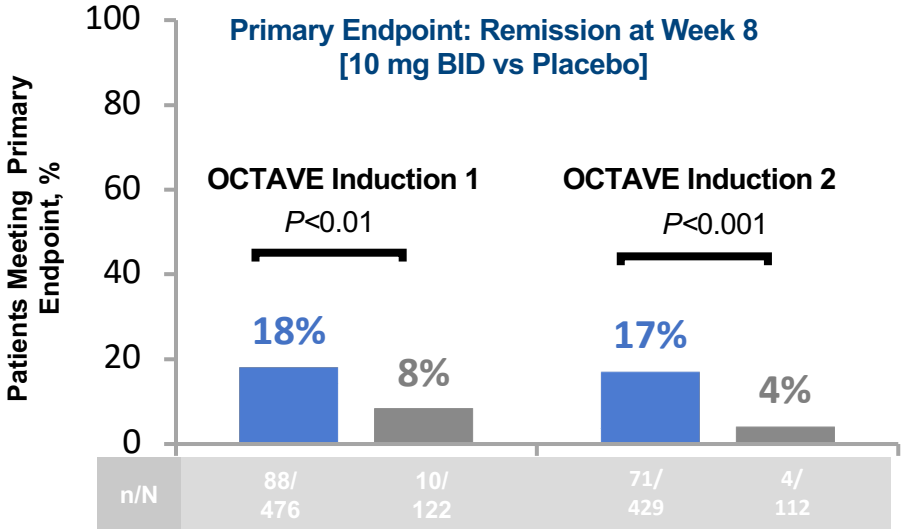
Intracellular Signaling through the JAK/STAT Pathway Is Integral for Many Cytokines

Cytokines that signal through JAK/STAT combinations

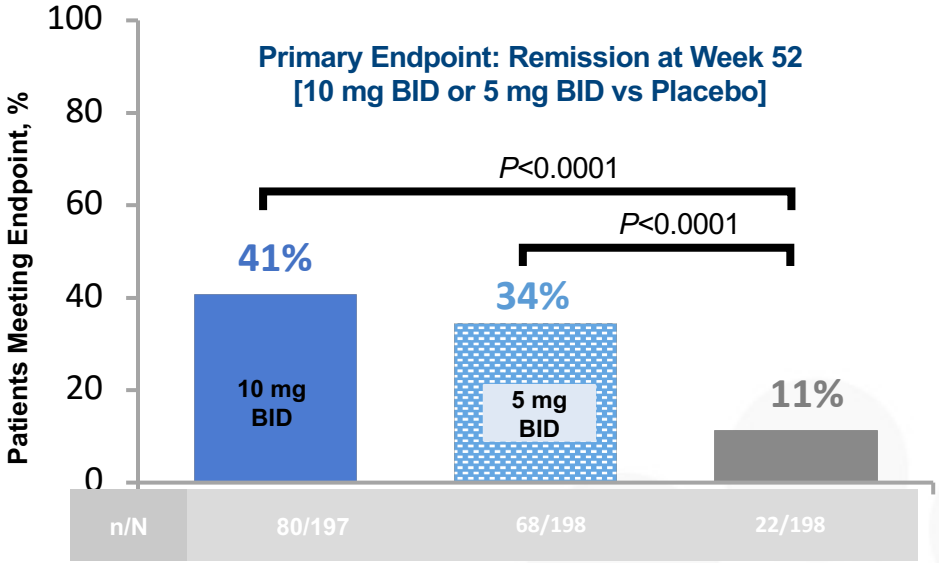
JAKs are involved in lipid metabolism, too

STAT = signal transducer and activator of transcription; IFN = interferon; IL = interleukin; EPO = erythropoietin; TPO = thrombopoietin; GM-CSF = granulocyte-macrophage colony-stimulating factor.

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



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

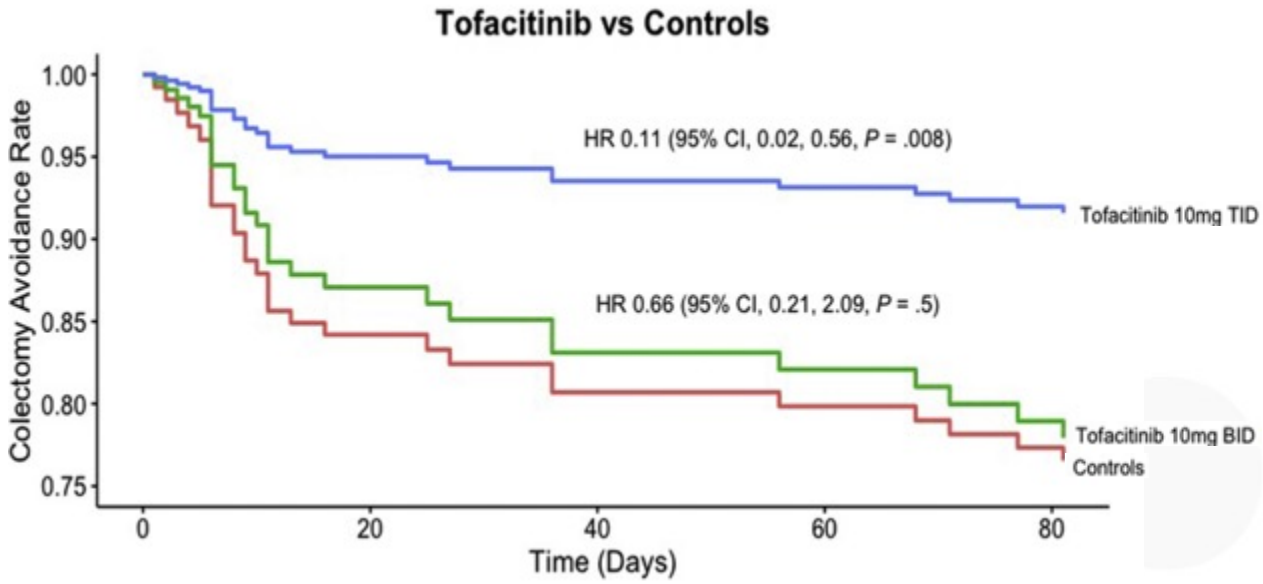


Corticosteroid tapering was required upon entrance to maintenance study for patients receiving corticosteroids at baseline

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

Sandborn WJ, et al. *N Engl J Med*. 2017;376(18):1723-1736.

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



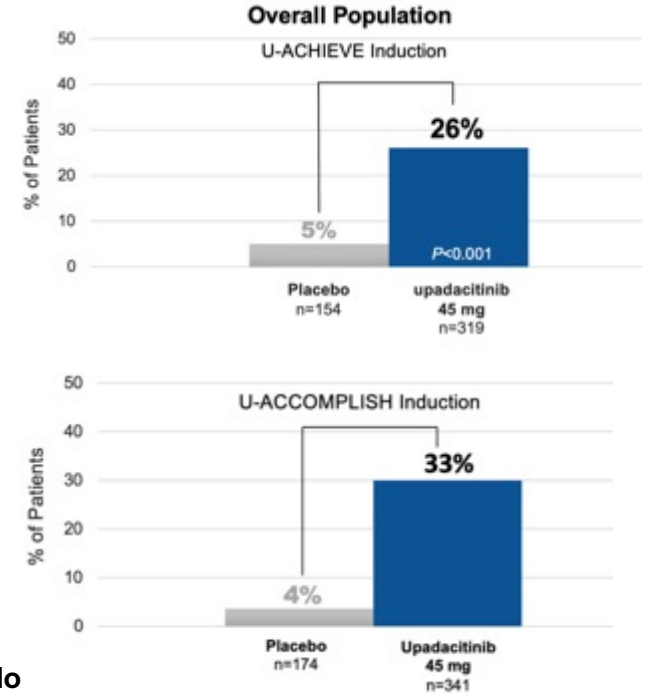
HR = hazard ratio; CI = confidence interval.

Berinstein JA, et al. *Clin Gastroenterol Hepatol*. 2021;19(10):2112-2120.e1.

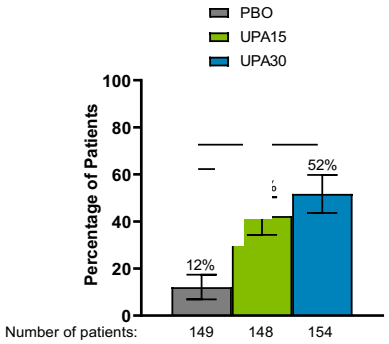
Upadacitinib in Induction and Maintenance in Patients with UC

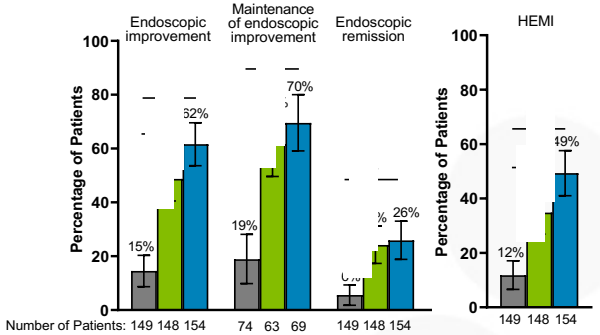
Induction Clinical Remission at Week 8

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



Maintenance Primary Endpoint: Clinical Remission at Week 52



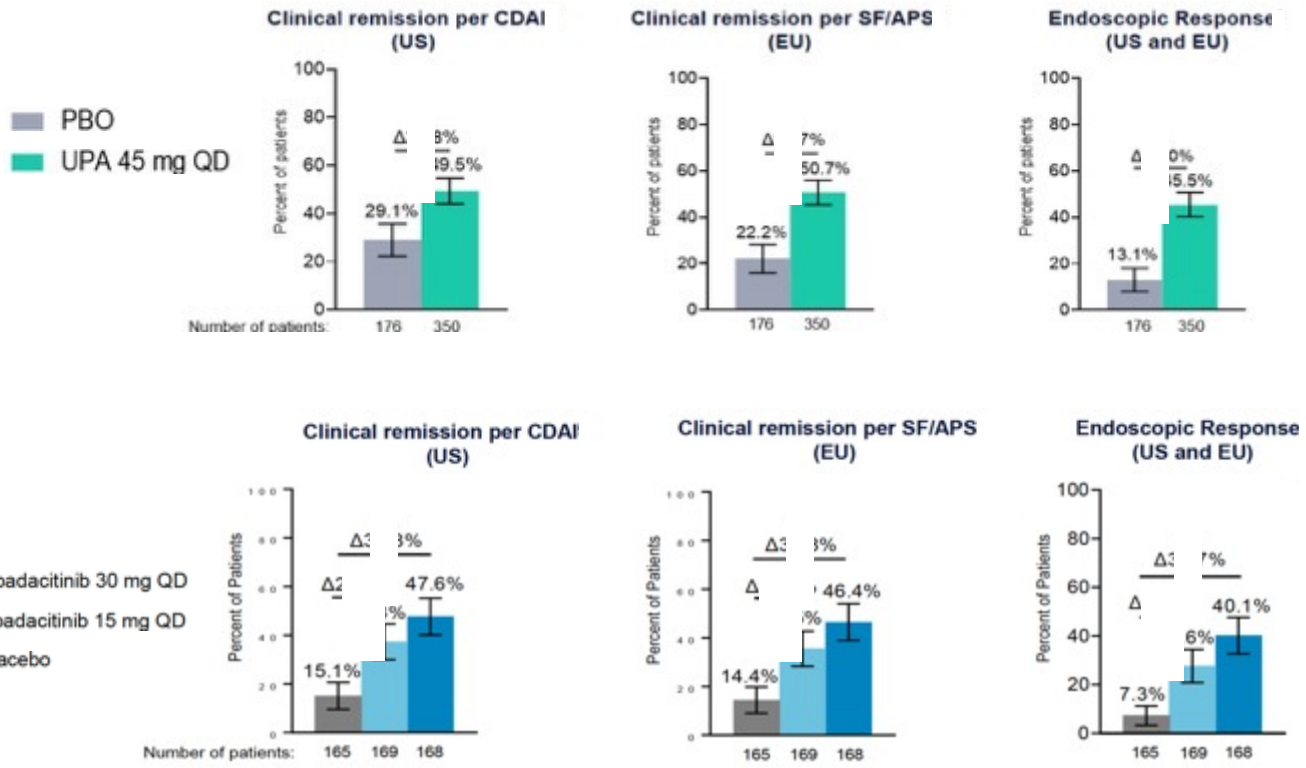


HEMI = histolo

Secondary Endpoints: Endoscopy and Histology

Danese S, et al. *Lancet*. 2022;399(10341):2113-2128. Panaccione R, et al. Presented at: United European Gastroenterology Week (UEGW); 2021.

Upadacitinib in Moderate to Severe Crohn's Disease Weeks 12 and 52 (Phase 3)

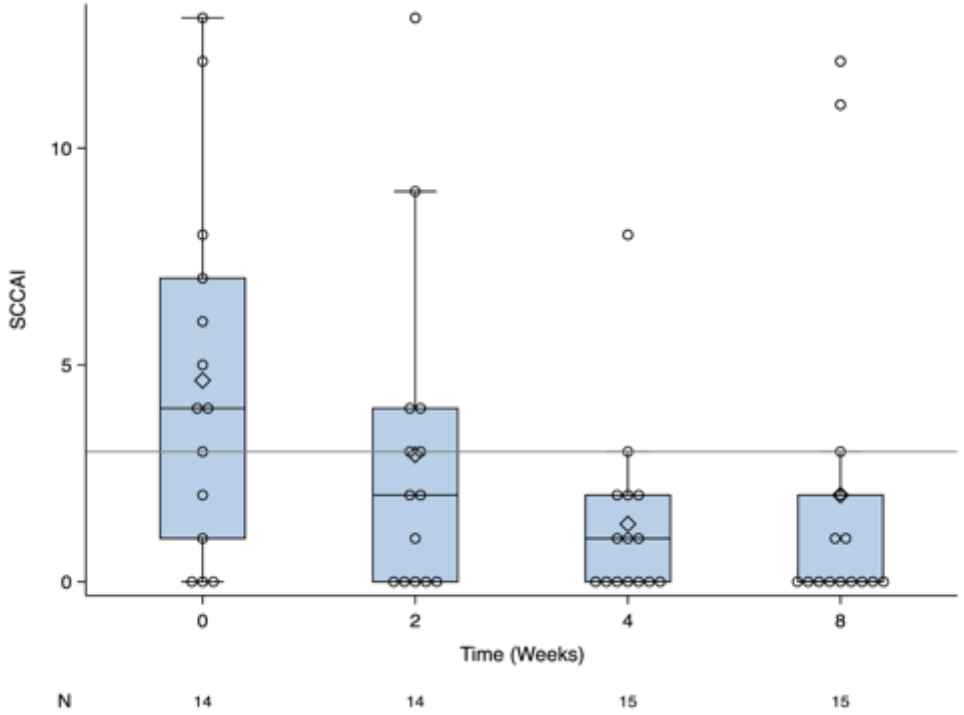


APS = abdominal pain score; CDAI = CD Activity Index.

Loftus EV, et al. *United European Gastroenterol J*. 2022;10(s8). Panes J, et al. *Am J Gastroenterol*. 2022;17(s8).

Upadacitinib Is Effective in Patients Who Have Failed Tofacitinib

SCCAI over Time for Patients with UC Exposed to Tofacitinib

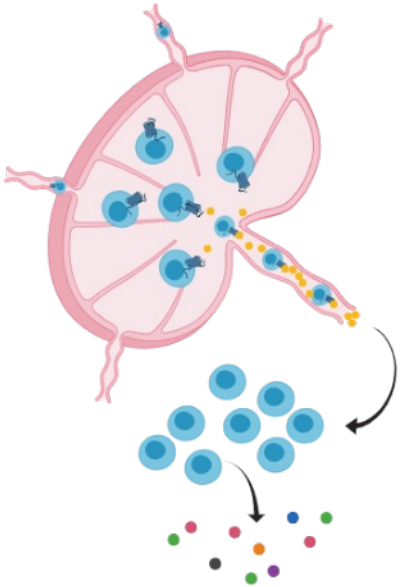


Friedberg S, et al. *Clin Gastroenterol Hepatol*. 2023 [Epub ahead of print].

$S1P_1$ Modulation Selectively Reduces Migration of Lymphocytes From Lymph Nodes

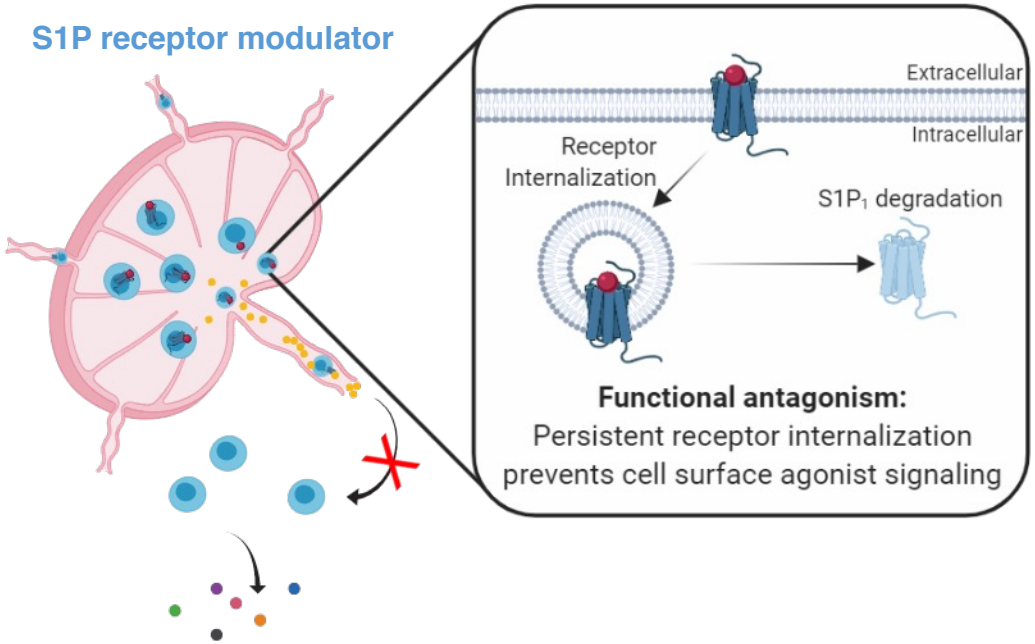
Lymphocyte | $S1P_1$ | S1P | Cytokine | S1P Receptor Modulator

No S1P receptor modulator



- Circulating lymphocytes exit lymph nodes ➔ tissues ➔ cause inflammation & tissue damage

S1P receptor modulator



- Reduced egress ➔ fewer circulating lymphocytes ➔ decreased inflammation & tissue damage
- Immune surveillance maintained
- Minimal effect on circulating effector memory T cells & NK cells

1. Peyrin-Biroulet L, et al. *Automimmune Rev*. 2017;16:495-503; 2.Olivera P, et al. *Gut*. 2017;66(2):199-209

S1P Receptor Modulator Mechanism of Action

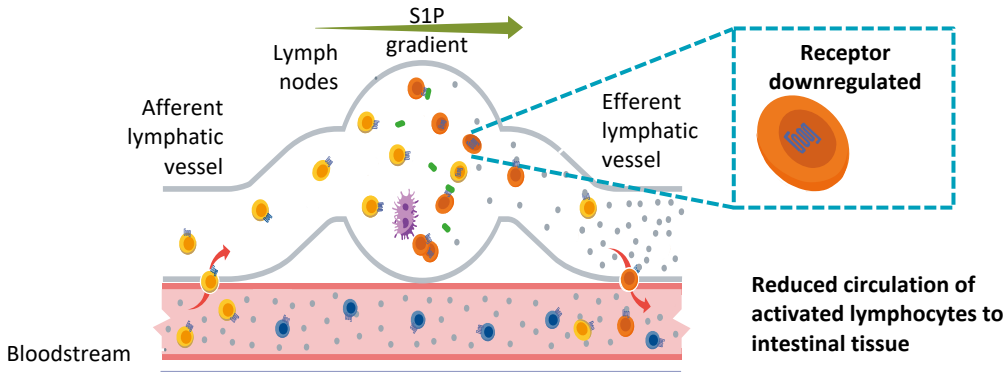
1. Lymphocytes exit lymphoid tissue

2. Migrate to sites of inflammation in response to signalling cues

3. Enter tissue and perpetuate inflammation

S1P Receptor Modulator

Possible direct effects on gut tissue and inflammation



Lymphocytes providing immune surveillance

Lymphocytes trafficking through lymphoid tissue

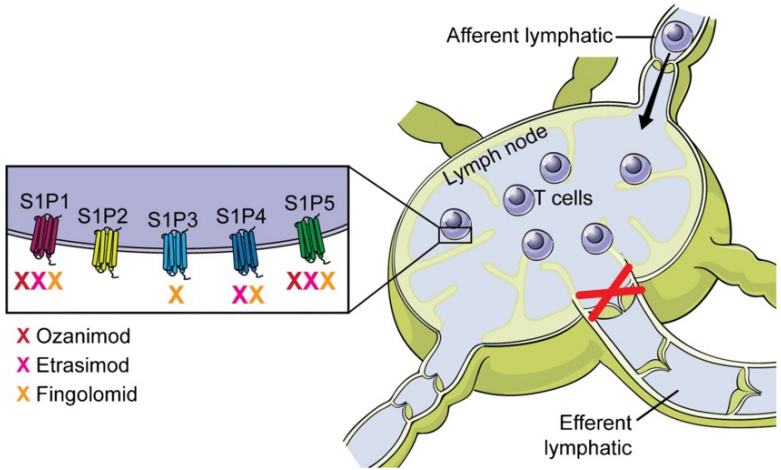
Activated lymphocytes

Antigen-presenting cell

$S1P_1$ receptor

S1P

NK = natural killer.



- Cells involved in immune surveillance (eg, monocytes and NK cells) are not negatively affected and continue to circulate.[3]

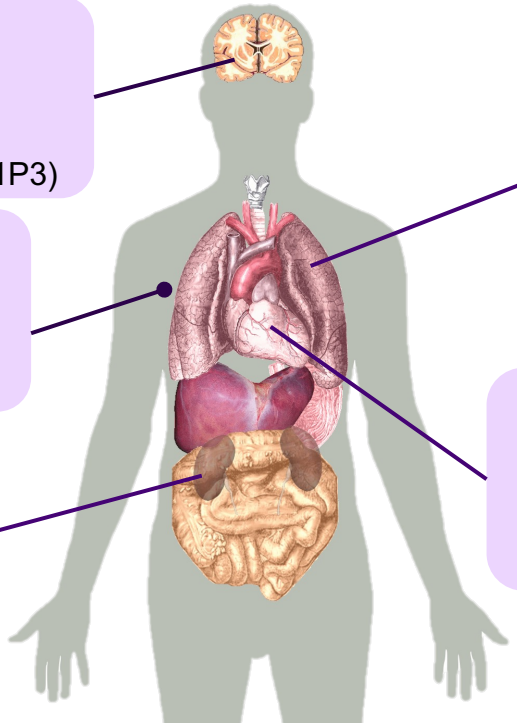
1. Scott FL, et al. *Br J Pharmacol*. 2016;173(11):1778-1792.
2. Danese S, et al. *J Crohns Colitis.* 2018;12(suppl_2):S678-S686.
3. Harris S et al. *Neurol Neuroimunol Neuroinflamm*. 2020;7(5):e839.

Sphingosine 1-Phosphate Receptors: $S1P_{1-5}$ OZA S1P1,5 and ETRA S1P1,4,5

Brain vasculature
- Endothelial permeability (S1P1)
- Transcellular transport (S1P1 and/or S1P3)
- Hearing and balance (S1P2 and/or S1P3)

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

Kidneys
- Vascular leakage (S1P1)
- Inflammation (S1P1)

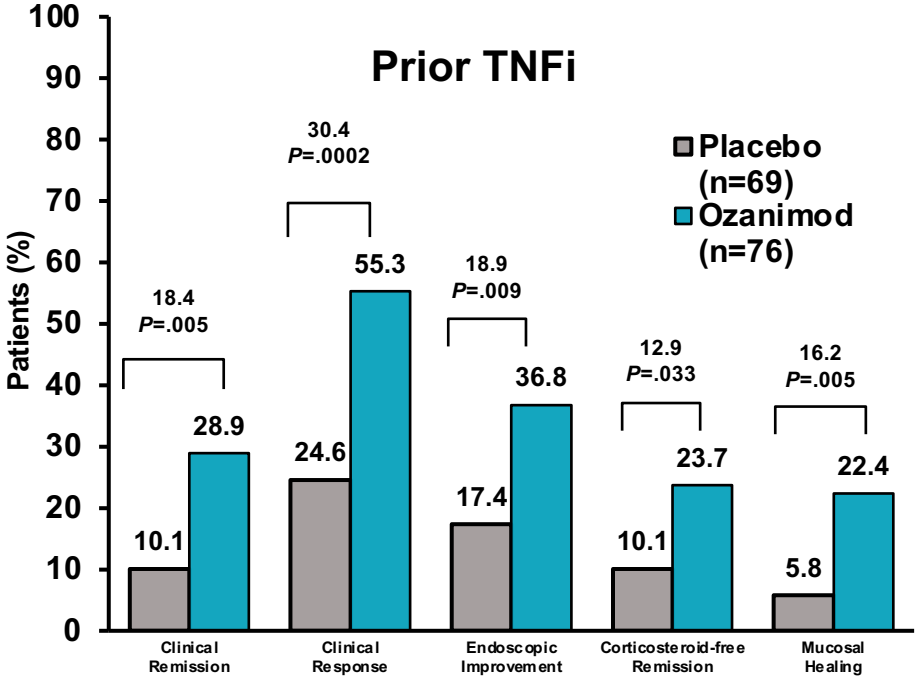


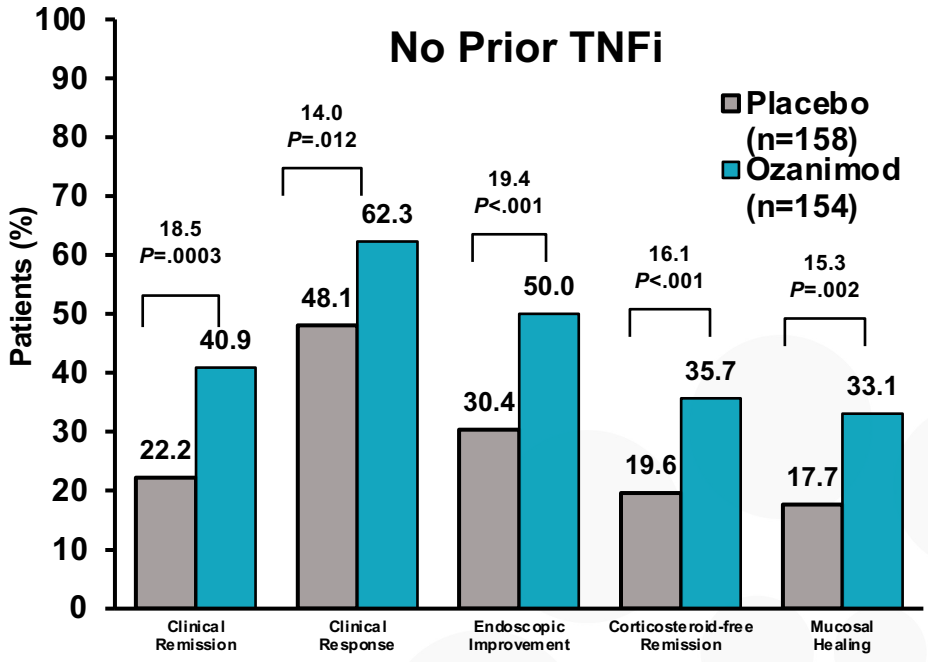
Lungs
- Leakage (S1P1 and/or S1P3)
- Inflammation (S1P1 and/or S1P2 and/or S1P3)
- Airway hyper-responsiveness (multiple S1P receptors)

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

Adapted from Marsolais D, et al. *Nat Rev Drug Discov*. 2009;8(4):297-307. Rivera J, et al. *Nat Rev Immunol*. 2008;8(10):753-763.

Efficacy of Ozanimod in Moderate to Severe UC by Prior TNF Inhibitor Use at Week 52





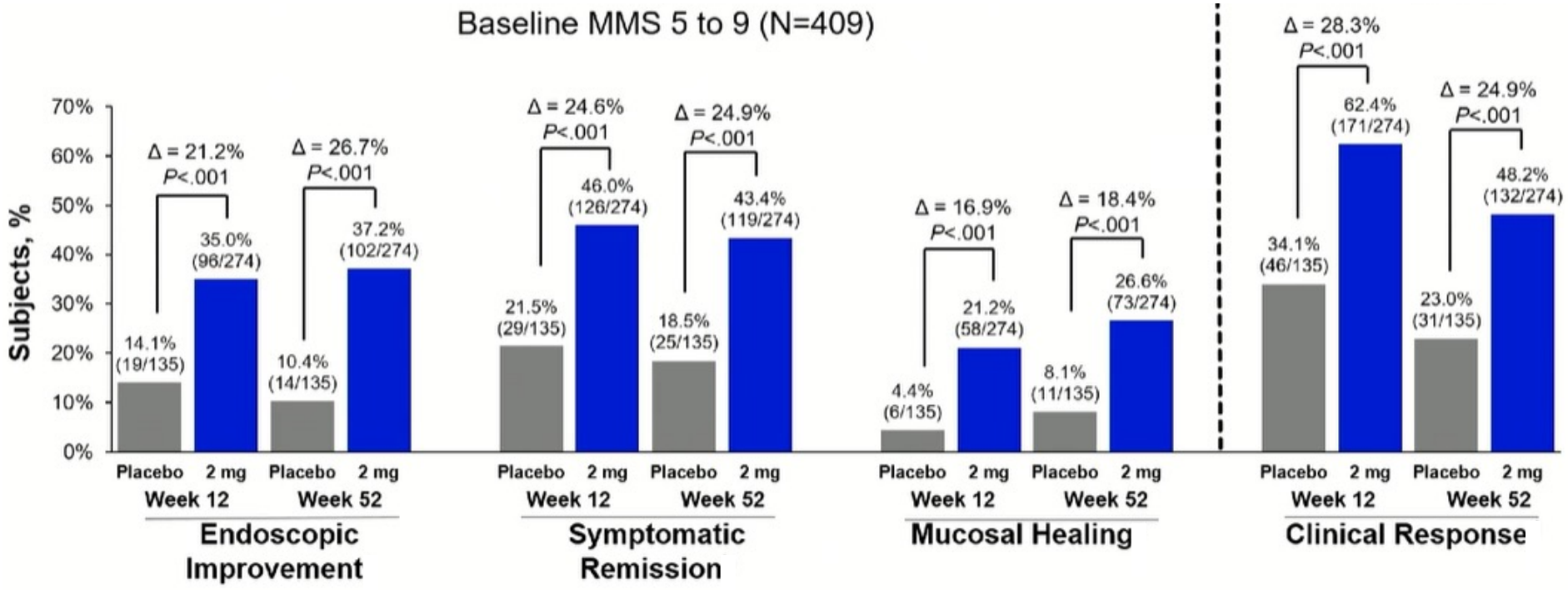
Sandborn WJ, et al. *N Engl J Med*. 2021;385(14):1280-1291.

Ozanimod Users' Guide (Oral $S1PR_{1\&5}$ Modulator)

Baseline Assessment	Test	Specific Advice
Cardiac	ECG, blood pressure Check drug history for medications that may slow heart rate or AV conduction	Cardiac contraindications: MI unstable angina, class III or IV heart failure or admission for decompensated heart failure <6 month, Mobitz type II 2nd degree or 3rd degree AV block, sick sinus syndrome, SA block or significant QTc prolongation (unless functioning PPM)
Full blood count	Lymphocyte count	Patients with counts <0.8x10⁹/L excluded from True North Mean 50% reduction in total lymphocyte count after initiation
Liver function tests	AST, ALT, bilirubin	5% patients develop transaminitis >3x ULN
Ophthalmic assessment	Fundoscopy	Required in patients with history of diabetes, uveitis or macular oedema
Virology and TB	Standard virology screen including VZV serology TB IGRA	Consider vaccination if VZV IgG- (live vaccines require administration 1 month prior to initiation) Herpes zoster – commonest opportunistic infection
Other contraindications	TIA or stroke <6 months, severe untreated sleep apnea, monoaminoxidase inhibitor use	
Dosing Titrating	Titrate once daily dose to maintenance dose at one week: 0.25mg days 1-4, 0.5mg days 5-7, then 1mg OD	

Ozanimod [prescribing Information]

ELEVATE UC: Phase III RCT – Etrasimod



RCT = randomized controlled trial; MMS = modified Mayo score.
Sandborn WJ, et al. Presented at: DDW; May 21-24, 2022; San Diego, CA & Virtual. 968a.

Drug class		Ulcerative Colitis	Crohn's disease
Anti-tumor necrosis factor			
• Biosimilar has equal efficacy and safety • Same assays for TDM	Infliximab : Remicade infliximab-dyyb: Inflectra infliximab-abda: Renflexis infliximab-qbtx: Ixifi Infliximab-axxq: Avsola	X	X
	Adalimumab: Humira Adalimumab-atto:Amjevita Adalimumab:Cyltezo	X	X
	Golimumab	X	
	Certolizumab Pegol		X
Anti-Integrin inhibitors			
	Natalizumab		X
	Vedolizumab	X	X
Interleukin antagonists (IL-12/23 inhibitors)			
	Ustekinumab Rizankinumab Mirikizumab	**X** **X**	X X

How Do We Put Together the Puzzle of Therapy Selection?

DRUG

Efficacy

Indication
Rapidity of onset
Durability
Pharmacokinetics/TDM
Combination vs monotherapy
Positioning and sequence

Safety

Infection
Cancer
Specific concerns by agent or mechanism

PATIENT

Individual Characteristics

Age
Comorbidities
Preferences (IV/SQ/PO)
Insurance
Costs
Access to care

Disease Characteristics

CD vs UC
Disease behavior/complication
Disease severity
Early vs late
EIMs
Prior treatment success or failure

TDM = therapeutic drug monitoring; EIMs = extraintestinal manifestations.

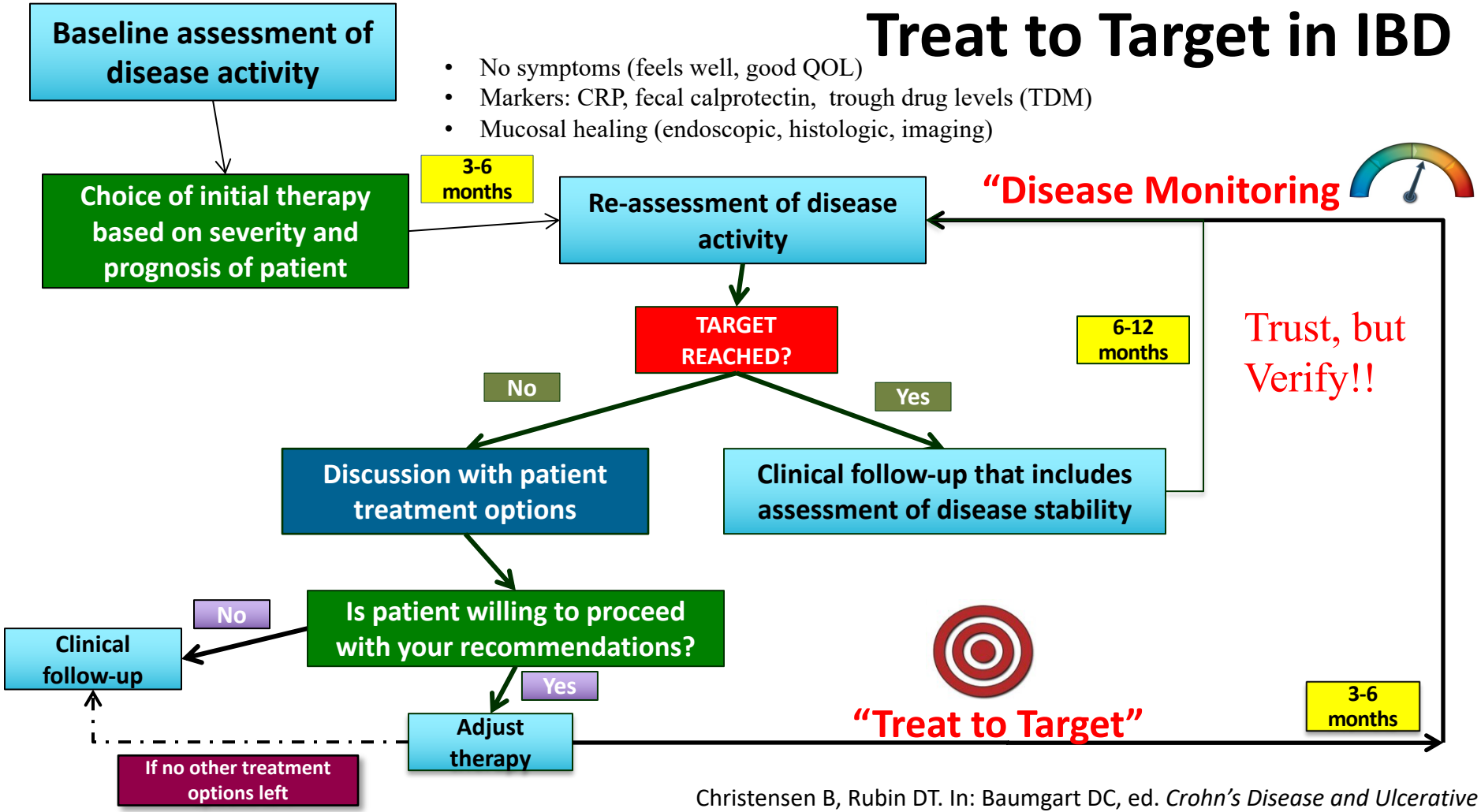
Treat to Target: New England (tampa bay?)

- The only target that counts: Superbowl Win

Current Goals in IBD

- Make the diagnosis quickly and accurately
  - Include elements of prognosis
- Achieve normal bowel function
  - Improve quality of life (PRO's: Patient Reported Outcomes)
- Induce remission rapidly
- Maintain steroid-free remission over time
  - Emphasis on mucosal healing, other biological markers ("deep remission")
- Modify long-term outcomes of the disease
  - Avoid hospitalization and surgery
  - Eliminate disability
  - Minimize exposure to steroids
  - Avoid Narcotics
  - Reduce costs of care
  - Avoid unnecessary CT scans!

Treat to Target in IBD



Christensen B, Rubin DT. In: Baumgart DC, ed. *Crohn's Disease and Ulcerative Colitis*. 2nd ed. Cham, Switzerland: Springer Nature; 2017:267-78.

Treat to Target Studies in Crohn's Disease

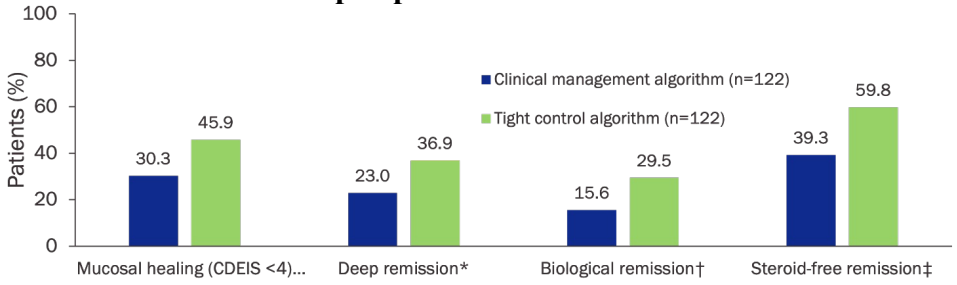
CALM

- Adalimumab +/- azathioprine
- CDAI, prednisone
- CRP, Fecal calprotectin

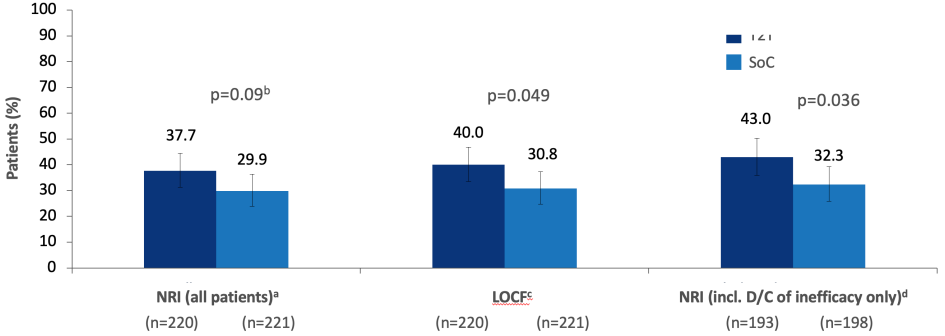
STARDUST

- Ustekinumab
- Endoscopic response

Study endpoints after 48 weeks of escalating adalimumab treatment on the basis of prespecified treatment failure criteria

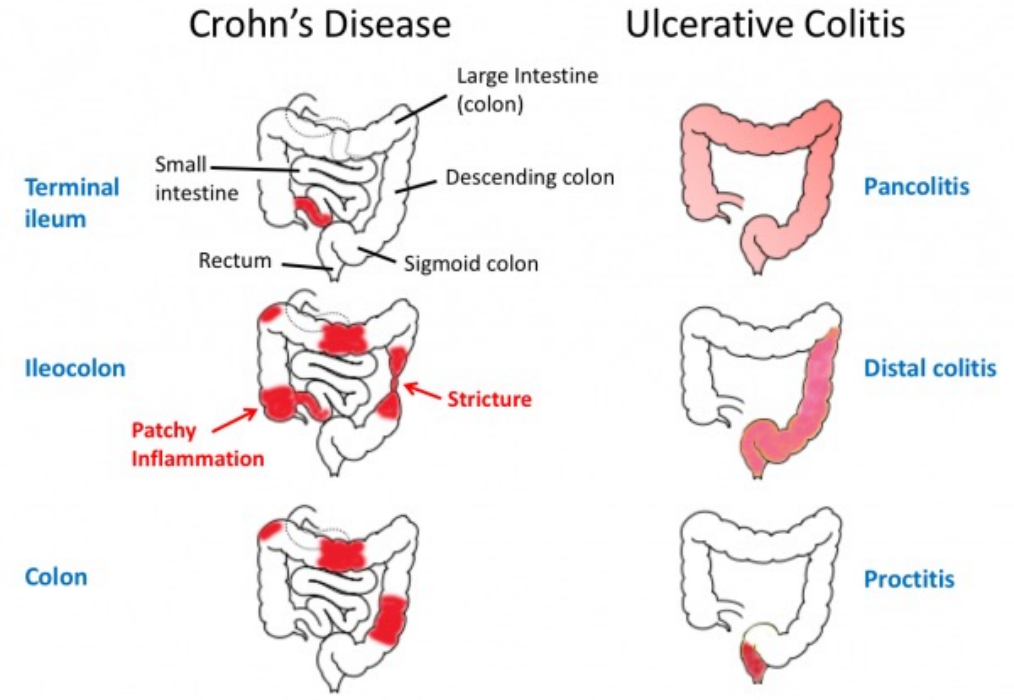


Endoscopic Response (SES-CD Improvement ≥50% [95% CI]) at Week 48 (RAS)



Colombel JF, et al. Lancet. 2018;390:2779-2789.
Danese S, et al. UEG Week Virtual 2020. 2020;LB11.

Classifying Inflammatory Bowel Disease: Montreal Classification



Classifying Inflammatory Bowel Disease: Montreal Classification

Crohn's

Age of onset	Location	Behaviour
≤16 years (A1)	Ileal (L1)	Non-stricturing, Non-penetrating (B1)
17—40 years (A2)	Colonic (L2)	Stricturing (B2)
>40 years (A3)	Ileo-colonic (L3)	Penetrating (B3)
	*Isolated upper GI disease (L4)	+ 'p' if peri-anal disease

*L4 is a modifier that can be added to L1 — 3 when concomitant upper gastrointestinal (GI) disease is present.

Ulcerative Colitis

Maximal extent of inflammation observed at colonoscopy	
Proctitis	E1
Left-sided — extending up to splenic flexure	E2
More extensive disease	E3

Is the diagnosis of IBD secure? GI trained pathologist, review the initial presentation and data that led to diagnosis if first time seeing pt

Silverberg MS, et al. *Can J Gastroenterol.* 2005;19(suppl A):5A-36A.

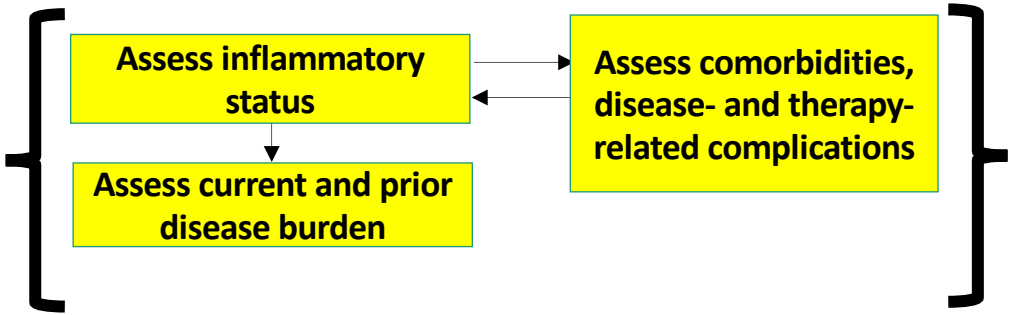
ACG UC Activity Index

	Remission	Mild	Moderate-Severe	Fulminant
Stools (#/day)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (µg/g)	<150-200	>150-200	>150-200	>150-200
Endoscopy (Mayo subscore)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8

Modified from Truelove SC, Witts LJ. *Br Med J.* 1955;2:1041-8.

Crohn's Disease: Diagnosis and Risk Stratification Are Used to Guide Treatment

- Location
- Extent
- Severity
- EIMs

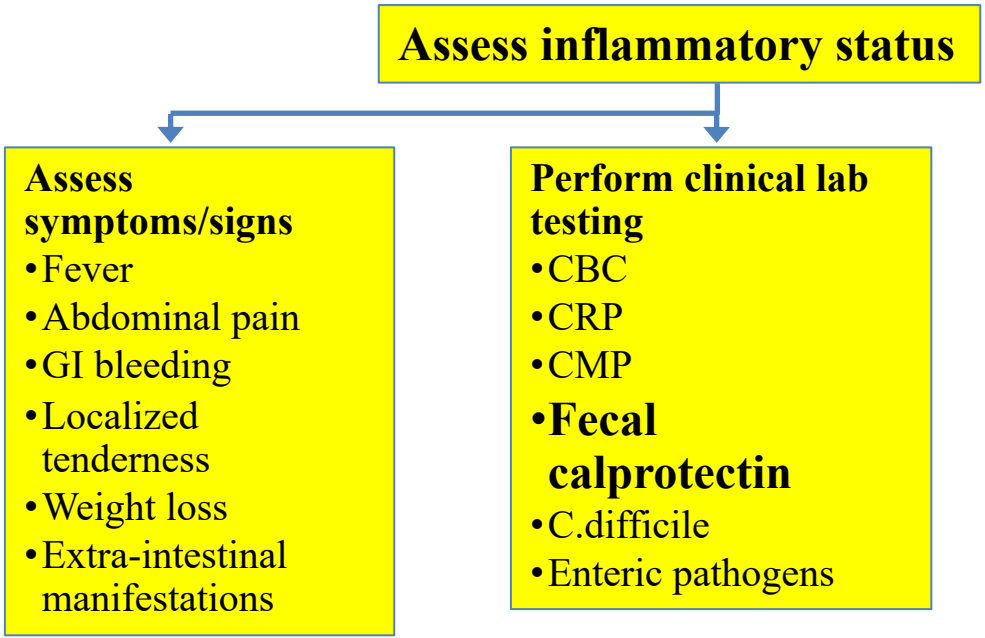


- Infections
- Strictures
- Surgical hx
- Adverse rxns
- Fistulas

ACG 2018 statement: **IBD type, location, and disease activity should be documented in the medical record**.

ACG Clinical Guidelines: Management of Crohn's disease in adults. Am J Gastroenterol.2018;113:481-517.
Sandborn WJ. *Gastroenterology*. 2014;147(3):702-705.

Diagnosing Crohn's Disease: Assessing Inflammatory Status



ACG 2018 guideline: Fecal calprotectin → differentiate IBD vs IBS

ACG 2018 statement: IBD serologies, IBD genetics *NOT* indicated

ACG Clinical Guidelines: Management of Crohn's disease in adults. Am J Gastroenterol.2018;113:481-517Sandborn WJ. *Gastroenterology*. 2014;147(3):702-705.

Prognosis and Assessing Disease Severity in IBD

Ulcerative Colitis

Low Risk for Colectomy

- Limited anatomic extent
- Mild endoscopic disease

High Risk for Colectomy

- Extensive colitis
- Deep ulcers
- Age <40
- High CRP and ESR
- Steroid-requiring disease
- History of hospitalization
- *C. difficile* infection
- CMV infection

Crohn's Disease

Low Risk

- Age at initial diagnosis > 30 years
- Limited anatomic involvement
- No perianal and/or severe rectal disease
- Superficial ulcers
- No prior surgical resection
- No stricturing and/or penetrating behavior

Moderate/High Risk

- Age at initial diagnosis < 30 years
- Extensive anatomic involvement
- Perianal and/or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Stricturing and/or penetrating behavior

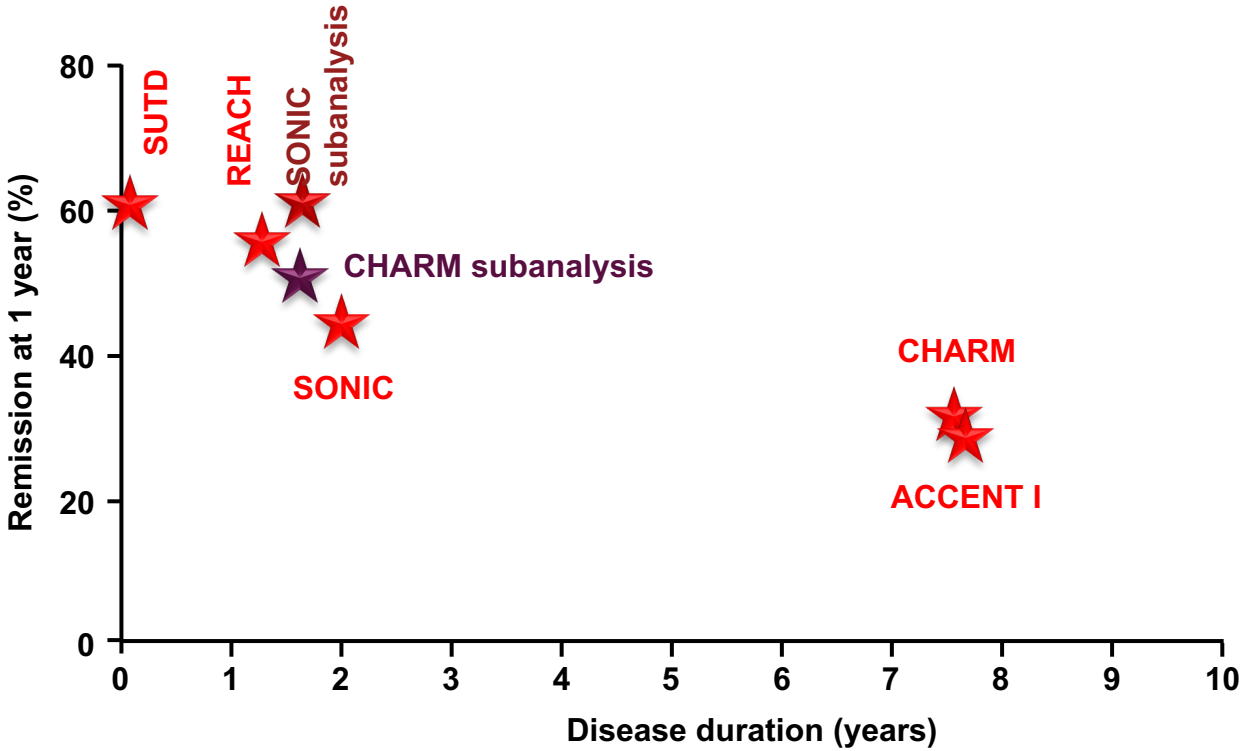
Other Considerations for Clinically At-Risk IBD

- Overlapping immune conditions (spondyloarthropathies, skin manifestations, PSC)
- Mental health disorders
- Disability
- Cumulative burden of inflammation

Implications for early treatment and aggressive monitoring

Lichtenstein GR, et al. Am J Gastroenterol. 2018;113(4):481-517.
Sandborn WJ. *Gastroenterology*. 2014;147(3):702-703.
Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413.
Dassopoulos T, et al. *Gastroenterology*. 2015;149(1):238-45.
Szigethy E, et al. Clin Gastroenterol Hepatol. 2017 Jul;15(7):986-997.

Anti-TNF therapy is most effective in early disease

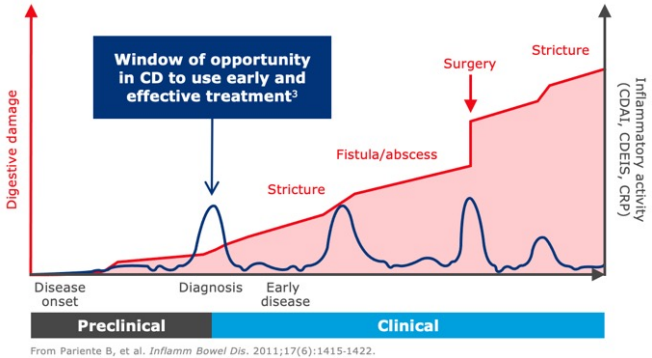


Hyams J et al. Gastroenterology 2007; Colombel JF et al. N Engl Med J. 2010; Hanauer SB et al. Lancet. 2002; Colombel JF et al. Gastroenterology. 2007; Colombel JF et al. Aliment Pharmacol Ther. 2015

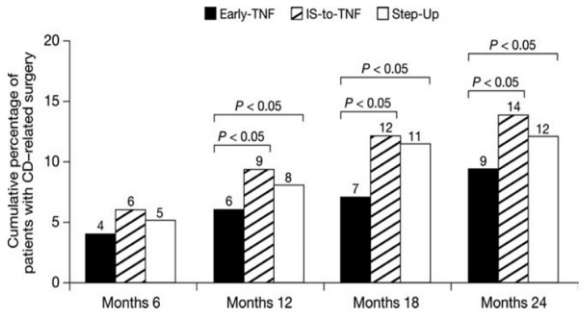
ACCENT, **A Crohn's Disease Clinical Trial Evaluating Infliximab;** SUTD, Step-Up Top-Down; Study of Biologic and Immunomodulator Naive Patients in Crohn Disease; TNF, tumor necrosis factor

Optimizing Response to Biologics in Crohn's Disease

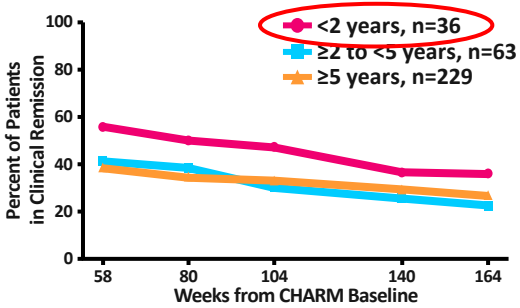
- **CD patients with shorter disease duration treated with anti-TNF:**
  - **Respond better[1]**
  - **Lose response less often[2]**
  - **Have less surgery[3]**



Early Use of anti-TNF is Associated with Reduced CD Surgery



Clinical remission with adalimumab in ADHERE



[1]Schreiber S, et al. *J Crohns Colitis*. 2013;7(3):213-21.
[2]Schreiber S, et al. *Am J Gastroenterol*. 2010;105(7):1574-82.
[3]Rubin DT, et al. *Inflamm Bowel Dis*. 2012;18(12):2225-2231.

Early Biologic Therapy Reduces Complications in Ulcerative Colitis

Cody Ashcroft[1], Michael Craig[1], Thomas Weiss[2], Robert Byrne[3], Cynthia Theigs[4], Jodi Walker[4], David Dulaney[3], Anish Patel[3]

1. Department of Internal Medicine, Brooke Army Medical Center, San Antonio, TX
2. Uniformed Services University of Health Sciences, Bethesda, MD
3. Department of Gastroenterology, Brooke Army Medical Center, San Antonio, TX
4. AbbVie, North Chicago, IL

-Retrospective cohort of 371 UC patients in the Military Heath System

-Data: military's universal electronic health record January 1, 2013 to December 30, 2020.

-Biologic started within 2yr vs >2 yrs

-Clinical course clinical, biochemical, radiologic, and endoscopic and histologic findings.

-Complications assessed included UC-related emergency room visits, steroid use, hospitalizations, and surgeries.

Table 1: Demographic Data

	<2 (n,%)	>2 (n, %)	P-value
Male	106 (59%)	138 (73%)	0.0042
Race			0.0211
White (non-Hispanic)	32 (18%)	64 (34%)	
White (Hispanic)	49 (27%)	42 (22%)	
Black	41 (23%)	49 (26%)	
Asian	18 (10%)	13 (6.8%)	
Native American	1 (0.5%)	2 (1.0%)	
Pacific Islander	1 (0.5%)	2 (1.0%)	
Unknown or not reported	39 (22%)	18 (9.5%)	
Age of diagnosis	33.4 ± 11.4	30.8 ± 10.6	0.0218
BMI	27.6 ± 5.5	28.1 ± 5.2	0.1555
Thiopurine use	55	98	<.0001

Figure 1: Survival without composite of complications

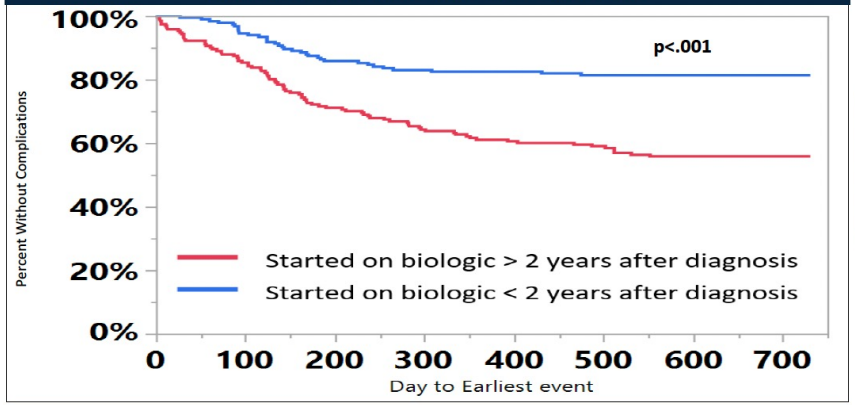


Table 2: Events Compared

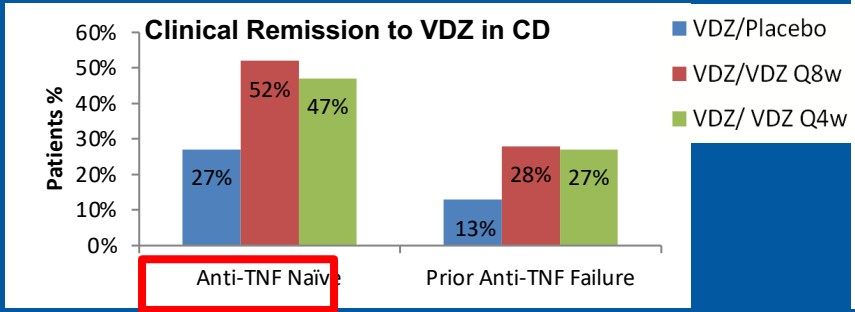
	<2 (n, %)	>2 (n, %)	NNT
Number of patients	181	190	
ER visits	35 (19.3%)	84 (44.2%)	4
Hospitalizations	30 (16.6%)	58 (30.5%)	7.2
Surgery	29 (16.0%)	53 (27.9%)	8.4
Steroid prescriptions	12 (6.62%)	15 (7.89%)	79

We hypothesized that early initiation of biologic therapy would lead to fewer UC-related complications and higher response rates.

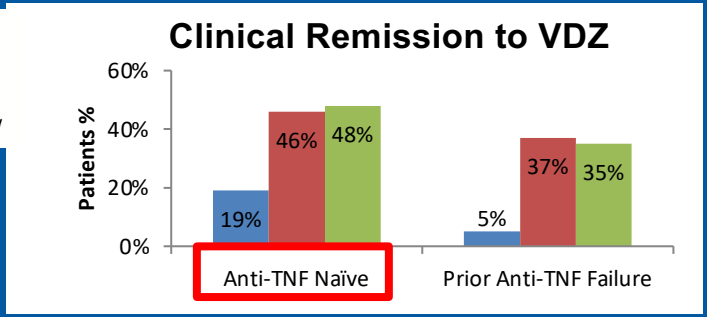
Initiation of biologic therapy within 2 years of diagnosis of UC is associated with an absolute risk reduction of complications of approximately 26%

Anti-TNF Naïve Patients Do Better with Other MOAs

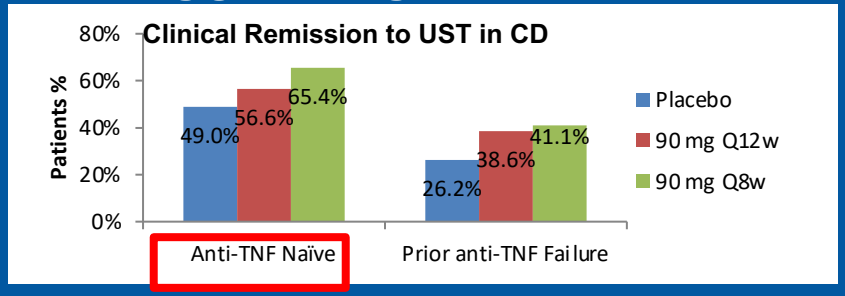
VEDOLIZUMAB



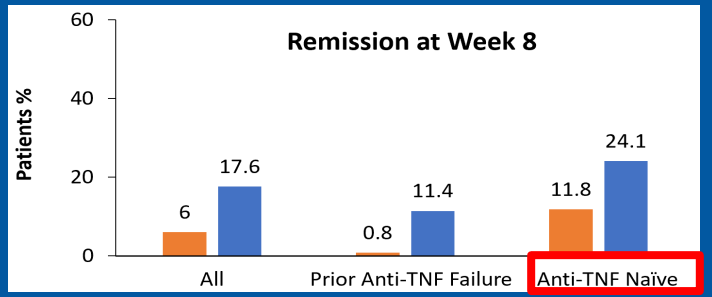
VEDOLIZUMAB



USTEKINUMAB



TOFACITINIB



Sandborn WJ, et al. N Engl J Med. 2013;369:711-721
Feagan BG, et al. N Engl J Med. 2013;369:699-710
Sandborn W, et al. Gastroenterology. 2016;150(4 Suppl 1):S157-S158
Data on file. Pfizer Inc, New York, NY

Principles for all novel therapies

- Biologically experienced group→ lower response
- Biologically naïve group→ higher response

- Seen in previous trials of biologics and small molecule inhibitors
- Important to consider when assessing response/remission/endoscopic healing, etc. in the absence of head to head comparative trials

- Remission at 1 year <50% regardless of agent…

What to Use First?

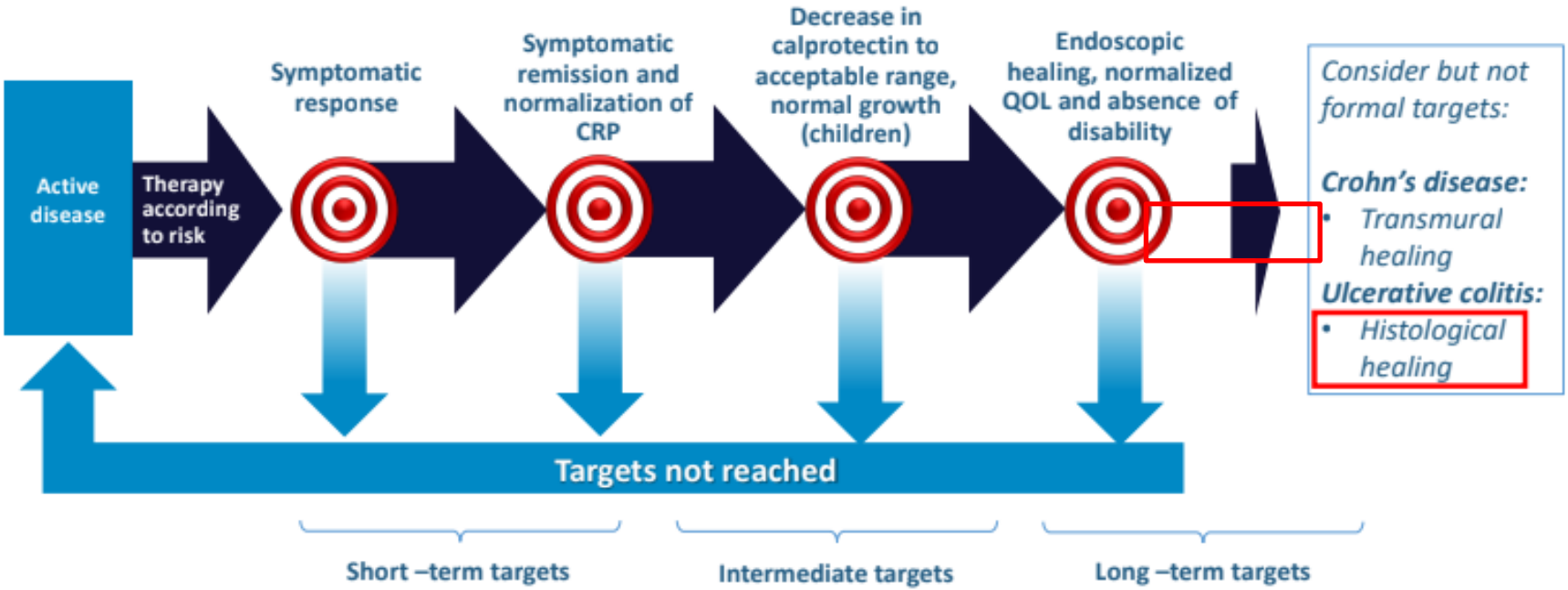
- Patient factors: IV/SQ/PO preference; medical comorbidities; costs; insurance!
- Disease factors: phenotype; surgery
- Activity versus Severity
- Efficacy and Safety
- First drug works best (usually)

ACTIVITY: how sick the patient is NOW

SEVERITY: includes elements of PROGNOSIS

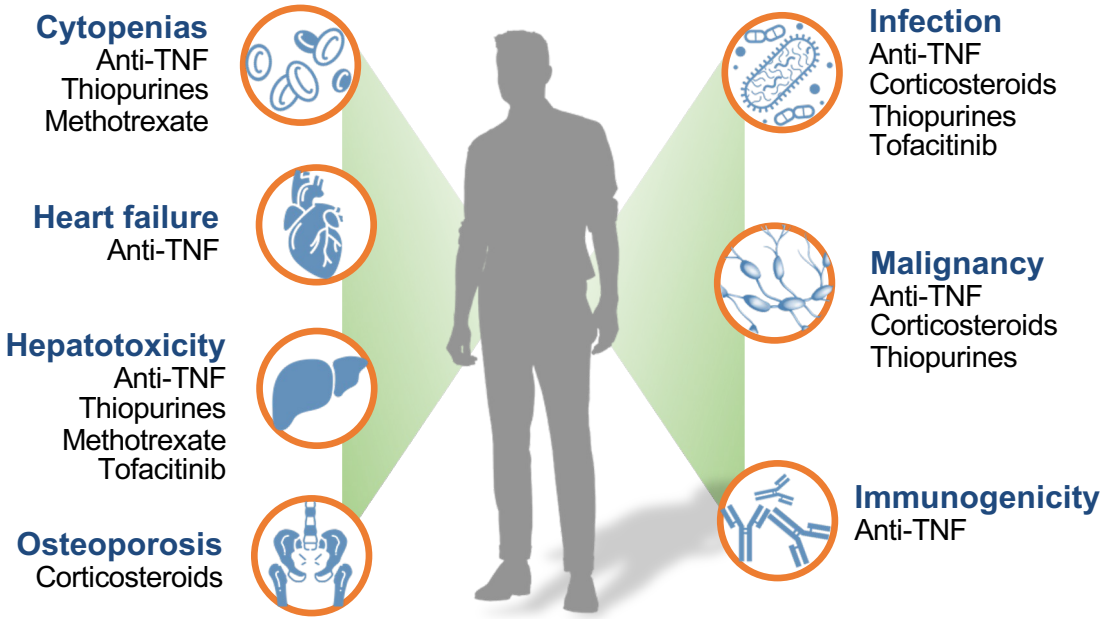
STRIDE 2 Consensus of Treatment Targets in IBD

Selecting Therapeutic TaRgets in Inflammatory Bowel Disease Endpoints



Turner. Gastroenterology. 2021

Key Safety Considerations With IBD Therapies



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.

Health Maintenance Checklist

CROHN'S & COLITIS FOUNDATION

Name: _____

MR#: _____ D.O.B.: _____

Vaccines	Which Patients	How Often
☐ COVID-19 vaccine (Moderna, Pfizer, Novavax)	All patients with IBD.	Follow recommendations for the general population.
☐ Influenza, Fluzone High Dose, Flublok recombinant, Fluad adjuvanted	All adult patients with IBD should receive a standard dose. Those on Anti-TNF monotherapy should receive a high dose influenza vaccine.[1] Older Adults aged ≥65 should receive the high dose, recombinant or adjuvanted inactive influenza vaccine.[2]	Annually.
☐ Pneumococcus (PCV 15, PCV 20 or PPSV23)	All patients ≥19 years age receiving systemic immunosuppression.*	Vaccine naïve should receive PCV20 or PCV 15 then 8 weeks apart PPSV23 in one year. Those previously vaccinated with PCV13 and PPSV23 should receive one PCV 20 at least one year since last dose of pneumococcal vaccine. Older adults > 65 should receive a dose of PCV 20.
☐ Recombinant Herpes Zoster (RZV) (adjuvanted- non-live) SHINGRIX	All patients with IBD ≥19 years of age.[3]	Should receive two dose recombinant herpes zoster vaccine 2–6 months apart.
☐ Human Papilloma Virus (HPV) 9valent GARDASIL	All Adults 18–26. Adults 26-45* shared decision who are likely to have a new sexual partner.	Should receive 3 doses series 0, 1–2 months and 6 months.
☐ Hepatitis B Heplisav® Engerix® or Recombivax®:	All adult patients with IBD. Universal vaccination is recommended for all adults 19–59.[4]	Heplisav®: Two dose series (HepB-CpG) at 0 and 1 month. Engerix® or Recombivax®: Three doses series on 0, 1, 6-month schedule 3 doses series Hep A-Hep B (Twinrix® at 0, 1, 6-months).
☐ Measles, Mumps, and Rubella (MMR) two-dose live vaccine	Patients with IBD not immune to MMR. If immune status is uncertain, obtain immunization history. IgG antibody titer can be checked but not recommend by ACIP. MMR live vaccine should not be given to patients currently on systemic immunosuppressive therapy.[5]	Should receive a 2-dose series, at least 4 weeks apart.
☐ Varicella two-dose live vaccine	Documentation of two doses or varicella vaccine. Serology not recommended by ACIP for evaluation of vaccine induced immunity in those with appropriate documentation.[6]	All patients who are not immune should receive a 2-dose series, 4–8 weeks apart, ≥4 weeks before immunosuppression, if therapy can be postponed.

Health Maintenance Checklist

CROHN'S & COLITIS FOUNDATION

Cancer Screening	Which Patients	How Often
☐ Colorectal	All IBD patients with extensive colitis (>1/3 of the colon) for ≥8 years should undergo surveillance colonoscopy every 1–3 years, depending on cancer risk.	Patients with IBD with a diagnosis of PSC should undergo colonoscopy, starting at the time of PSC diagnosis, and annually thereafter. Patients with IBD with features that are high-risk for developing colon cancer (i.e. prior history of adenomatous polyps, dysplasia, family history of colon cancer and extensive colitis) should have colonoscopies more frequently than every 3 years.
☐ Cervical	All women with IBD who are being treated with systemic immunosuppression.*	Should undergo cervical cancer by cytology annually (if cytology alone) or every 3 years (if HPV negative).[7]
☐ Skin	All IBD patients being treated with systemic immunosuppression.*	Should have annual total body skin exams to screen for skin cancer.

Other Screenings	Which Patients	How Often
☐ Mental Health	All	Annual; Depression (PHQ2) and anxiety (GAD7) at baseline, and then annually. Refer for counseling/ therapy when identified.
☐ Osteoporosis	All	Screen for osteoporosis by central (hip and spine) DXA scan in all patients with IBD if ANY risk factors for osteoporosis; low BMI, >3 months cumulative steroid exposure, smoker, post-menopausal, hypo-gonadism. Repeat in 5 years and no sooner than 2 years[1] if initial screen is normal. Vitamin D (800-1000 IU per day) and calcium (1200 mg/day) for Women >65 yo, male > 70 yo (regardless of clinical risk factors).
☐ Smoking	All	Refer current smokers for smoking cessation therapy.
☐ Latent infections Hepatitis B and tuberculosis	Patients with IBD starting on anti-TNF therapy.	Evaluate prior to starting anti-TNF therapy.
☐ Nutritional deficiencies	Patients with IBD annually.	Ferritin, Transferrin %, Vitamin D, Vitamin B12, and Vitamin B6.

* Systemic immunosuppression refers to current treatment with prednisone (>20mg/day for more than 14 days), azathioprine (>2.5 mg/kg/day) mercaptopurine (>1.5 mg/kg/day), methotrexate (>0.4 mg/kg/week), cyclosporine, tacrolimus, infliximab, adalimumab, golimumab, certolizumab, ustekinumab, rizankizumab, ozanimod, upadacitinib or tofacitinib.

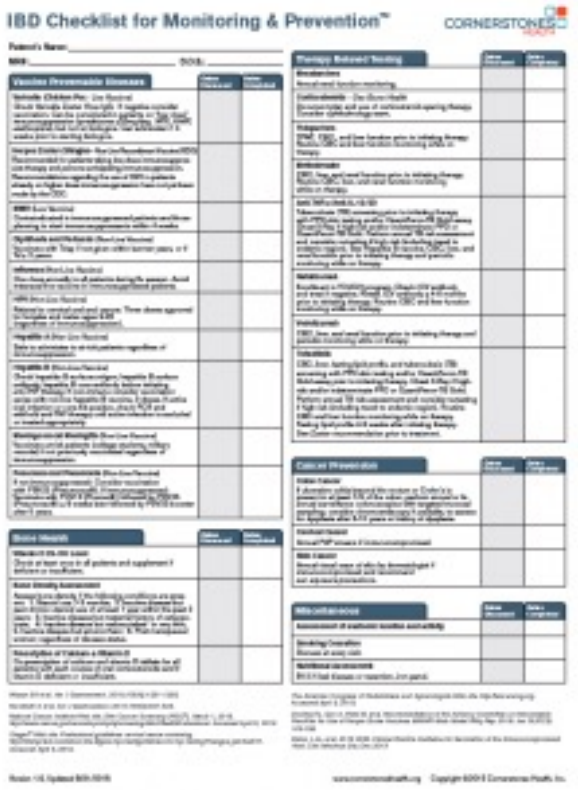
References:

1. Caldera F, Hillman L, Saha S, Wald A, Grimes I, Zhang Y, Sharpe AR, Reichelderfer M, Hayney MS. Immunogenicity of High Dose Influenza Vaccine for Patients with Inflammatory Bowel Disease on Anti-TNF Monotherapy: A Randomized Clinical Trial. Inflamm Bowel Dis. 2020 Mar 4;26(4):593-602. doi: 10.1093/ibd/izz164. PMID: 31504526.
2. Grohskopf LA, Blanton LH, Ferdinands JM, Chung JR, Broder KR, Talbot HK, Morgan RL, Fry AM. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022-23 Influenza Season. MMWR Recomm Rep. 2022 Aug 26;71(1):1-28. doi: 10.15585/mmwr.rr7101a1. PMID: 36006864; PMCID: PMC9429824.
3. Anderson TC, Masters NB, Guo A, et al. Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:80–84.
4. Weng MK, Doshani M, Khan MA, et al. Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:477–483
5. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013 Jun 14;62(RR-04):1-34. Erratum in: MMWR Recomm Rep. 2015 Mar 13;64(9):259. PMID: 23760231.
6. Marin M, Güris D, Chaves SS, Schmid S, Seward JF; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007 Jun 22;56(RR-4):1-40. PMID: 17585291.
7. Osteoporosis Prevention, Screening, and Diagnosis: ACOG Clinical Practice Guideline No. 1. Obstetrics & Gynecology 138(3):p 494-506, September 2021. | DOI: 10.1097/AOG.0000000000004514

Crohn's & Colitis Foundation Professional Education Sub-Committee; Freddy Caldera, MD, Shubha Bhat, PharmD, Shail Govani, MD | 8/29/2022

Monitoring & Prevention

- Vaccine preventable illness
- Bone Health
- Therapy related testing
- Cancer prevention
  - Colon
  - Skin
  - Cervical
- Miscellaneous
  - Smoking cessation
  - Nutritional assessment
  - Behavioral/psychological


IBD Checklist for Monitoring & Prevention™

CORNERSTONE

Patient's Name:

DOB: DOV:

Vaccine Preventable Diseases

Bone Health

Therapy Related Testing

Cancer Prevention

Miscellaneous

Educational Resources

- CCFA: https://www.crohnscolitisfoundation.org

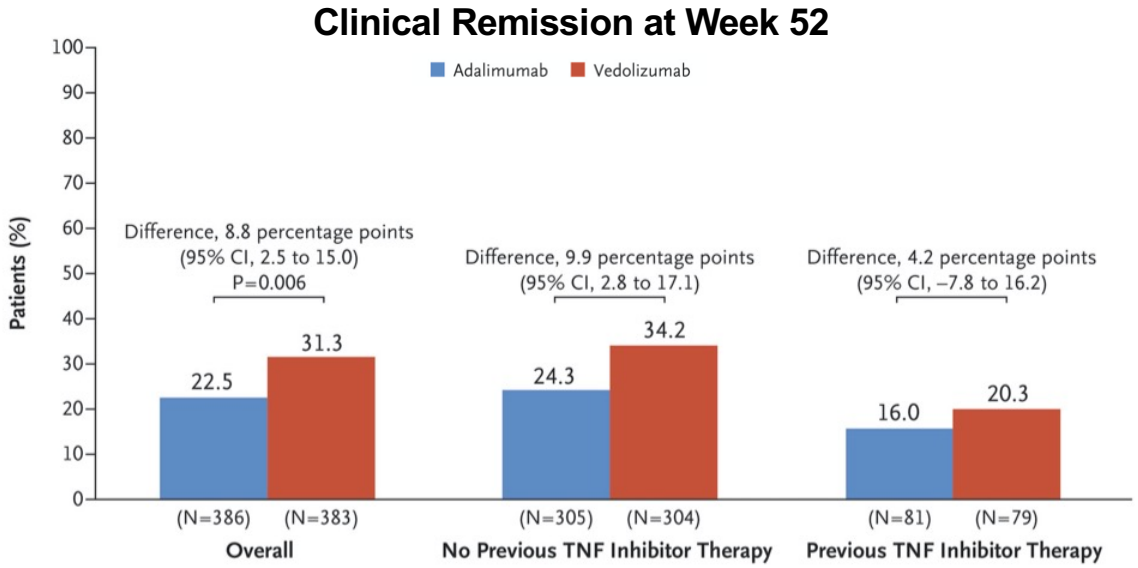
  888-my-gut-pain (M-F, 9-5)

  Phone: 800-932-2423
  E-mail: info@crohnscolitisfoundation.org

- ACG: gi.org (Education Universe - FREE)
- IBDandMe.org
- IBD CIRCLE (for health care providers)
- Written information about IBD
- Written questions, family member/advocate
- Frequent follow-up appointments early on
- Communication with other caregivers
  - It takes a village
  - Heads up: 6MP/AZA, Biologics, small molecule inhibitors

Vedolizumab vs Adalimumab in Patients with Moderate-Severe UC (VARSITY)

First head-to-head biologic trial comparing standard-dosing adalimumab to vedolizumab in those with moderate-severe UC (N=769)



Some limitations to VARSITY

- No difference between groups if on steroids or immunomodulators
- No dose escalation permitted
- No drug levels

Sands BT, et al. *N Engl J Med*. 2019;381:1215-1226.

Head-to-Head Trial: Ustekinumab vs. Adalimumab for Moderate-to-Severe Crohn's Disease: The SEAVUE Study

- Multicenter, randomized, double-blinded, parallel-group, active-controlled study
- **Biologic-naïve patients** failing or intolerant to conventional therapy with an ulcer of any size on baseline ileocolonoscopy
- Randomized 1:1 to UST (approximately 6mg/kg IV at BL then 90mg SC every 8 weeks) or ADA (160/80mg SC at BL/W2, then 40mg SC every 2 Weeks)

N=386

Figure 1: Primary Endpoint
Clinical Remission (CDAI<150) at week 52

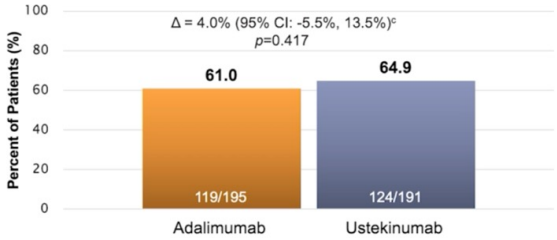
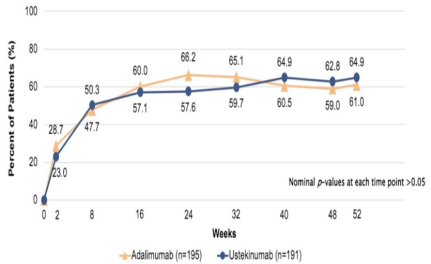


Figure 2: Clinical Remission (CDAI <150) Through Week 52



Sands B, et al. Presented at DDW. May 2021. Abstract 775d.

An Analysis of the EVOLVE Expansion Study Data Investigated Vedolizumab and Ustekinumab Treatment Outcomes in Biologic-Naïve Patients With Complex CD

Study design

Multicenter, observational, retrospective medical chart review study

Eligibility criteria for EVOLVE Expansion

- Biologic-naïve patients aged ≥18 years with previously diagnosed CD
- Initiated treatment with vedolizumab or ustekinumab in Australia, Belgium, or Switzerland during the eligibility period[a]
- ≥6 months of follow-up, 99 pts in Vedo, 97 in Uste (IPTW)

Complex CD definition

Patients with ≥1 of the following:

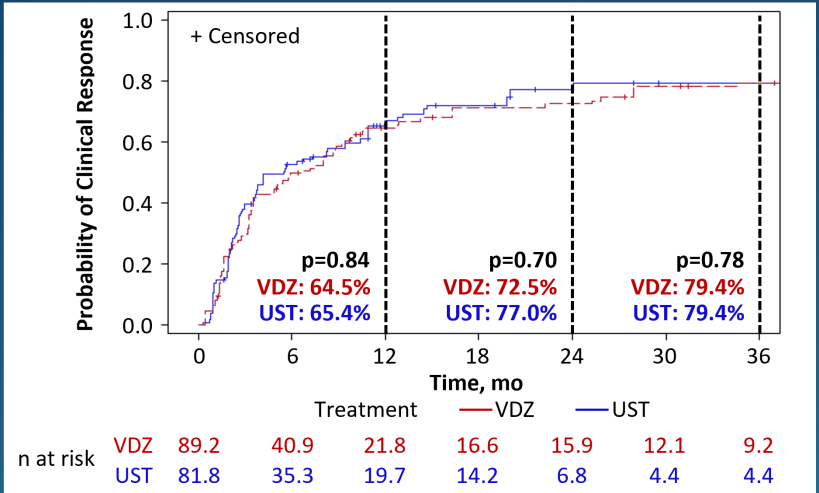
- Active fistula at treatment initiation
- Any prior CD-related surgery since CD diagnosis
- Any CD-related hospitalization within 12 months prior to treatment initiation

CD, Crohn's disease.

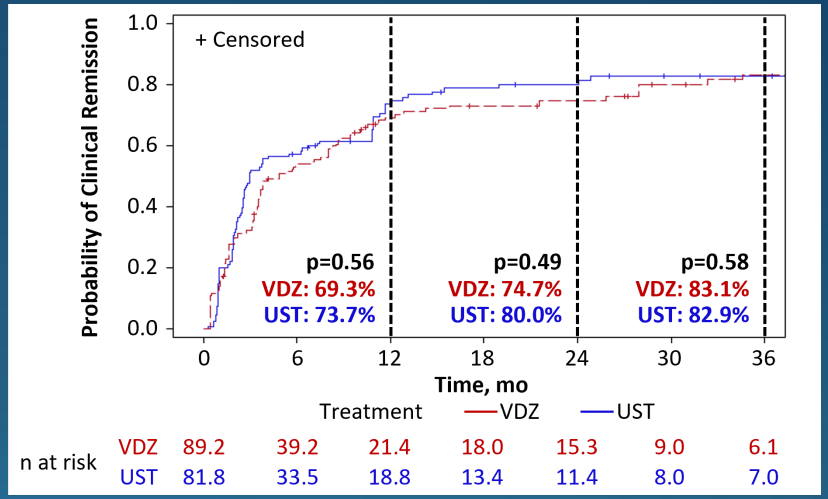
[a]Australia, March 1, 2017, to May 2021; Belgium, November 11, 2016, to May 2021; Switzerland, June 2, 2017, to May 2021.

Cumulative Rates of Clinical Response and Clinical Remission Were not Significantly Different During 36 Months of Treatment

Weighted cumulative clinical response over 36 months in patients treated with vedolizumab and ustekinumab



Weighted cumulative clinical remission over 36 months in patients treated with vedolizumab and ustekinumab

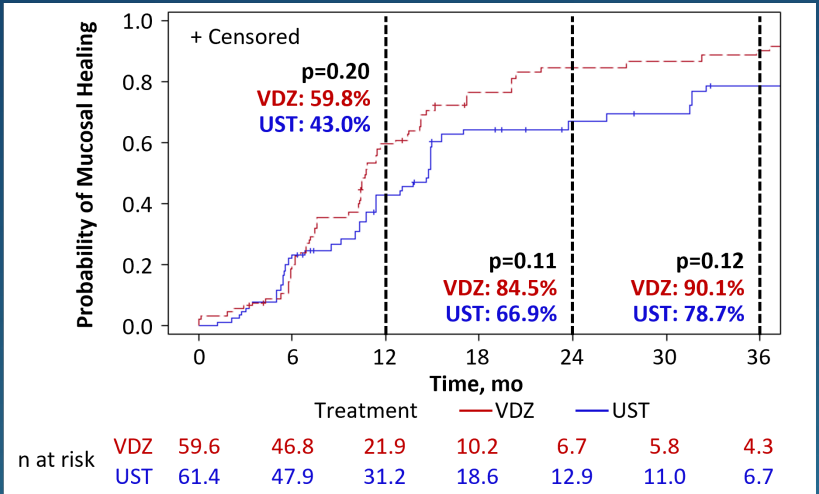


Clinical response was defined using a 4-step algorithm: (1) CDAI positive change in category from baseline (CDAI categories: score of <150; score of 151–219; score of 220–450; score of >450) OR if unknown, (2) HBI overall decrease of ≥3 points from baseline OR if unknown, (3) modified HBI decrease of ≥3 points from baseline OR if unknown, (4) treatment response recorded in the medical chart as "complete response" or "partial response." Clinical remission was defined using a 4-step algorithm: (1) CDAI score of <150 points OR if unknown, (2) HBI score of ≤4 OR if unknown, (3) modified HBI score of ≤4 OR if unknown, (4) remission status recorded in the medical chart as "in remission." n at risk is the sum of patient weights for each group of patients still receiving treatment who have clinical outcomes that can be assessed. p values were calculated using log-rank test. Patients were censored at the time of index treatment discontinuation, loss to follow-up, end of study period, or death, whichever was earliest.

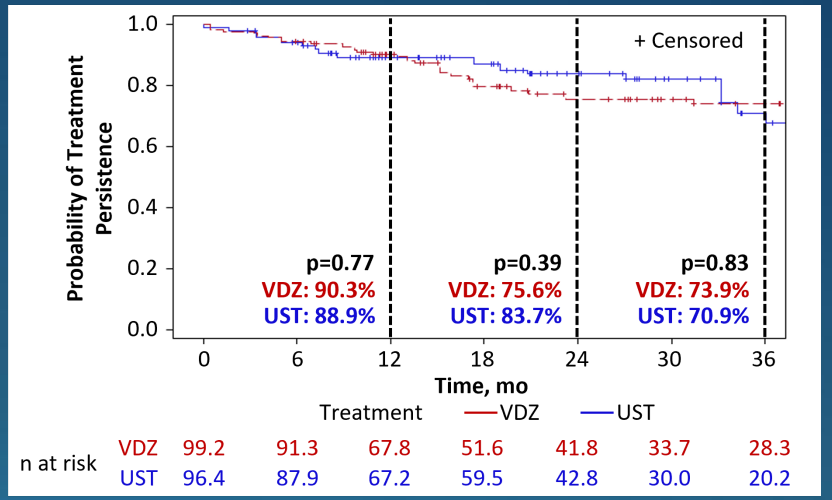
CDAI, Crohn's disease activity index; HBI, Harvey-Bradshaw Index; mo, months; UST, ustekinumab; VDZ, vedolizumab.

Cumulative Rates of Mucosal Healing and Treatment Persistence Were not Significantly Different During 36 Months of Treatment

Weighted cumulative mucosal healing over 36 months in patients treated with vedolizumab and ustekinumab



Weighted cumulative treatment persistence over 36 months in patients treated with vedolizumab and ustekinumab



Mucosal healing was defined using a 4-step algorithm: (1) endoscopic assessment score of 0 or 1 (ie, normal or inactive disease or mild disease) OR if unknown, (2) SES-CD score of <3 OR if unknown, (3) "lack of ulceration" defined by ≥1 of the following endoscopic procedure finding(s): either selection of "no ulcers" or free-text indication of "lack of ulceration" OR if unknown, (4) ≥1 endoscopic procedure finding(s) indicating inactive disease (no findings/no active disease, no erosion, no ulcers, no inflammation or inflammatory activity, or no pathological findings). n at risk is the sum of patient weights for each group of patients still receiving treatment who have clinical outcomes that can be assessed. p values were calculated using log-rank test. Patients were censored at the time of index treatment discontinuation, loss to follow-up, end of study period, or death, whichever was earliest.

SES-CD, Simple Endoscopic Score for Crohn's Disease; mo, months; UST, ustekinumab; VDZ, vedolizumab.

Ustekinumab or Vedolizumab in Crohn's Patients with Prior Anti-TNF Failure?

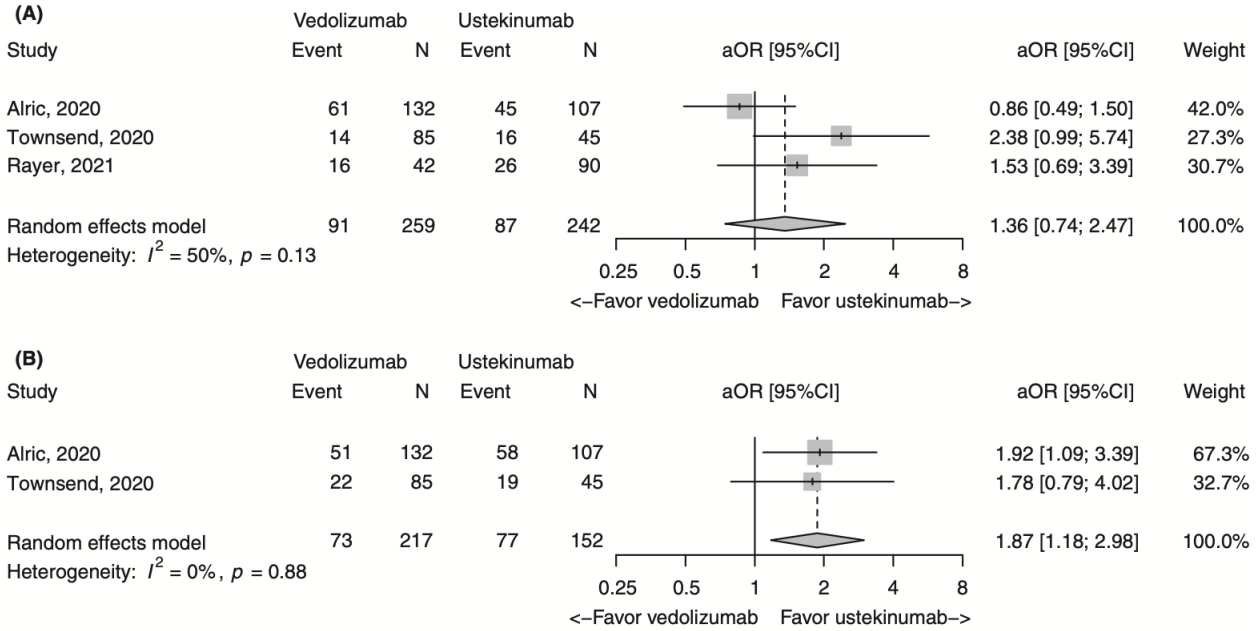


FIGURE 2 Clinical remission at week 14 (A) and week 52 (B). aOR [95%CI]: adjusted odds ratio [95% confidence interval]

Parrot L, et al. Aliment Pharmacol Ther. 2021;00:1–9.

One-Year Comparative Effectiveness of Ustekinumab Versus Tofacitinib for Ulcerative Colitis After Anti-Tumor Necrosis Factor Failure

Design: Retrospective cohort study

Population: Adults with UC and ≥1 prior anti-TNF failure who initiated tofacitinib or ustekinumab May 1, 2018 - April 1, 2021

Setting: The Mass General Brigham health system (Boston, MA).

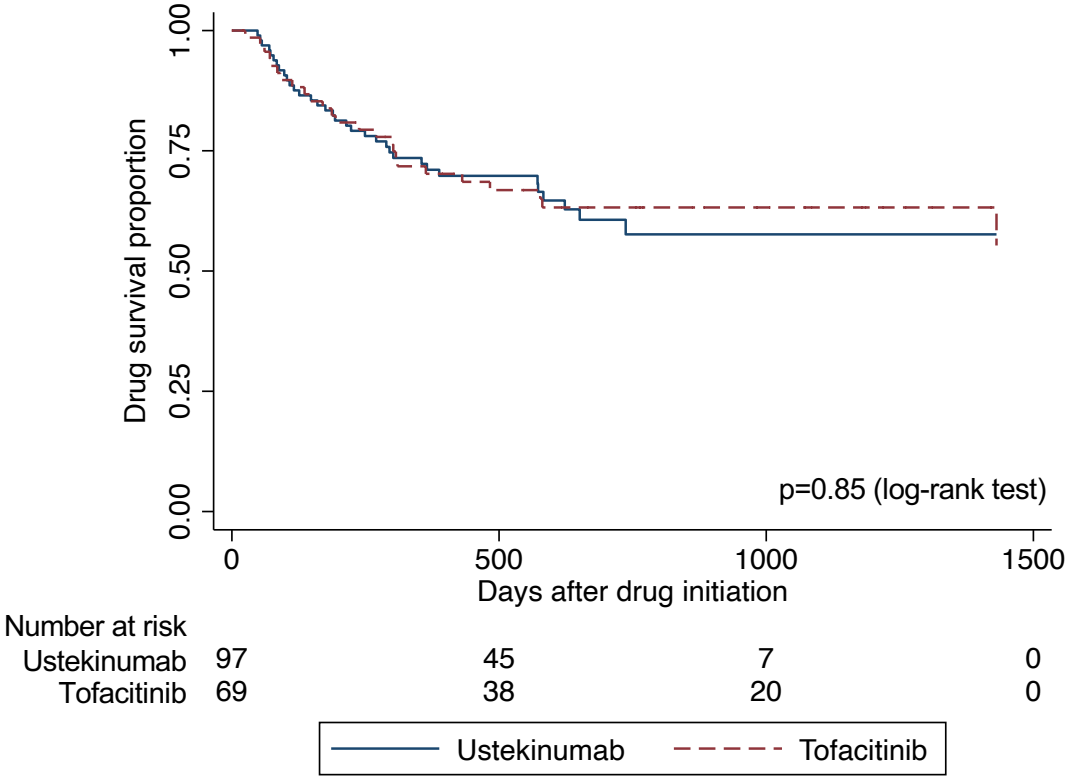
Primary endpoints: Proportion of patients in steroid-free clinical remission at 12 weeks and 52 weeks (i.e. SFCR 12 and SFCR 52). +/- 4 weeks were allowed to account for variability in timing of real-world assessments.

Secondary endpoints: Drug survival, endoscopic response/remission, biochemical response/remission, improvement in arthralgia, hospitalization, colectomy, adverse events requiring discontinuation, drug discontinuation within 52 weeks.

Analysis: Inverse probability of treatment-weighted (IPTW) logistic and Cox regression. Covariate balance confirmed with <|10%| standardized differences. Kaplan-Meier analysis with log-rank test were used to compare drug survival.

Dalal R, et al. ACG 2022

Results: Drug Survival



IPTW Cox Model	HR	P-value	95% LCL	95% UCL
Tofacitinib vs Ustekinumab	1.26	0.399	0.74	2.15

Abbreviations: HR = hazard ratio, LCL = lower confidence limit, UCL = upper confidence limit

Bottom Line: No Difference!
UST or Tofa ok in UC post Anti-TNF failure

Comparative Effectiveness of Upadacitinib Versus Ustekinumab for Ulcerative Colitis at 8-16 Weeks: A Multicenter Retrospective Cohort Study

Rahul S. Dalal, MD, MPH[1], Govind Kallumkal, MD[2], Heidy J. Cabral, BS[1], Salam Bachour, MD, MS[3], Edward L. Barnes, MD, MPH[4], Jessica R. Allegretti, MD, MPH[1]

Methods

Design: Multicenter retrospective cohort study

Population: Adults who initiated upadacitinib or ustekinumab for UC between January 1, 2021 - February 1, 2023

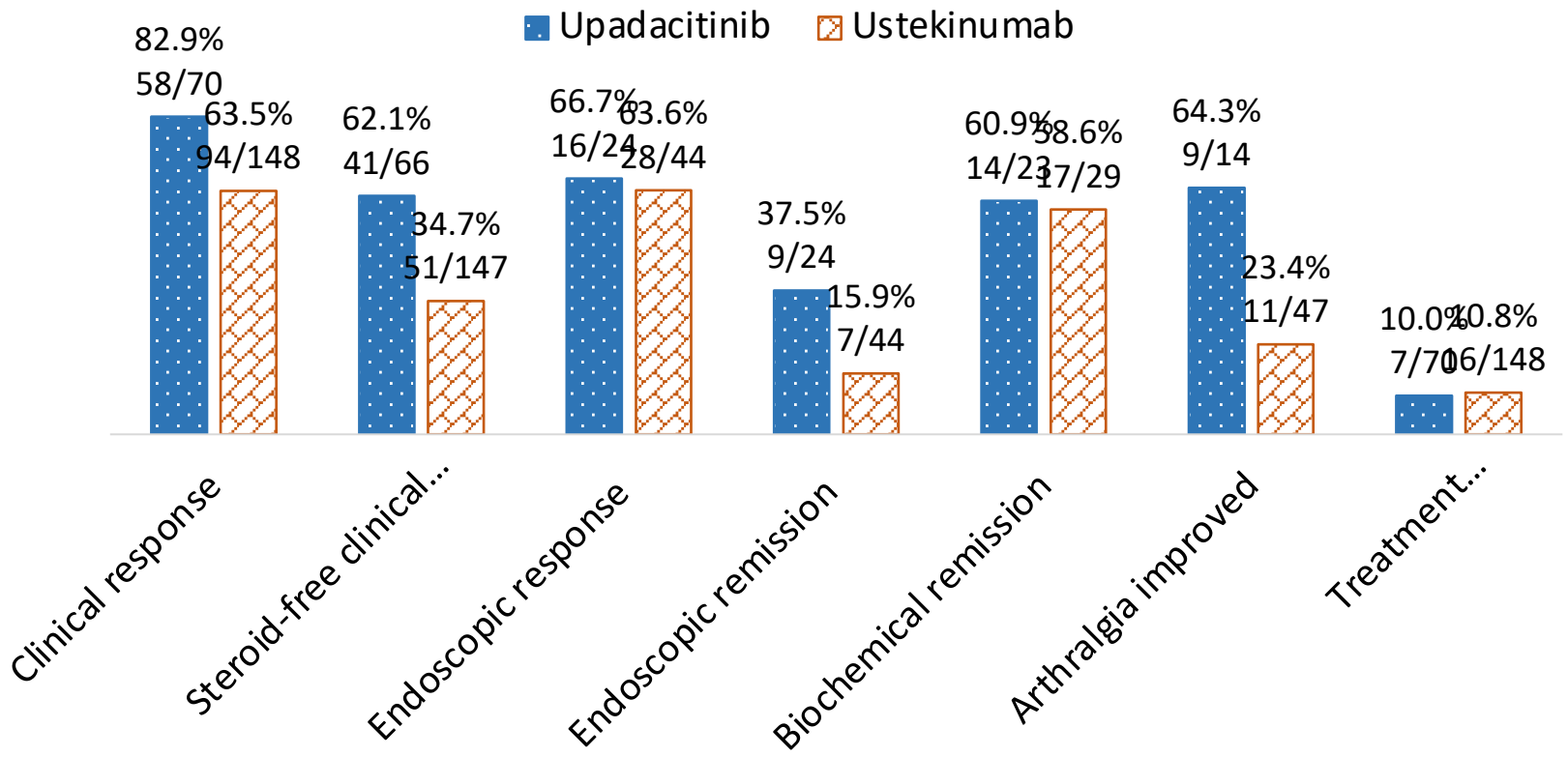
Setting: Mass General Brigham (Boston, MA), University of North Carolina (Chapel Hill, NC)

Primary endpoint: Clinical response at 8-16 weeks

Secondary endpoints: Steroid-free clinical remission at 8-16 weeks, endoscopic response and remission within 52 weeks

Analysis: Inverse probability of treatment-weighted (IPTW) logistic regression. Covariate balance was confirmed with <|10%| standardized differences.

Results: Outcomes (Unweighted)



Results: IPTW Logistic Regression

Outcome	Weighted Odds Ratio*	95% LCL	95% UCL
Clinical Response	**2.39**	**1.04**	**5.49**
Steroid-free clinical remission	**3.17**	**1.55**	**6.46**
Endoscopic response	1.49	0.45	4.95
Endoscopic remission	**5.10**	**1.34**	**19.3**

*Odds ratios reflect upadacitinib compared to ustekinumab (reference).
LCL = lower confidence limit, UCL = upper confidence limit

Summary and Conclusions

Summary: This study identified significantly higher odds of clinical response and SFCR at 8-16 weeks and endoscopic remission within 52 weeks for upadacitinib versus ustekinumab.

Strengths: Balance of relevant confounders via IPTW, granular outcome data

Limitations: Retrospective design, incomplete data for certain markers of disease severity, short-term follow-up

Implications: In a largely bio-exposed population, upadacitinib may be more effective than ustekinumab for the induction of UC.

Future work: Future studies should examine the long-term durability and safety of upadacitinib compared to other advanced therapies for UC.

Treatment Considerations in your IBD Patient

- If choosing based on safety:
  - VDZ, UST, RIZ likely best safety (age, prior malignancy, infection risk, etc.)
  - Anti-TNF and JAK associated with higher risk of infections
  - Anti-TNF relative contraindication in CHF, MS, endemic areas of opportunistic infections
  - CTZ no placental transfer

- If based on efficacy:
  - Difficult to determine which is 'superior' – more head to head studies
  - Based on network meta analysis: Upadacitinib and Infliximab most effective

- If choosing on 'convenience':
  - Some will prefer infusion to injection
  - Many likely to prefer oral formulation

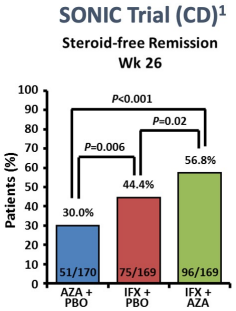
- If choosing based on sensitization (non-compliance):
  - Tofa, Upa not associated with sensitization
  - UST has lowest (to date) sensitization rate (?RIZ)

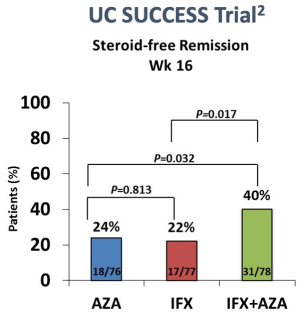
Specific Scenarios

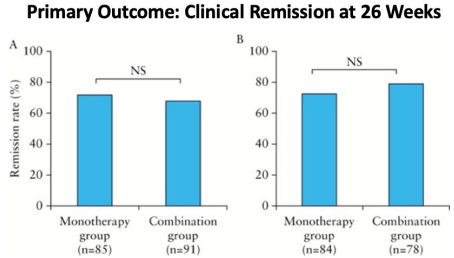
Disease	Modifier	First drug consideration	Reason
IBD	Psoriasis	Ustekinumab Rizankinumab	On label
CD	Female of Childbearing age pregnancy	Certolizumab	Does not cross Placenta*
IBD	>60 yo	Vedolizumab	Higher risk of infections/ cancer
UC	Synovitis Arthritis	Anti-TNF or Tofacitinib Upadacitinib	On label
UC	Low Albumin	Cyclosporine Tacrolimus Tofacitinib Upadacitinib	Small molecule

Combination Therapy is Not Needed for All Biologics

- **For infliximab in CD and UC, probably[1,2]**
- **Prospective randomized study with adalimumab in Japan suggests not needed[3]**
- **Retrospective and subset analyses with vedolizumab and ustekinumab demonstrate no benefit[4]**
- **Vedolizumab and ustekinumab have very low immunogenicity**
- **Incorporation of HLA DQ1*05 to predict immunogenicity is uncertain at this time**





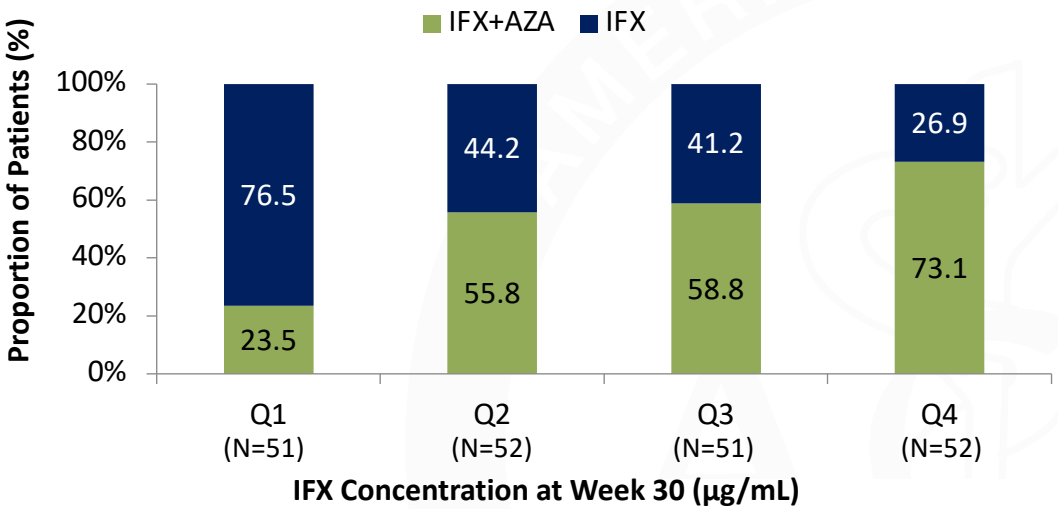


adalimumab vs adalimumab with azathioprine

[1]Colombel JF, et al. *N Engl J Med*. 2010;362(15):1383-95.
[2]Panaccione R, et al. *Gastroenterology*. 2014;146(2):392-400.
[3]Matsumoto T et al. *J Crohns Colitis*. 2016;10(11):1259-66.
[4]Yang E, et al. *Aliment Pharmacol Ther*. 2020;51(11):1031-38.

Infliximab Level is More Predictive than Being on Combination Therapy: SONIC Post Hoc Analysis

- Patients in the IFX+AZA group contributed a greater number of patients to higher IFX concentration quartiles than IFX monotherapy

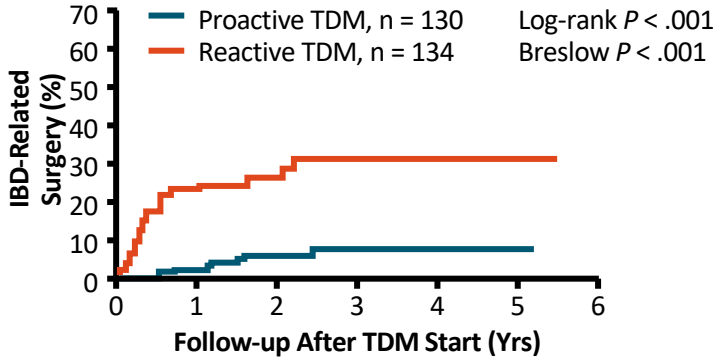


Q1: <0.84 µg/mL; **Q2**: 0.84-2.36 µg/mL; **Q3**: 2.36-5.02 µg/mL; **Q4** ≥5.02 µg/mL.

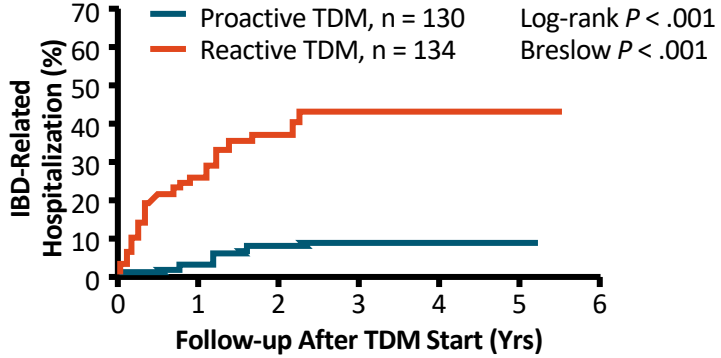
Colombel JF, et al. *Clin Gastroenterol Hepatol.* 2018. [Epub ahead of print]

Proactive Therapeutic Drug Monitoring Associated With Less Surgery and Hospitalization

- Observational, retrospective, multi-center study of consecutive IBD patients on infliximab maintenance who underwent either proactive or reactive TDM (N = 264)



– Proactive TDM for infliximab maintenance associated with significantly less IBD-related surgery/hospitalization



– ROC analysis identified an infliximab trough concentration threshold ≤ 4.65 µg/mL associated with IBD-related hospitalization (SN: 0.63, SP: 0.61)

Papamichael K, et al. Clin Gastroenterol Hepatol. 2017;15:1580-1588.

Slide credit: clinicaloptions.com

Suggested Drug Trough Concentrations for Clinical Remission in Maintenance Therapy

Agent	Concentration, µg/mL
Infliximab	≥ 5
Adalimumab	≥ 7.5
Certolizumab pegol	≥ 20
Golimumab	Unknown (? >5.7)
Vedolizumab	> 20 (6 week level) , >12-14
Ustekinumab	>4.5 (>0.8-1.6*)

- Trough concentrations may be higher for:
  - Induction therapy
  - Mucosal healing, perianal fistula healing

Feuerstein JD, et al. Gastroenterology. 2017;153:827-834.. Cheifetz-personal communication

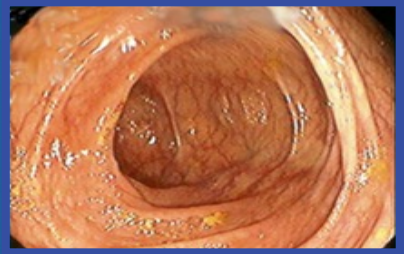
Slide credit: clinicaloptions.com

Early Assessment of Drug Levels Predict

Disease and Drug	Early Assessment	Cutoff Level	Outcome
Ulcerative Colitis			
Infliximab	**Wk 8**	≥33 µg/mL	Clinical remission at weeks 30 and 54
Infliximab*	**Wk 6**	≥33 µg/mL	Clinical remission at week 8
Infliximab*	**Wk 6**	>22 µg/mL	Clinical response at week 8
Ustekinumab	**Wk 8**	6 mg/kg : ≥8.6 µg/mL 130 mg : ≥2.5 µg/mL	Clinical remission at week 44 (week 52 after induction)
Crohn's Disease			
Infliximab	**Wk 14**	>4 µg/mL	Clinical remission at week 54
Infliximab	**Wk 6**	>8.3 µg/mL	Clinical remission at week 14
Infliximab*	**Wk 6**	≥15.9 µg/mL	Clinical response at week 14
Infliximab	**Wk 2**	>6.8 µg/mL	Primary-nonresponse at week 14

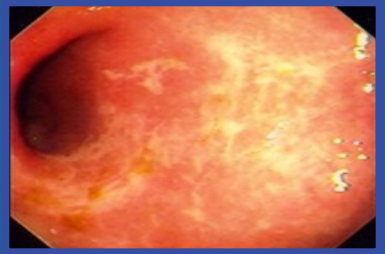
Sands BE, et al. *N Engl J Med*. 2019;381:1201-1214.
Reinisch W, et al. *Gastroenterol Hepatol*. 2015 Mar;13(3):539-547.e2.
Clarkston K, et al. *J Pediatr Gastroenterol Nutr*. 2019;69:68-74.
Adedokun OJ, et al. *Gastroenterol*. 2014;147:1296–307.e5.
Courbette O, et al. *J Pediatr Gastroenterol Nutr*. 2020 Mar;70(3):310-317.
Singh N, et al. *Inflamm Bowel Dis*. 2014;20(10):1708-1713.
Bar-Yoseph H, et al. *Aliment Pharmacol Ther*. 2017 Nov 9;47(2):212-218.
deBruyn JCC. *Front Pediatrics*. 2021 Jul;29(9):668978.

Endoscopic Severity of UC



NORMAL

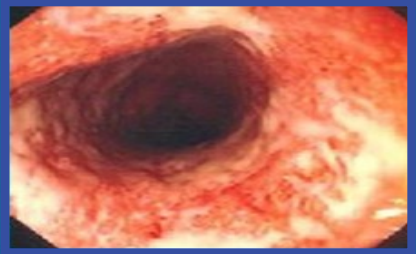
MAYO: 0



MILD

Diminished vascular markings, mild erythema, granularity, and friability

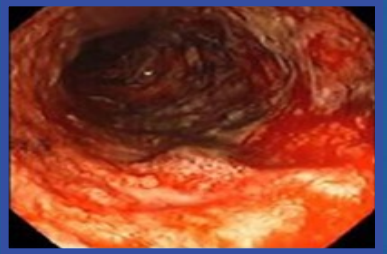
MAYO: 1



MODERATE

Marked erythema, absent vascular markings, contact friability, no ulcers

MAYO: 2

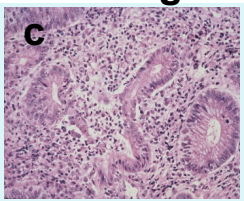
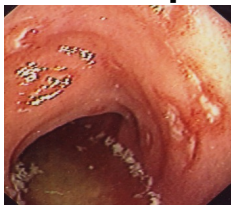
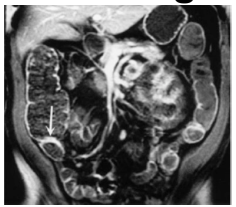
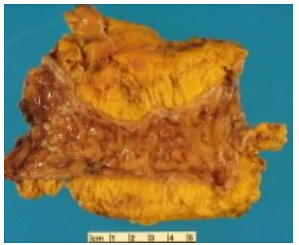


SEVERE

Spontaneous bleeding, ulcers

MAYO: 3

Recurrence is clinically silent initially

Histologic	Endoscopic	Radiologic	Clinical	Surgical
				
Within 1 week	70-90% by 1 yr	Tissue damage	30% 3 yr 60% 5 yr	50% by 5 yrs

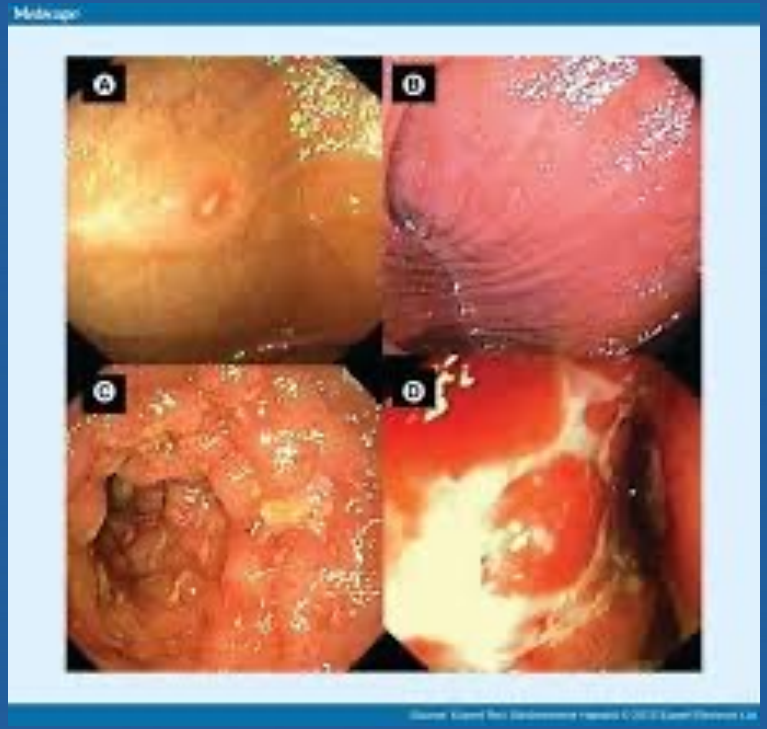
Surgery

1. D'Haens G, Geboes K, Peeters M, et al. Gastroenterology 1998;114:262-267.
2. Olaison G, S medh K, Sjodahl R. Gut 1992;33:331-335.
3. Rutgeerts P, Geboes K, Vantrappen G, et al Gastroenterology 1990;99:956-983.
4. Sachar DB. Med Clin North Am 1990;74:183-188.

Rutgeert's Score

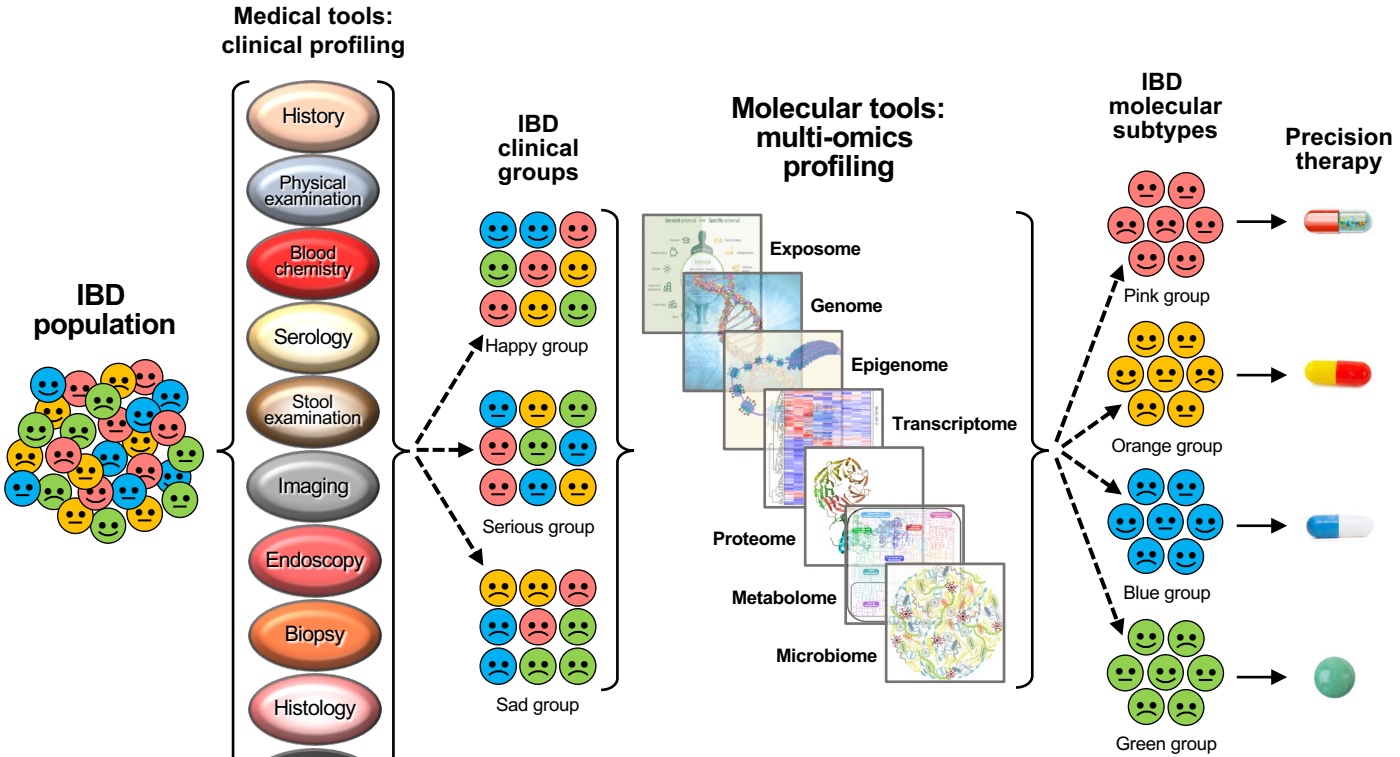
Rutgeerts' score	Endoscopic description of findings
i0	no lesions
i1	≤5 aphthous ulcers
i2	>5 aphthous ulcers with normal intervening mucosa, skip areas of larger lesions, or lesions confined to ileocolonic anastomosis
i3	diffuse aphthous ileitis with diffusely inflamed mucosa
i4	diffuse inflammation with larger ulcers, nodules and/or narrowing

Adapted From Rutgeerts et al.[7]



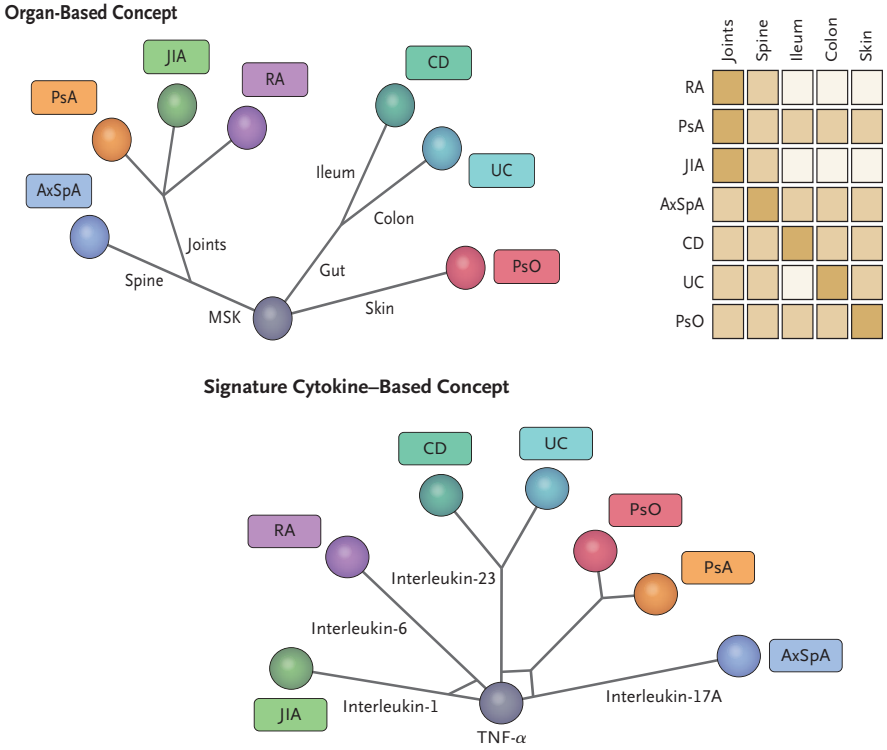
6-12 months post surgery: assess for recurrence
Ulcers at the anastomosis do not count

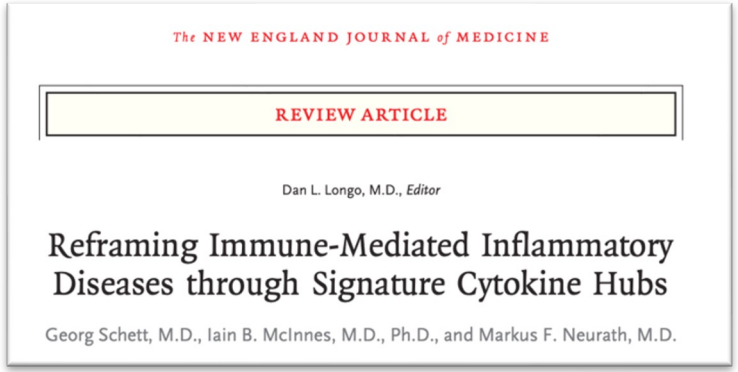
Multi-omics + bioinformatics: the path to precision therapy



Adapted from Hurgobin B et al. *Respirology* 2018;23:1117-1126

Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs





PsO = psoriasis; MSK = musculoskeletal; AxSpA = axial SpA; JIA = juvenile idiopathic arthritis.
Schett G, et al. *N Engl J Med*. 2021;385(7):628-639.

IBD Landscape: *personalizing* the choice of advanced therapy

TNFi
(IFX, ADA, CTZ, GOL)

- IV and SQ options
- Rapid onset of action
- Best with IMM (SONIC)
- +EIMs/perianal disease
- Immunogenicity
- Infection risk
- Lymphoma risk (with IMM)

Anti Integrin
(VDZ)

- IV (SQ now available in USA)
- Better results in TNFi naive
- Low immunogenicity
- Gut-selective with excellent safety profile

Anti IL23+/-12
(UST, RISA, MIRI)

- IV then SQ
- Fast onset of action
- Efficacy in TNFi naïve and failure
- Low immunogenicity
- +Psoriasis, PsA
- Excellent safety profile

JAKi
(TOFA, UPA)

- Oral, UC & CD, after TNFi
- Rapid onset of action
- Efficacy in TNFi naïve & failure
- No Immunogenicity
- +EIMs (RA, Psoriasis, AtDerm)
- Herpes Zoster
- MACE & VTE (RA >> UC)

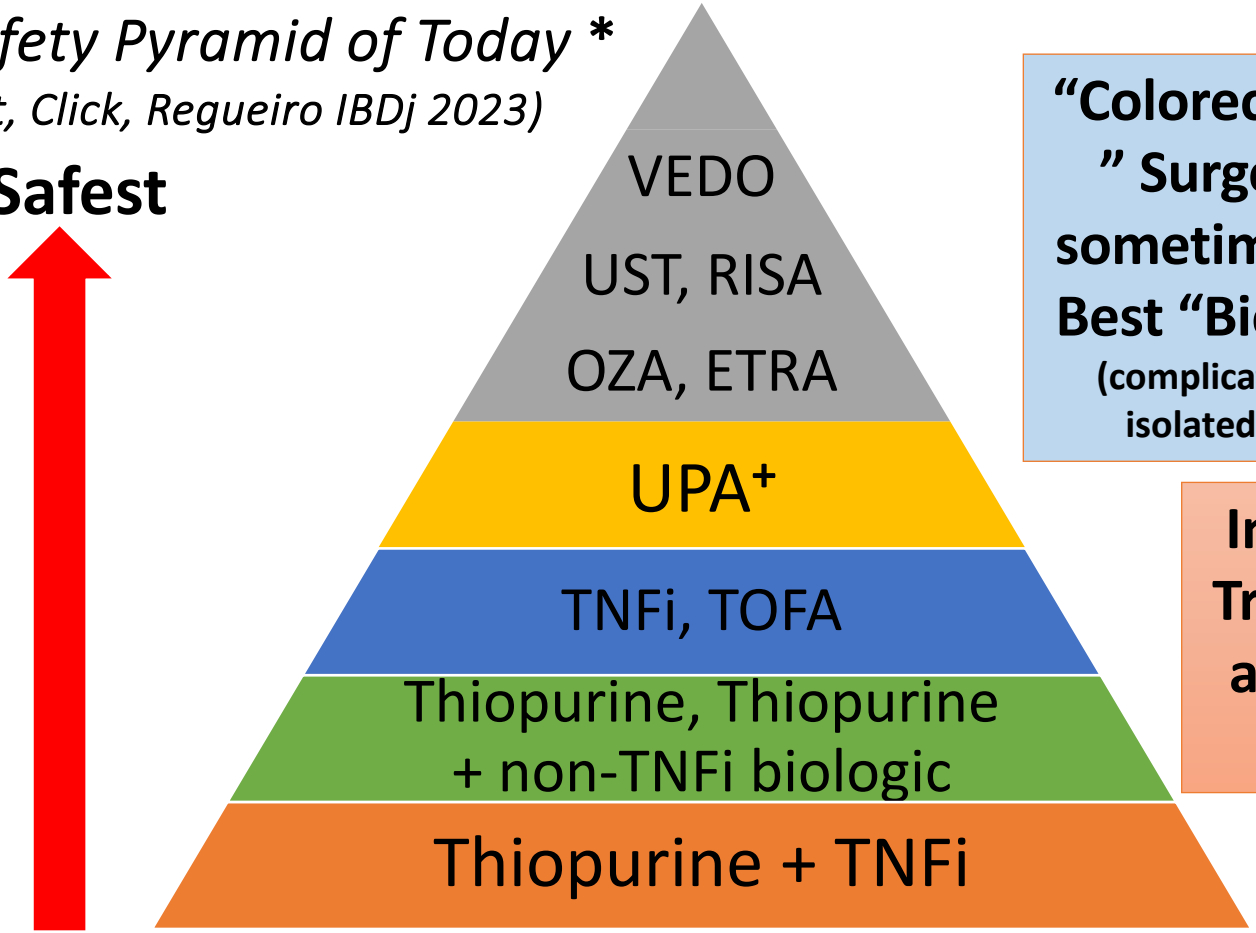
S1P
(OZA, ETRA)

- Oral, UC only
- Better results in TNFi naive
- No Immunogenicity
- +Multiple Sclerosis
- Good Safety
- Initial dose titration:1st dose HR ↓
- Expected decrease in lymphocytes

*The Safety Pyramid of Today **

(Bhat, Click, Regueiro IBDj 2023)

Safest



"Colorectomab" Surgery is sometimes the Best "Biologic"
(complications or isolated TI ds)

Inadequate Treatment is an Adverse Event

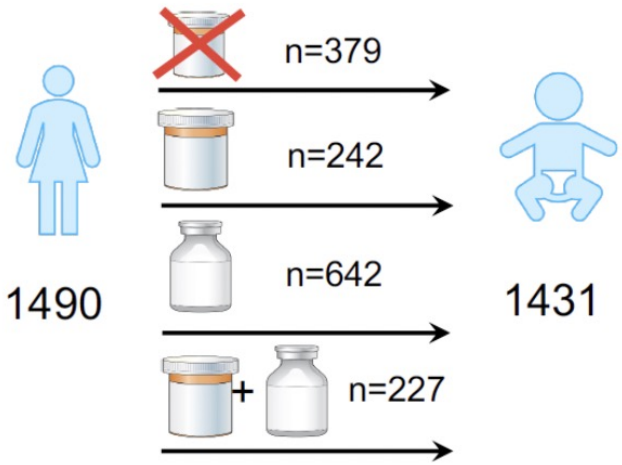
+Does selectivity = safer?

STEROIDS

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

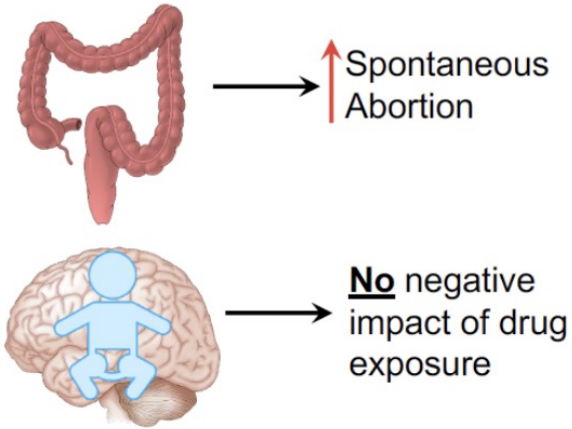
Data from the PIANO Registry

PIANO: Pregnancy and Neonatal Outcomes after Fetal Exposure To Biologics and Thiopurines among Women with Inflammatory Bowel Disease



No increase in:

- Congenital malformations
- Spontaneous abortions
- Preterm birth
- Low Birth Weight
- Infections in year
  - But ↑ with preterm birth



Mahadevan U et al. Gastroenterology. 2021 Mar;160(4):1131-1139. doi: 10.1053/j.gastro.2020.11.038. Epub 2020 Nov 21. PMID: 33227283; PMCID: PMC7956164.

Risk of Tofacitinib-Related Adverse Events in Patients With Ulcerative Colitis: A Nationwide Propensity-Matched Cohort Study.

Gursimran S Kochhar, Aakash Desai Raymond Cross, Frank A Farraye, Stephen B Hanauer, Parambir S. Dulai

- A recent randomized, open-label, phase IV trial found an increased risk of major adverse cardiovascular events (MACE) and malignancy in patients >50 yo with RA on MTX who received tofacitinib compared to tumor necrosis factor inhibitor (TNFi)
- These risks have not been seen in IBD patients in clinical trials with tofacitinib but limited numbers and follow-up period within the trials
- FDA Blackbox warning: must fail anti-TNF prior to use of Jak inhibitors
- Retrospective cohort study TriNetX, a multi-institutional database of more than 70 million patients from 49 healthcare organizations inthe USA
- The 1-, 2- and 3-year risk of MACE, malignancy, opportunistic infections (OIs) and venous thromboembolism (VTE) between patients with UC on tofacitinib and other biologic agents (control cohort)

Tofacitinib safety in UC

- *Of a total of 94,321 patients with UC,*
  - *1056 patients received tofacitinib (mean age 47 +/- 16, 53% male),*
  - *4,285 received an TNFi,*
  - *2,402 patients received vedolizumab (VDZ)*
  - *1,335 received ustekinumab.*
- *There was **no difference** in the 1-, 2-, and 3-year risk of MACE, malignancy, OIs, and VTE between patients on tofacitinib compared to other biologic agents .*
- *In sub-group analysis, there was **no difference** in the 1-, 2- and 3-year risk of MACE, malignancy and VTE between patients on tofacitinib compared individually to TNFi, vedolizumab and ustekinumab (Table 1)*
- *There is an increased 1-year risk of OIs in patients on tofacitinib compared to TNFi and vedolizumab, and an increased 1-, 2- and 3-year risk of OIs compared to ustekinumab*

Biologic and Small Molecule Therapies Are Not Associated with Increased Major Adverse Cardiovascular Events (MACE) or VTE in IBD: A Propensity Matched Cohort Study

Thabet Qapaja, MD[1], Khaled Alsabbagh Alchirazi, MD[1], Ahmad Naser, MD[2], Motasem Alkhayyat, MD[1], Serge Baroud, MD[3], Miguel Regueiro, MD[1]

1- Cleveland Clinic Foundation

2- Jacobi Medical Center

3- MetroHealth Medical center

ACG 2023
October 20-25, Vancouver, Canada

Background and Study Objective

- Biologic and small molecule therapies, collectively known as advanced therapies, are effective at treating IBD
- Certain advanced therapies have been implicated in an increased risk of MACE/VTE, e.g. Oral Surveillance Study with Tofacitinib in RA.
- The primary objective: to evaluate the rates of MACE and VTE in IBD patients on biologic or oral small molecule therapies.

Ytterberg, Steven R., et al. "Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis." *New England Journal of Medicine* 386.4 (2022): 316-326.

Methods

- Study type: a retrospective cohort study using the TriNeTx multi-institutional database (January 1, 2021 to June 2023)

- Population:

1. Adult IBD patients who received biologics: Infliximab, Adalimumab, Golimumab, Certolizumab, Vedolizumab, Natalizumab, or Ustekinumab were compared to IBD patients who did not receive biologics.
2. Adult IBD patients who received oral small molecule therapies: Tofacitinib, Upadacitinib, or Ozanimod were compared to those who did not receive small molecules.

Methods

- ICD-10 codes to identify IBD patients and MACE and VTE.
- 1:1 propensity score matching for age, race, sex, cardiovascular risk factors, and *non-advanced therapy* medications including immunomodulators, 5-ASAs, and steroids.
- MACE and VTE were assessed at least 30 days after initiation of therapy.

Results – Biologics Were Associated with Decreased Rates of MACE/VTE

Outcomes after propensity score matching	IBD on biologics N=67,607	IBD not on biologics N=67,607	aOR	95% CI	p-value
Coronary artery disease	3,206 (4.74%)	4,541 (6.71%)	**0.691**	(0.66,0.724)	< 0.0001
Myocardial infarction	896 (1.33%)	1,344 (1.98%)	**0.662**	(0.608,0.721)	< 0.0001
Stroke	985 (1.46%)	1,380 (2.04%)	**0.71**	(0.653,0.771)	< 0.0001
Venous thromboembolism (DVT or PE)	3,001 (4.44%)	3,512 (5.2%)	**0.848**	(0.806,0.891)	< 0.0001

Results – Small Molecules Were Not Associated with Increased Rates of MACE/VTE

Outcomes after propensity score matching	IBD on small molecules N=3,194	IBD not on small molecules N=3,194	aOR	95% CI	p-value
Coronary artery disease	144 (4.5%)	138 (4.32%)	1.046	(0.823,1.328)	0.7148
Myocardial infarction	27 (0.84%)	26 (0.81%)	1.039	(0.605,1.784)	0.8903
Stroke	40 (1.25%)	46 (1.44%)	0.868	(0.567,1.33)	0.5148
Venous thromboembolism (DVT or PE)	122 (3.82%)	114 (3.57%)	1.073	(0.827,1.392)	0.5957

Cancer risk in anti-TNF

- Swedish Biologic, RA and Cancer Registries
  - 6366 pts with RA on anti-TNF 1/1999-7/2006
    - 25,693 person-years of follow-up: 240 cancers
  - National Bio-naïve RA registry: n=61,160; new MTX n=5,989 and new DMARD+AntiTNF n=1,838
    - 330,498 person-years of followup: 4,244 cancers
  - RR=1.00 (0.86-1.15) vs. bio-naïve cohort
- 78,483 RA pts 1999; 8,562 on biologic 1999-2007
  - 4,650 cancers in Bio naïve RA vs. 302 in Bio exposed
  - 2:1 matched control: cancer site, age, sex, year of dx
  - No difference in stage or post cancer survival rates

Askling et al. Arthritis & Rheumatology 2009;60(10):3180-3189
Raaschou et al. Arthritis & Rheumatology 2011;63(7):1812-1822

Don't worry about cancer: Danish Registry

- Danish National Patient Registry and Cancer Registry
- Adults (≥ 18): IBD, RA, Psoriasis and primary cancer diagnosed 1/1/199-12/31/2016
- Matched 1:10 anti-TNF exposed: unexposed
- 25,738 pts with IMIDs and cancer
- 434 pts who received anti-TNF after cancer dx, matched to 4328 pts in control group
- During 18,753 person years (median 5.6 years) 635 developed recurrent or new cancers:
- 72 in anti-TNF vs. 563 in control group
- 30.3 cases/1000pt years vs. 34.4
- Adjusted Hazard ratio: 0.82 (CI 0.61-1.11)

The Lancet: Gastroenterology&Hepatology 2019: Waljee, Higgins, et al.
http://doi.org/10.106/S2468-1253(19)303362-0

Combo Biologics for aggressive IBD (Belt & Suspenders)

Table 1. Primary Literature on Dual Biologics for the Treatment of IBD

Study	Year	Study Type	Biologics	Number of Patients	Disease	Findings
Sands et al[3]	2007	RCT	IFX + natalizumab	79	CD	Combination therapy was well tolerated. Combination therapy was superior to IFX alone.
Glassner et al[6]	2020	Retrospective cohort study	Various	50	CD, UC	Increased risk of infection was seen in patients on combination therapy compared with biologic monotherapy; however, the risk was lower in those not on a concomitant immunomodulator.
Kwapisz et al[7]	2021	Retrospective study	Various	15	CD, UC	Combination biologics with different mechanisms may be safe and effective; an anti-TNF or VDZ plus UST was most effective.
Privitera et al[5]	2020	Retrospective study	Various	16	CD, UC	Three adverse events were reported; however, none of them were serious. Clinical response was seen in all patients.
Yang et al[4]	2020	Retrospective study	Various	22	CD	Dual biologic therapy was associated with clinical, biomarker, and endoscopic healing in patients with refractory CD.
Olbjørn et al[11]	2020	CS	IFX + UST IFX + VDZ	13	CD, UC	This pediatric study demonstrated safety of combination therapy and clinical remission in 9 of the 13 patients.
Buer et al[8]	2018	CS	Anti-TNF + VDZ	10	CD, UC	Dual biologic therapy in this study was safe and may represent a long-term treatment option for patients with refractory IBD.
Mao et al[27]	2018	CS	Various	4	CD	Dual biologic therapy with VDZ appears to be safe and effective.
Yzet et al[23]	2016	CS	Anti-TNF + UST	3	CD, UC	Use of dual biologics appears to be safe and well tolerated. Use of UST was not effective in the treatment of paradoxical psoriasis.
Fischer et al[24]	2017	CR	VDZ + CZP	1	UC	No side effects were reported; spondyloarthritis symptoms and colitis improved with clinical remission.
Roblin et al[10]	2018	CR	GOL + VDZ	1	UC	After 1 year of combined therapy, the patient had clinical and endoscopic remission of UC.
Liu, Loomes[15]	2017	CR	UST + VDZ	1	CD	No adverse events were reported; the patient had mucosal healing.
Huff-Hardy et al[14]	2017	CR	UST + VDZ	1	CD	There were no infectious complications. Perianal disease significantly improved.
Afzali, Chiorean[25]	2016	CR	VDZ + ADA	1	CD	Six months of combination therapy resulted in endoscopic and clinical improvement in a patient with refractory disease.
Hirten et al[26]	2015	CR	IFX + VDZ	1	CD	Combination therapy resulted in improved symptomatology and endoscopic findings.
Bethge et al[9]	2017	CR	VDZ + ETN	1	UC	Combination therapy with VDZ and ETN was safe with no adverse events after 40 weeks of treatment.

ADA, adalimumab; CD, Crohn's disease; CR, case report; CS, case series; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; IBD, inflammatory bowel disease; IFX, infliximab; RCT, randomized controlled trial; TNF, tumor necrosis factor; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab.

Table 2. Systematic and Other Recent Reviews on Dual Biologics for the Treatment of IBD

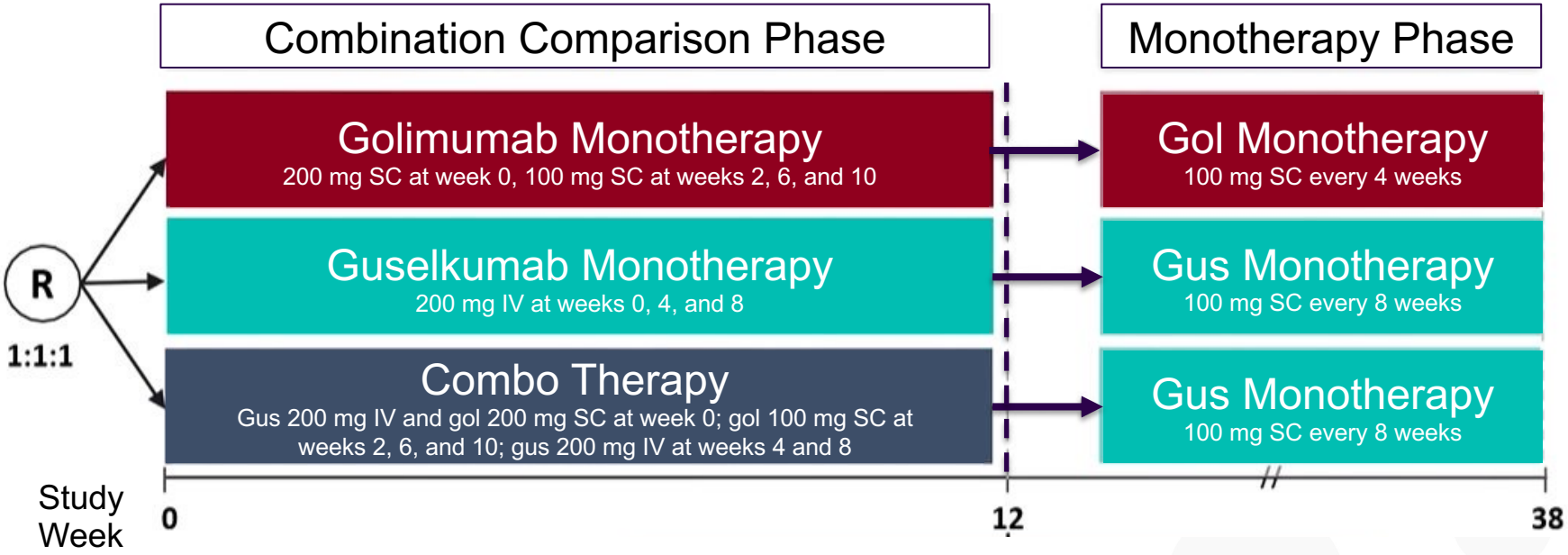
Study	Year	Type of Review	Findings
Ahmed et al[13]	2021	Systematic review with meta-analysis	This review included 30 studies with 288 patients on dual biologic therapy. The review also included combination therapy with a small molecule and a biologic. No severe safety concerns were identified. The authors concluded that dual biologic or other combination therapy may be an option for patients with severe, refractory IBD.
Ribaldone et al[12]	2019	Systematic review with pool analysis	This review included 7 studies (18 patients) with a combination of TNF inhibitors and VDZ as well as VDZ with UST. Clinical improvement was seen in all patients, and endoscopic improvement was reported in 93% of patients. No safety concerns were identified.
Hirten et al[17]	2018	Narrative review	This review included data on combination biologic therapy in patients with IBD, dermatologic conditions, rheumatologic conditions, and other immune-mediated inflammatory conditions.

IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab.

Gold SL, Steinlauf AF. Efficacy and Safety of Dual Biologic Therapy in Patients With Inflammatory Bowel Disease: A Review of the Literature. Gastroenterol Hepatol. 2021 Sep;17(9):406-414. PMID: 34602905; PMCID: PMC8475252.

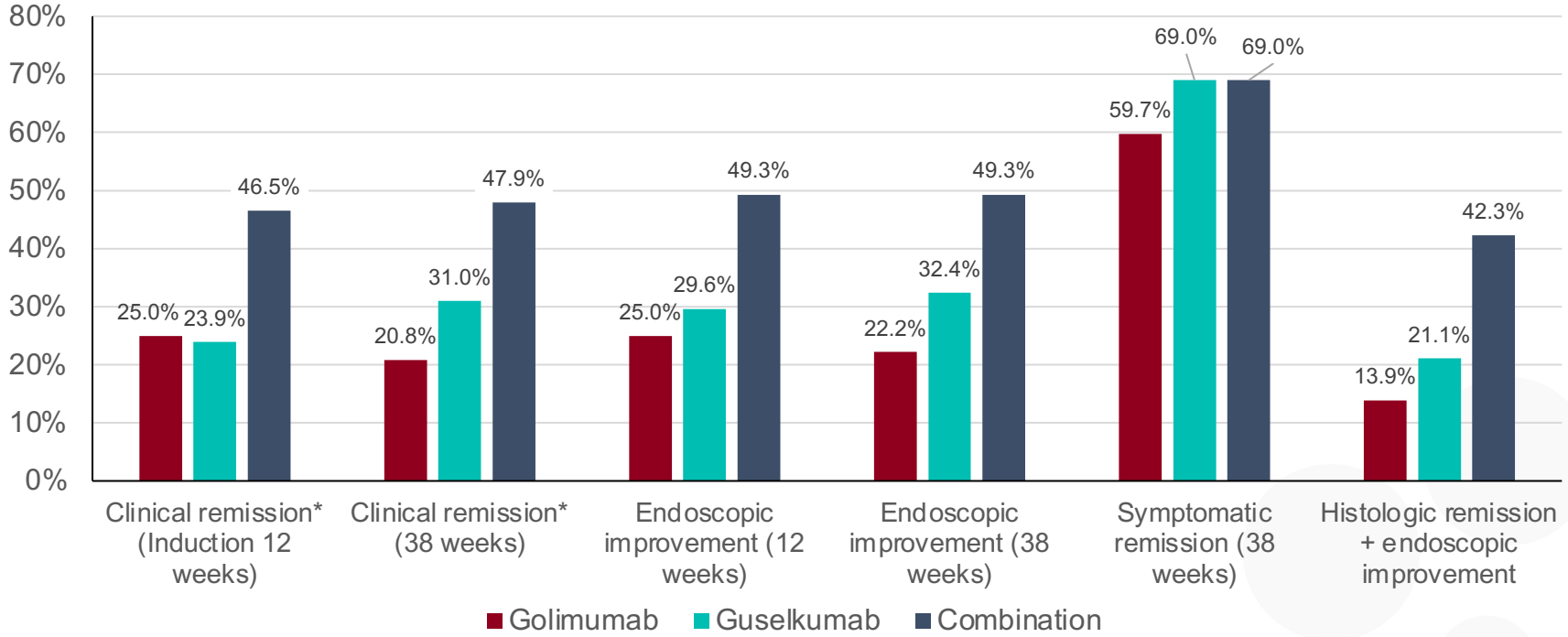
VEGA: Anti-TNF, Anti-IL-23, or Combination Therapy in Moderate to Severe UC

- TNF-naïve patients refractory to conventional therapy



Panés J, et al. Presented at: United European Gastroenterology Week (UEGW); October 8-11, 2022; Vienna, Austria & Virtual. OP087. Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2023;8(4):307-320.

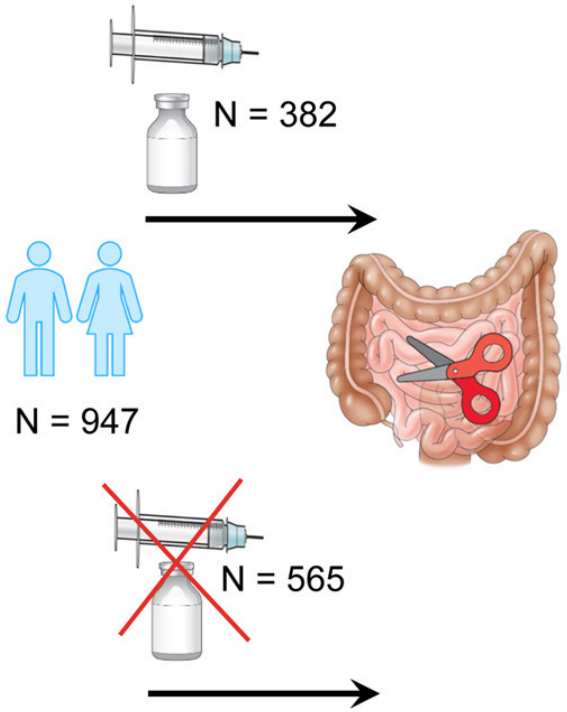
VEGA: Golimumab, Guselkumab, or Combo in UC



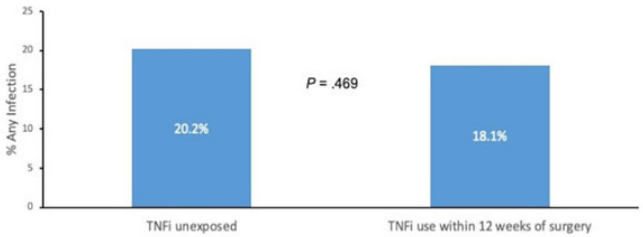
*Clinical remission using modified Mayo score: Mayo SF subscore of 0 or 1, where the SF subscore has not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
Endoscopic improvement: Endoscopy subscore of 0 or 1 with no friability present on endoscopy.

Panés J, et al. Presented at: UEGW; October 8-11, 2022; Vienna, Austria & Virtual. OP087. Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2023;8(4):307-320.

Prospective Cohort Study to Investigate the Safety of Preoperative Tumor Necrosis Factor Inhibitor Exposure in Patients with Inflammatory Bowel Disease Undergoing Intra-abdominal Surgery (PUCCINI)

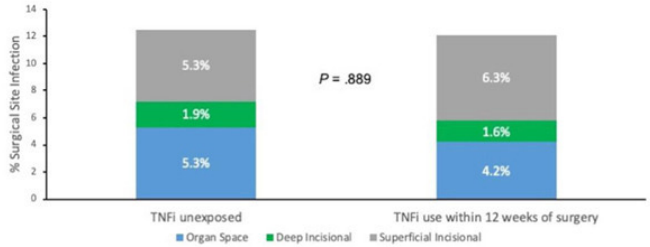


Frequency of Any Infection by Patient Reported TNFi Exposure



Not associated with Any Infection or SSI

Frequency of Surgical Site Infection Type by Patient Reported TNFi Exposure



Corticosteroids

Past Diabetes

\+ association with Any Infection & SSI

Gastroenterology

PUCCINI. Cohen, B et. Al. https://doi.org/10.1053/j.gastro.2022.03.057

Orthopedic surgeries (joints) on Biologics, JAKs

- **ACR: stop anti-TNF 1 cycle prior and restart 1 week after surgery**
- **Britain: 3-5 half lives pre, start after wound healing**
- **Japan: stop 2-4 weeks before, start after wound healing , 10-14 days**
- **Stop JAKi 3 days before, resume after wound healing**
  (Arthritis Care & Research Vol. 74, No. 9, September 2022, pp 1399–1408 DOI 10.1002/acr.24893)

- **2472 ortho surgeries in IRD and 47,887 in degenerative or post trauma. 2% vs 0.8% infections. 2.5x risk if more than one DMARD or anti-TNF. 12% risk if surgery was done within one interval of the last anti-TNF dose**
  (Scherrer et al. Arthritis Care Res, 2013;65:2032-2040)
- **268 TKR with RA; 104 on anti-TNF, 168 not on anti-TNF: 3.26 % local infection in TNF, 2.1% in non TNF (NS) (Johnson et al. J Rheumatol. 2013;40(5):617-623)**

IBD and COVID-19

- Vaccinations work and are safe and recommended
- IBD medicines safe (except steroids)
- IBD patients with COVID-19 are in general not at higher risk for poor outcomes

U.S. National Database Study: patients with IBD not at increased risk of severe disease or death from COVID-19

- Retrospective cohort utilizing U.S. EHR data (TriNetX): >40 million patients
  - 232 IBD patients and 19,776 non-IBD patients with COVID-19 PCR or ICD-10 code
- Severe COVID-19 defined as hospitalization and/or 30-day mortality
- Medication use extracted from encounters in preceding 12 months

	Before propensity matching			After propensity matching*		
Outcomes	Overall risk n/total (%)	Risk ratio (95% CI)	P-value	Overall risk n/total (%)	Risk ratio (95% CI)	P-value
Severe COVID-19	IBD 56/232 (24.14)	1.15 (0.92–1.45)	0.23	IBD 56/232 (24.14)	0.93 (0.68–1.27)	0.66
	Non-IBD 4,139/19,776 (20.92)			Non-IBD 60/232 (25.86)		
Hospitalizations	IBD 56/232 (24.14)	1.20 (0.96–1.51)	0.11	IBD 56/232 (24.14)	1.10 (0.74–1.40)	0.91
	Non-IBD 3,960/19,776 (20.02)			Non-IBD 55/232 (23.70)		

*Factors used for propensity score matching included age, race, body mass index, and comorbidities.
CI, confidence interval; COVID-19, coronavirus disease 2019; EHR, electronic health records; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; PCR, polymerase chain reaction.
Singh S, et al. Gastroenterology 2020;159:1575–8.

https://covidibd.org/

General Guidance from ACG, AGA, CrohnsandColitisFoundation, IOIB

- Stay on Maintenance medicines (including biologics, immunomodulators
- If COVID-19 +, ? hold for 2weeks (until better)
- ? Theoretical benefit of biologics vs Cytokine storm? Speculation!
- Avoid steroids (prednisone), ? Should we avoid combination rx

Brenner EJ, Ungaro RC, Colombel JF, Kappelman MD. SECURE-IBD Database Public Data Update. covidibd.org Accessed on 01/09/2022

COVID-19 in People with Inflammatory Bowel Disease

Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion

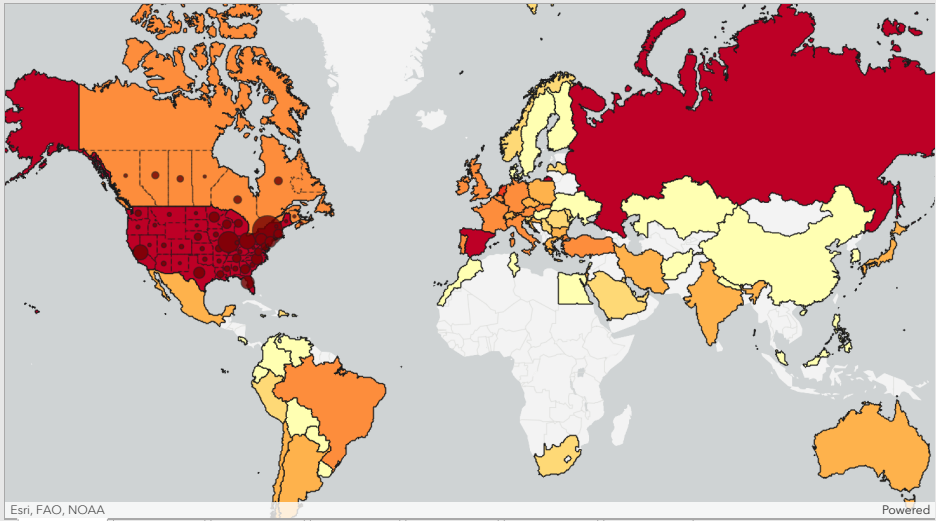
Country Breakdown: World

Please use the following citation if referencing the data on this page. Also see the Publications tab of this window.
Brenner EJ, Ungaro RC, Colombel JF, Kappelman MD. SECURE-IBD Database Public Data Update. covidibd.org. Accessed on MM/DD/YY.

About
Surveillance **E**pidemiology of **C**oronavirus **U**nder **R**esearch **E**xclusion (**SECURE-IBD**) is an international, pediatric and adult registry to monitor and report on outcomes of COVID-19 occurring in IBD patients. The SECURE-IBD registry is funded by the Helmsley Charitable Trust.

We encourage IBD clinicians worldwide to report ALL cases of COVID-19 in their IBD patients, regardless of severity (including asymptomatic patients detected through public health screening). Reporting a case to this Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE)-IBD registry should take approximately 5 minutes. Please report only confirmed COVID-19 cases, and *report after sufficient time has passed to observe the disease course through resolution of acute illness and/or death*. **To report a case of coronavirus, click here.**

Interactive Data Visualization Reference:
Windsor JW, Underwood FE, Brenner E, Colombel J-F, Kappelman MD, Ungaro R; Zhang X, Kaplan GG. Data Visualization in the Era of COVID-19: An Interactive Map of the SECURE-IBD Registry. The American Journal of Gastroenterology 2020;115 (11):1923-1924. doi: 10.14309/ajg.0000000000000953.



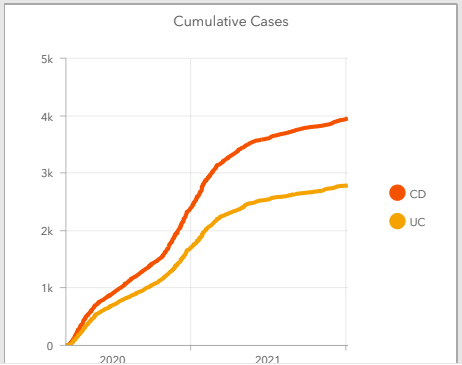
About | Publications | Directions

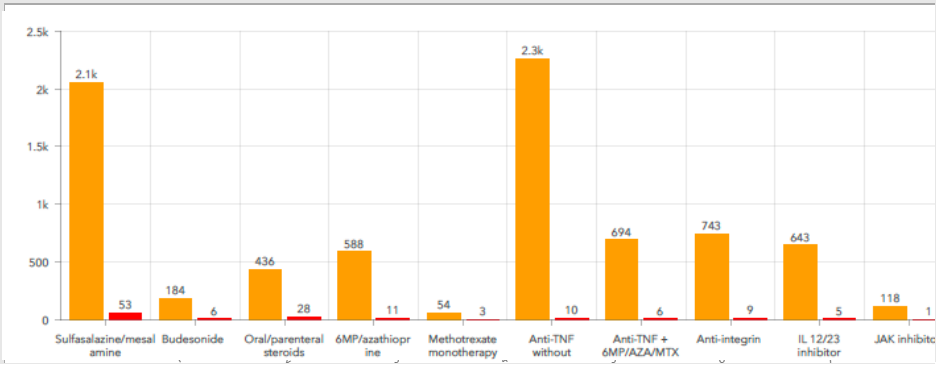
Jan. 2022 | Dec. 2021 | Aug. 2021 | Apr. 2021 | Dec. 2020 | Aug. 2020 | Apr. 2020

Cases 6,917

Hospitalizations 1,009

Deaths 106

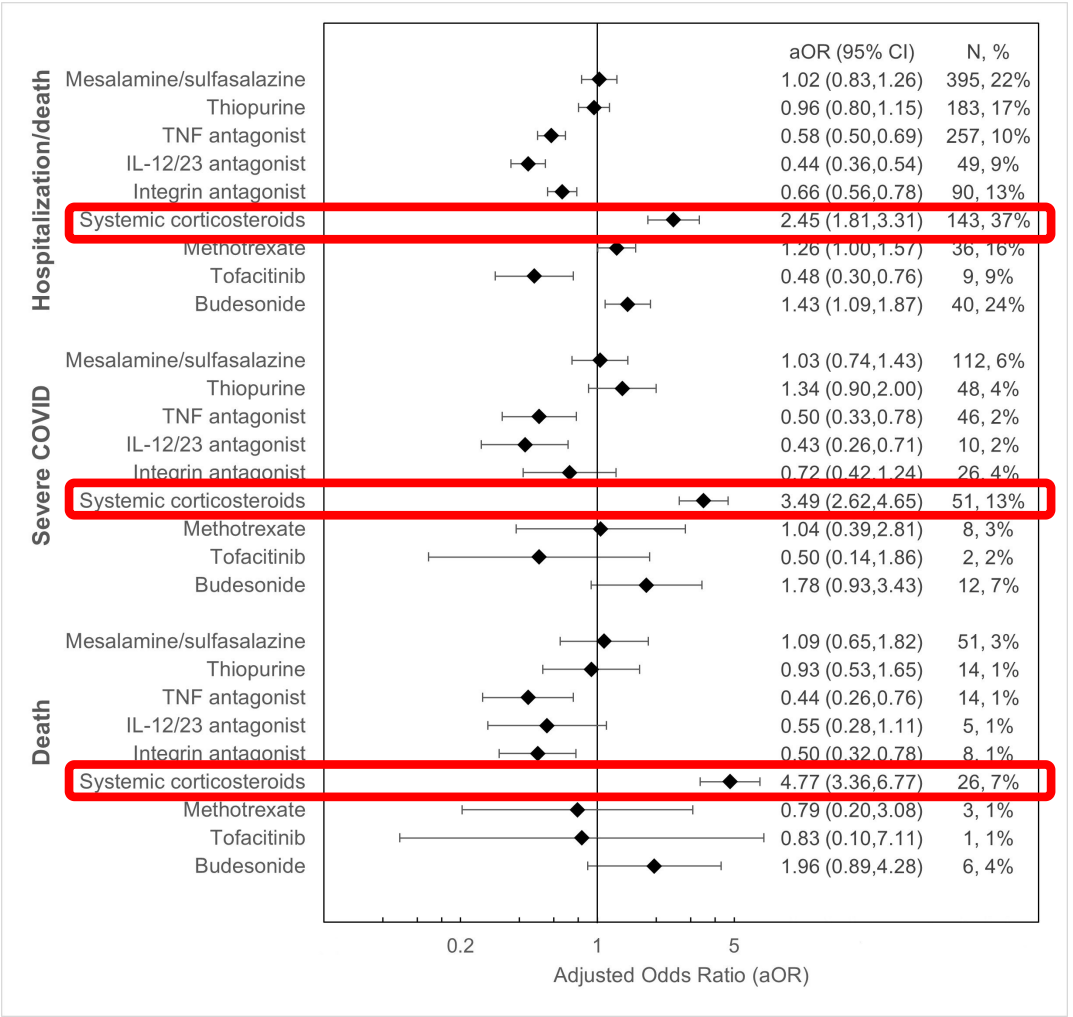




Data on 6000+ Patients from SECURE-IBD

Corticosteroids

- Consistently associated with increased risk of hospitalization, severe COVID-19, and death



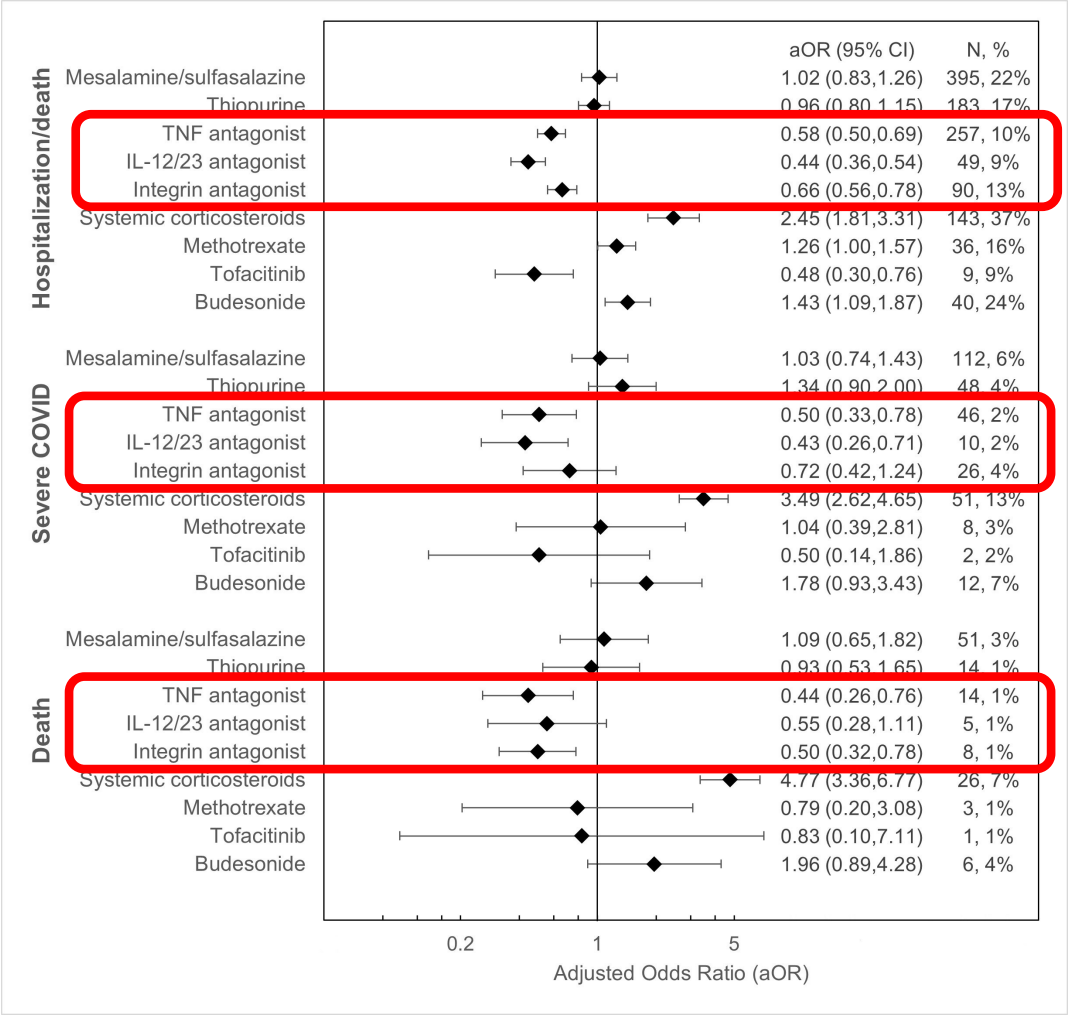
aOR: adjusted odds ratio; CI: confidence interval; TNF: tumor necrosis factor; IL: interleukin. N and % in right column represent number and proportion of patients with outcome within specified medication class.

Ungaro R, Brenner E, et al. Gastroenterology 2021.

Data on 6000+ Patients from SECURE-IBD

Biologics

- TNF, IL-12/23, and integrin antagonists all NOT associated with adverse COVID-19 events
- Potentially protective effect



aOR: adjusted odds ratio; CI: confidence interval; TNF: tumor necrosis factor; IL: interleukin. N and % in right column represent number and proportion of patients with outcome within specified medication class.

Ungaro R, Brenner E, et al. Gastroenterology 2021.

Corticosteroids, But Not Biologics or Immunomodulators are Associated with Severe COVID-19 Outcomes in AICID patients

- **Methods:**
  - N=39,686 (+ SARS-CoV-2 PCR)
  - Retrospective community-based study across Kaiser Permanente health system of immunosuppressed patients (AICID or organ transplant)
    - Primary Composite Outcome: Risk of hospitalization, intensive care unit admission, or death within 45 days

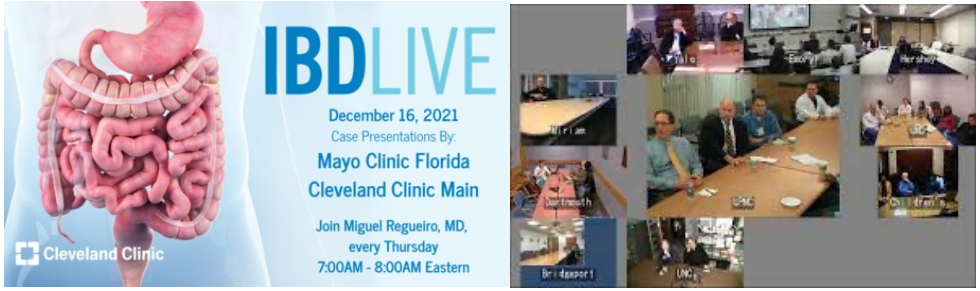
- **Results (39,686 patients)**
  - Risk of adverse outcomes (**Table**)
    - Increased risk with prednisone (aOR 1.31, 95%CI 1.08-1.60)
    - NO increased risk with biologics/small molecule inhibitors, immunomodulators, or combination therapy
    - NO increased risk from having inflammatory bowel disease

- **Conclusion:**
  - Outpatient prednisone use increases risk of severe COVID-19 whereas use of biologics/small molecule inhibitors, immunomodulators, or combination therapy does not

Medication/ Immune Condition	Adverse Outcome Odds Ratio (95% CI) N=3,977
Prednisone	**1.31 (1.08-1.60)**
Immunomodulators	0.88 (0.57-1.34)
Small molecule/Biologic	1.26 (0.79-2.00)
Inflammatory Bowel Disease	1.22 (0.82-1.81)

AICID: Autoimmune and Chronic Inflammatory Diseases

Velayos F, et al. Presented at DDW. May 2021. Abstract 252.



Thursday, Feb 3, 2022 – 7 to 8 AM (ET)

The First Cut is the Deepest: Using the LIR!C Study to Manage Crohn's Disease (Brown University)
58 year old woman with stricturing small bowel Crohn's Disease. abnormal pancreatic enzymes, and a renal mass (Yale)

CONNECT VIA WEBCAST or AUDIO ONLY:

Participate via WEBCAST

Enhanced Audio Dial in # 412-317-1076, Access Code: 4900330
Having technical issues? Chorus Call Operations: 412-858-1390
VIDEOCONFERENCE DETAILS: Conference Call IP #: 216.251.169.3

CREDIT CLAIM PROCESS & MOC:

· On the day of the broadcast, simply **scan the QR Code below** to claim credit for sessions that you attend. You will automatically receive *AMA PRA Category 1 Credits*™.

· IBD LIVE sessions in 2022 are eligible for **American Board of Internal Medicine** (ABIM), **American Board of Pediatrics** (ABP) and **American Board of Surgery** (ABS) MOC.

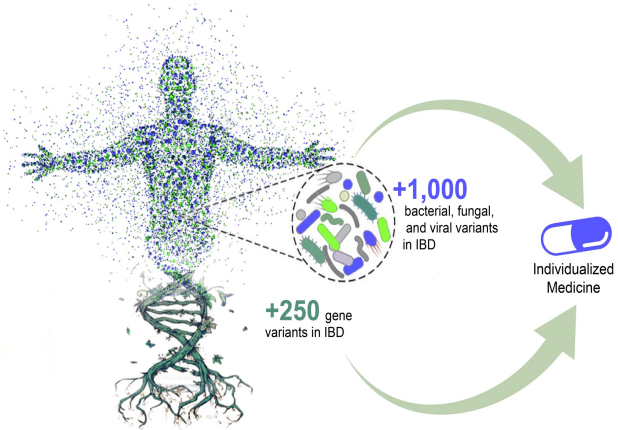
· All physician participants who wish to **upgrade their current and future credit to MOC** will simply complete a **ONE-TIME activity evaluation,** which is **available** by logging into your MyCME account .

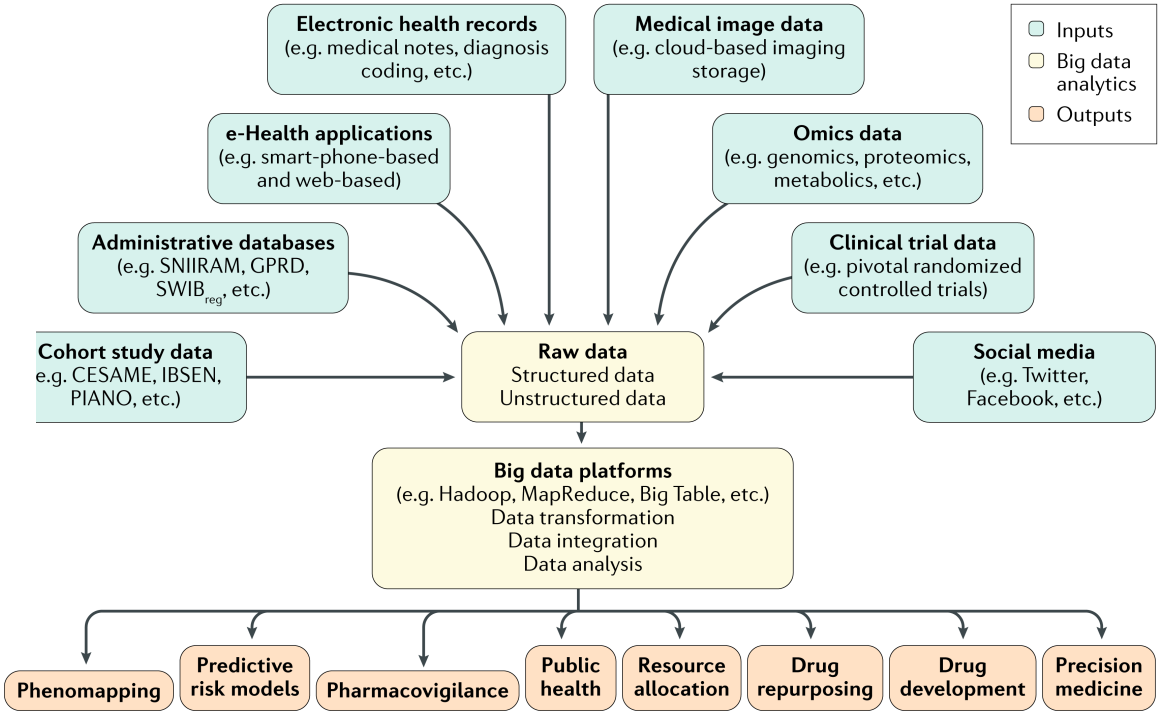
For more about the credit claiming process and MOC, please see CCF Credit Claiming Guide.

Learning objectives:

- Be able to identify current biological and small molecule agents available to treat IBD patients
- Understand mechanism of action, sequencing of therapies, and risk associated with therapies
- Be familiar with patient education resources and importance of vaccinations
- Understand the treat to target approach in utilizing therapies: patient reported outcomes, mucosal healing, fecal calprotectin and imaging

How will we treat IBD in the future?





Olivera, P., Danese, S., Jay, N. *et al.* Big data in IBD: a look into the future. *Nat Rev Gastroenterol Hepatol* **16,** 312–321 (2019). https://doi.org/10.1038/s41575-019-0102-5