Striking the Balance:
Treatment Selection Based on Disease Severity in Ulcerative Colitis

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IBD_Afzali

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UNIVERSITY OF Cincinnati

Learning Objectives

- Assess patient and disease-related factors which impact optimal treatment considerations
- Initiate early *appropriate* therapy tailored to disease severity
- Describe therapeutic options in UC to enhance patient outcomes and minimize adverse effects

Case Presentation

26-year-old female presents with intermittent bloody diarrhea and mild fecal urgency for the past 3 months

Labs:

Fecal calprotectin 350 ug/g

CBC, iron panel normal

Disease Activity vs Disease Severity

Activity

Reflects cross-sectional assessment of biologic inflammatory impact on symptoms, signs, endoscopy, histology, and biomarkers

POINT IN TIME

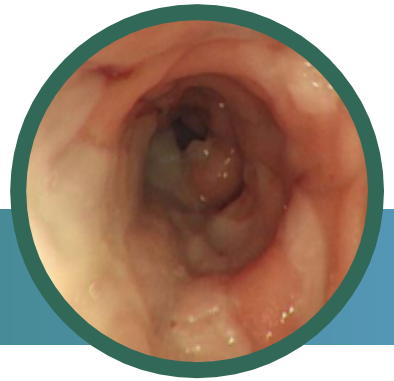
Severity

Includes longitudinal and historical factors that provide a more complete picture of the prognosis and overall “burden” of disease

FULL COURSE

Kjeldsen et al. Scandinavian J Gastroenterol 1993;28:1-9

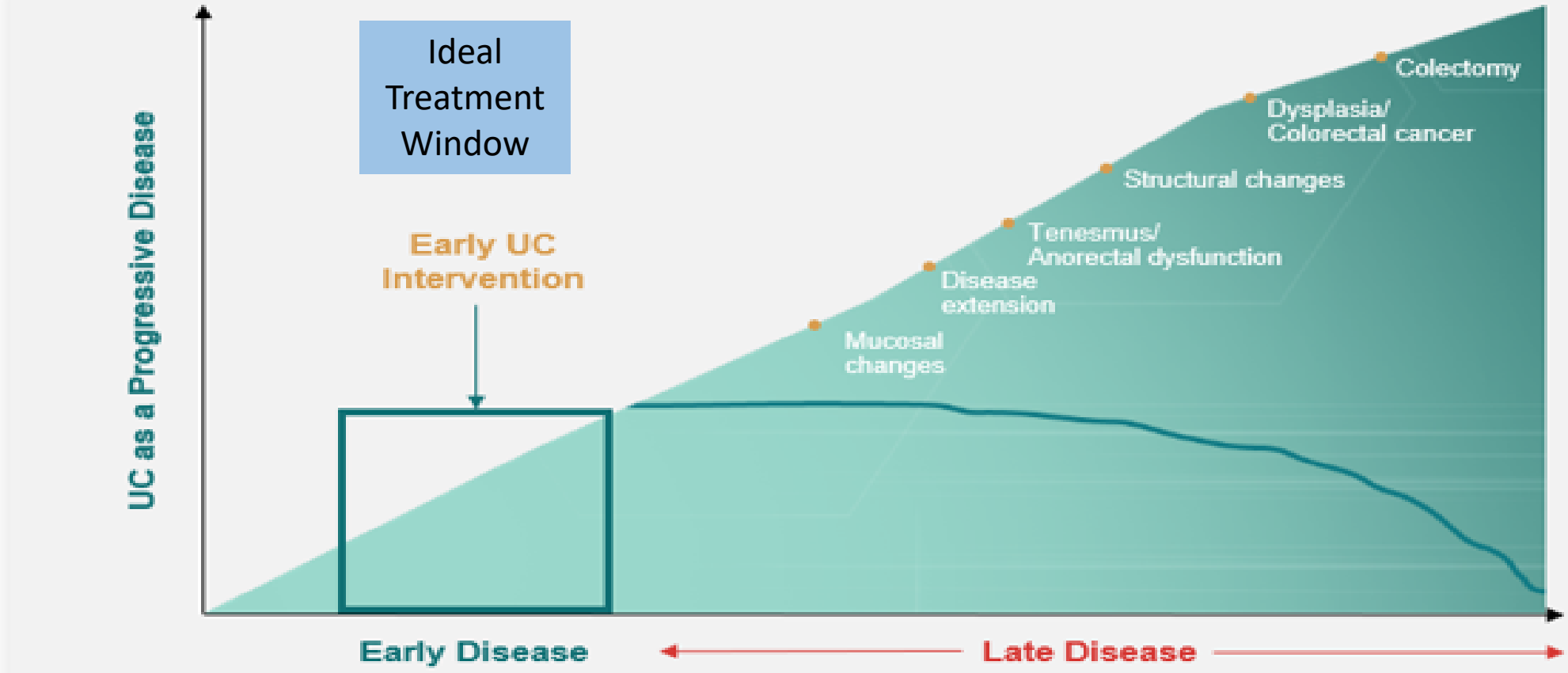
Risk Stratification UC – Early Appropriate Therapy



Low risk for rapid progression		High risk for rapid progression
>40 yr	Age at diagnosis	<40 yr
Proctitis	Anatomic extent	Extensive
Mayo 1	Endoscopy activity	Mayo 3 UCEIS ≥7
Superficial	Ulcers	Deep
Normal	Albumin	Low
Normal	CRP	Elevated
No	Hospitalization	Yes

Rubin et al . Am J Gastroenterol. 2019;114:384.

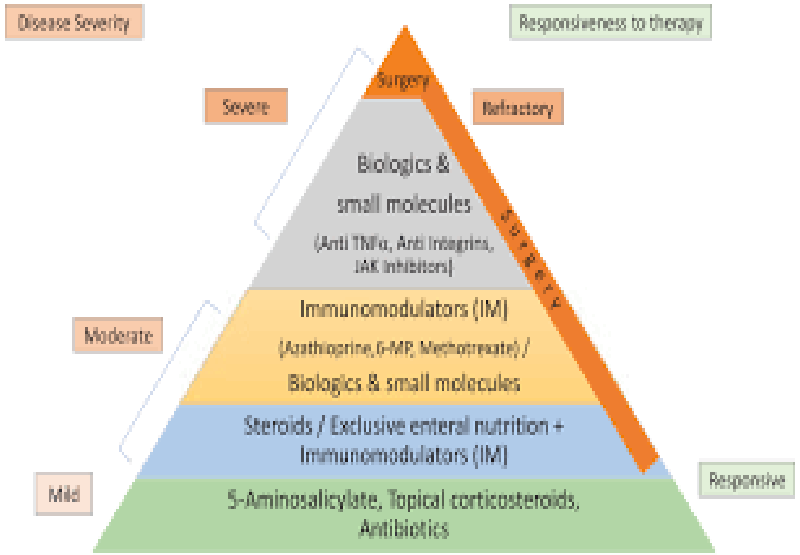
Why Is Early Treatment Important in UC?



There may be a window of opportunity to minimize risk of permanent damage or other complications

1. Solitano V. J Clin Med. 2020;9(8):2646. 2. Colombel JF, et al. Gastroenterology. 2017;152(2)351-361. 3. Vegh Z, et al. Curr Drug Targets. 2018;19(7):791-797. 4. Turner D, et al. Gastroenterology. 2021;160(20):1570-1583.

Assess Disease Severity at Early Stage



- Top-down:
  - Start advanced therapy to avoid **disease** complications
- Step-up:
  - Avoid advanced therapy to minimize risks of adverse events related to **therapy**

Start **Early Appropriate Therapy** for patients with **Aggressive Disease Phenotype**

Burden of UC: Disabling Disease Course with High Rates of Corticosteroid Excess

UC: Systematic review of long-term outcomes in 17 longitudinal, population-based global cohorts

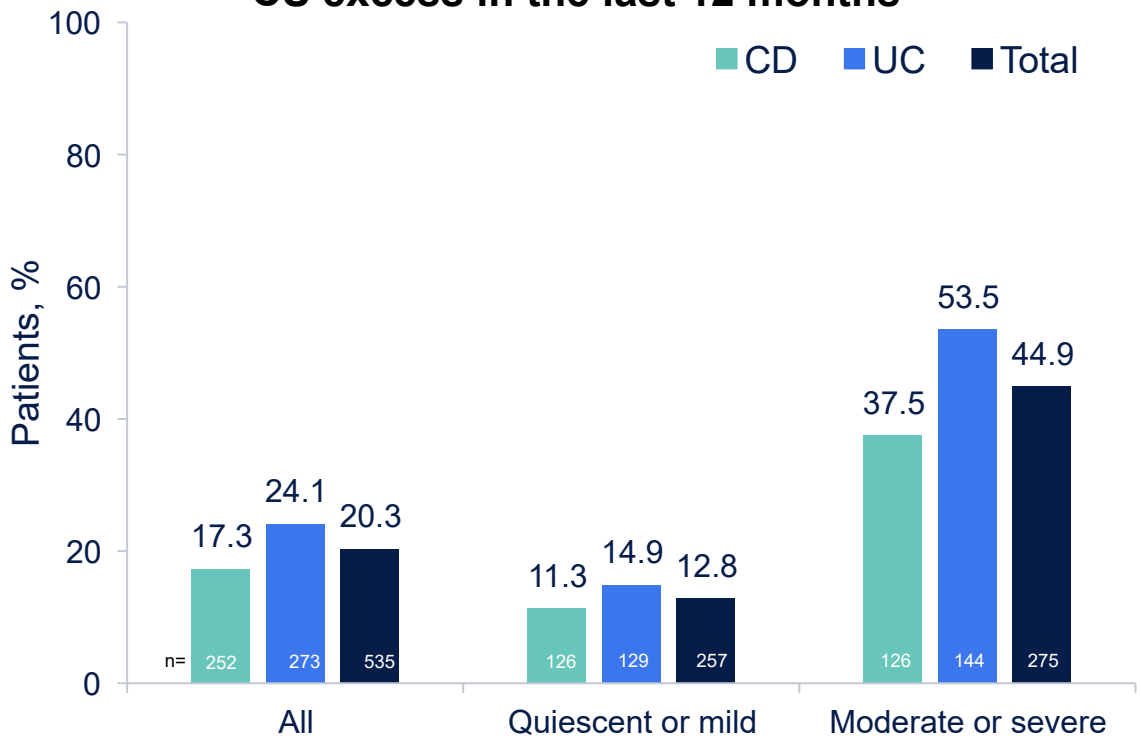
At 5-year follow-up:

29–54% cumulative risk of hospitalization

13% cumulative risk of disease progression

10–15% cumulative risk of colectomy

Patients reported to have CS excess in the last 12 months[3]



DICE Determinants, Incidence & Consequences of Corticosteroid Excess

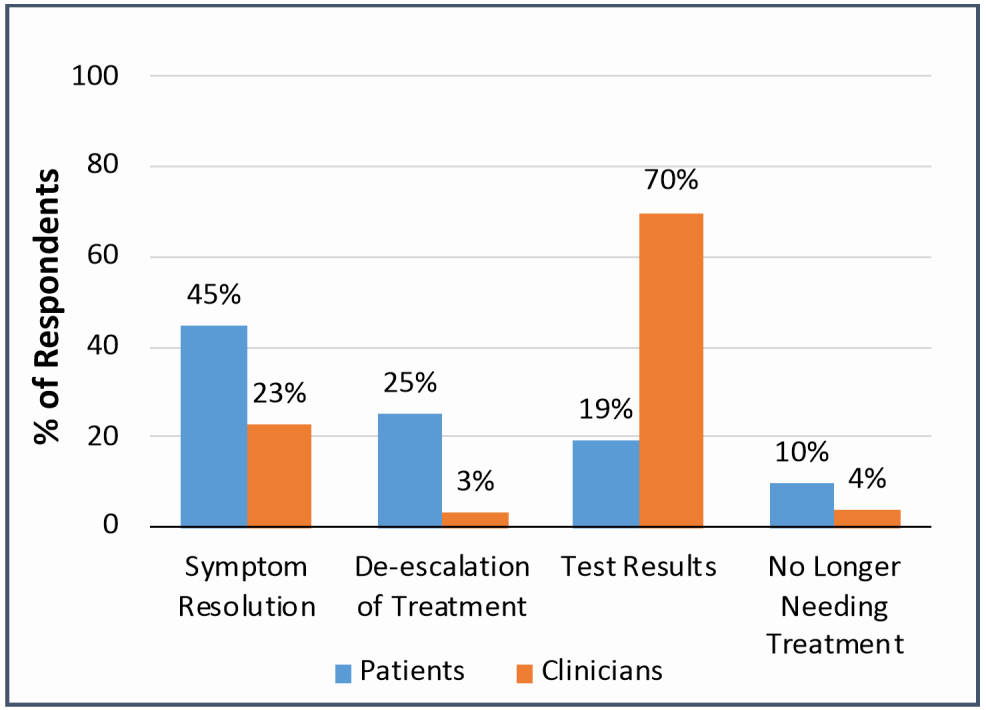
[‡]N=15,316 patients with UC; 60 studies. [§]5- and 10-year cumulative risk.
Figure (right) adapted from Wye J, et al. Presented at the United European Gastroenterology Week, 8–11 October 2022, Vienna, Austria and virtual: MP110.

1. Burisch J, et al. *Gut.* 2019;68:423–33; 2. Fumery M, et al. *Clin Gastroenterol Hepatol.* 2018;16:343–56;
3. Wye J, et al. Presented at the United European Gastroenterology Week, 8–11 October 2022, Vienna, Austria and virtual: MP110.

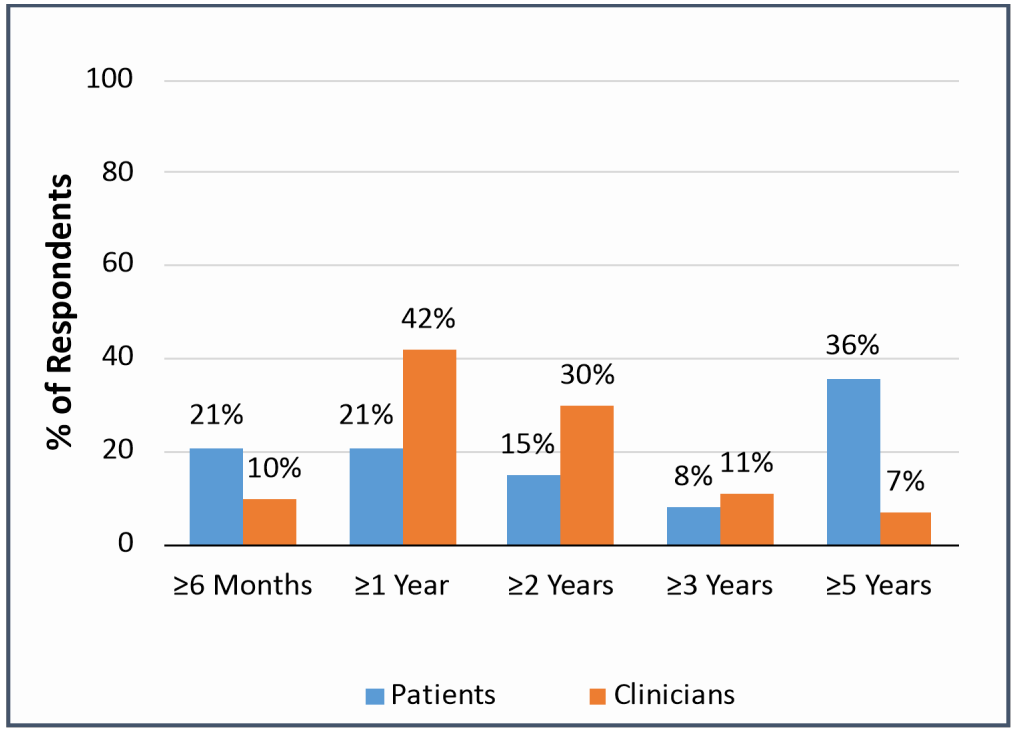
Differences in Disease Management Goals Exists between Patients and Clinicians

In the IBD-GAPPS 2019 survey that included UC patients* (n=1030) and clinicians (N=654), clinicians and patients differed in:

DEFINITION OF REMISSION

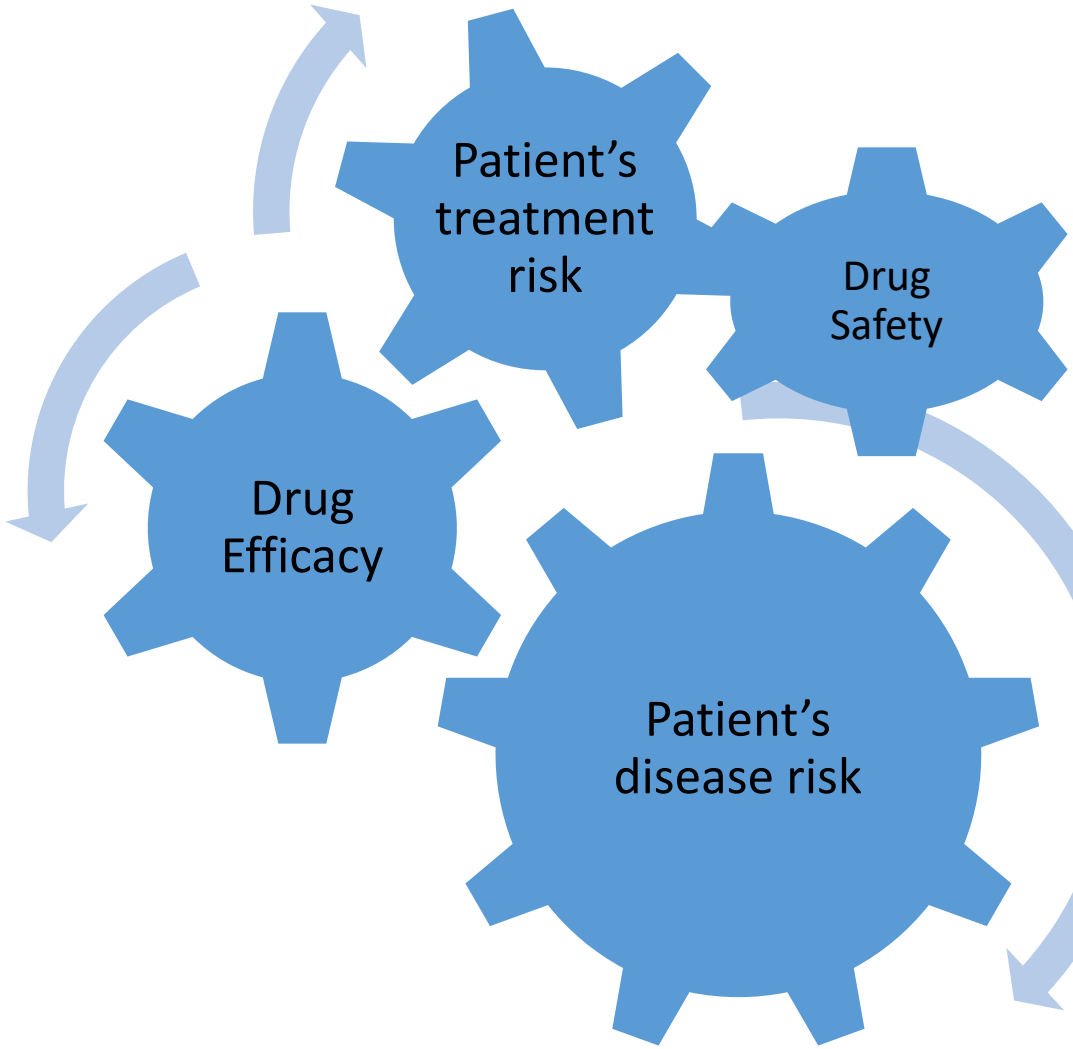


TREATMENT DURATION EXPECTATIONS



Afzali A, Rubin DT, et al. Inflamm Bowel Dis 2021;27:1942-53

IBD Management - Patient and Treatment Goals



Desired Outcomes
✓ Sustained clinical and endoscopic remission
✓ No disease complications including surgery, CRC
✓ No drug treatment complications
✓ No patient disability and improved QOL

STRIDE-II Defines Thresholds for Achieving Targets in UC

Throughout: Consider changing treatment if target has not been achieved

Assess at 3 months

Short-term target

Clinical response:
- Decrease of ≥50% in PRO2
  - **UC:** RB and SF

Intermediate target

Patient outcomes improved when combining targets

Clinical remission:
- UC: PRO2 RB score = 0 and SF = 0, or partial Mayo <3 and no score >1
- Insufficient as long-term target

Normalization of FC and CRP:
- CRP <ULN
- FC 100–250 µg/g

Assess at 6-12 months

Long-term target

Endoscopic healing:
- **UC:** MES = ≤1; or UCEIS ≤1[§]

Normalized QoL and absence of disability

Disease duration

Proactive Monitoring of Disease

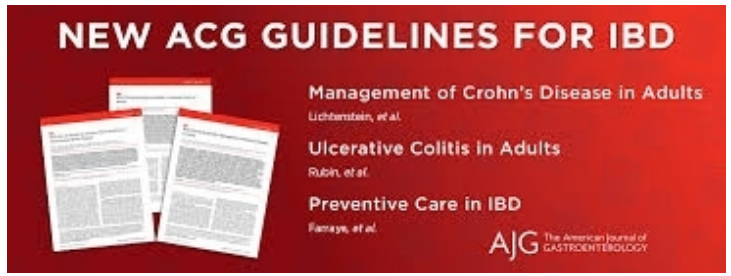
Turner D, et al. *Gastroenterology*. 2021;160:1570–83.

AJG The American Journal of GASTROENTEROLOGY

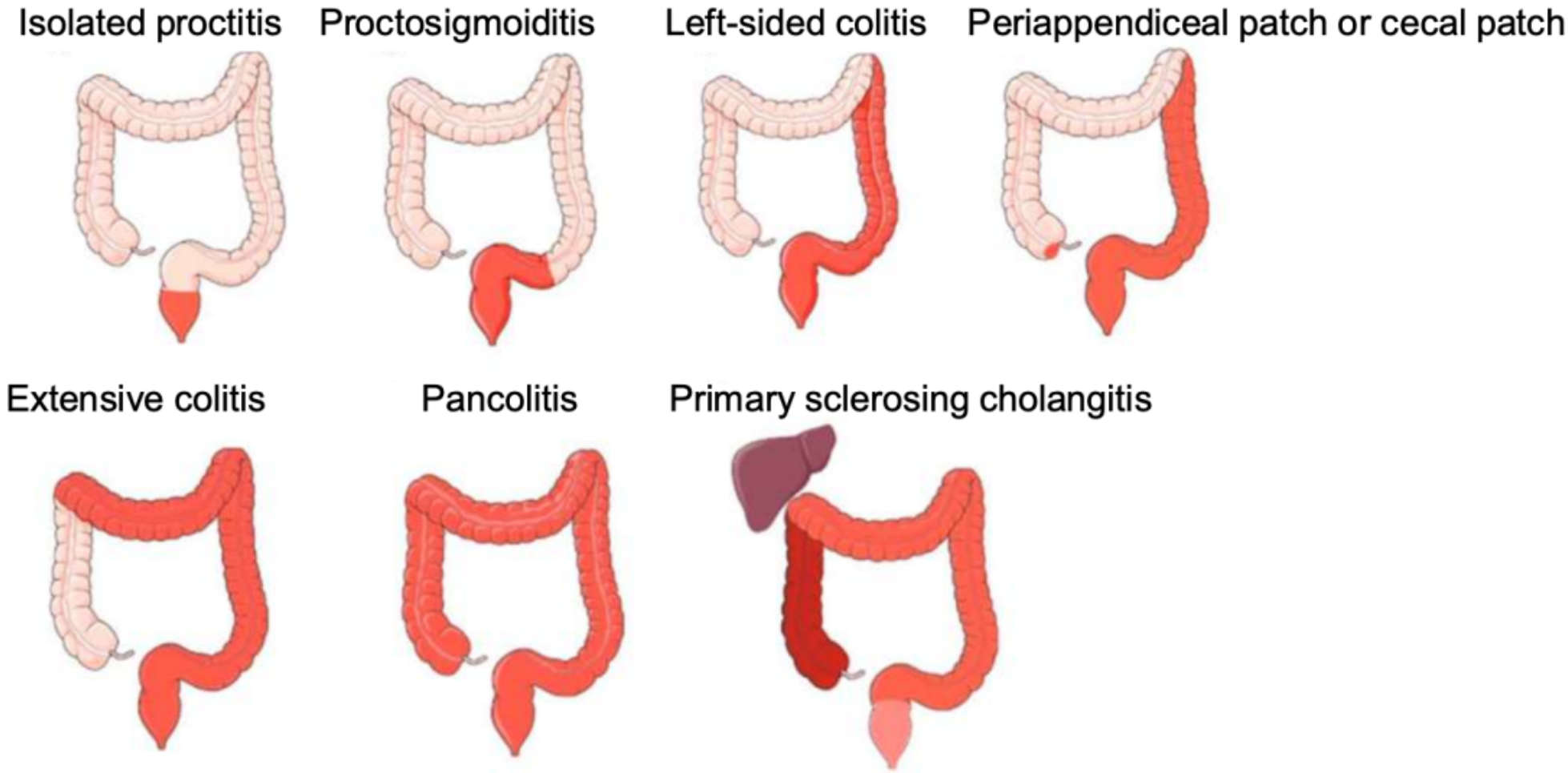
CME

ACG Clinical Guideline Update: Ulcerative Colitis in Adults

David T. Rubin, MD, FACG[1], Ashwin N. Ananthakrishnan, MBBS, MPH, FACG[2], Corey A. Siegel, MD, MS[3], Edward L. Barnes, MD, MPH, FACG[4] and Millie D. Long, MD, MPH, FACG[4]



UC Clinical Phenotypes



Rubin DT, et al. Am J Gastroenterol 2025;120(6):1187-1224

Treatment Options for Ulcerative Colitis

Class of Therapy Treatment	Treatment	Comment	
5-ASA	Mesalamine Sulfasalazine	Oral and rectal	Conventional Therapies (Traditional)
Corticosteroids	Budesonide Prednisone/Methylpred	Oral and rectal	
Thiopurines	6-mercaptopurine Azathioprine	Pharmacogenomics TPMT, NUDT15	Conventional Synthetic Therapies (Immunomodulators)
Calcineurin inhibitors	Cyclosporine Tacrolimus	IV and oral	
Anti-integrin	Vedolizumab	IV and SC maintenance	Biological Therapies
Anti-IL-23 (p40: IL-12/23 p19: IL-23)	Guselkumab (p19/CD64) Mirikizumab (p19) Risankizumab (p19) Ustekinumab (p40)	IV and SC maintenance Biosimilars to ustekinumab	
Anti-TNF	Adalimumab Golimumab Infliximab	Infliximab IV and SC maintenance Biosimilars to IFX and ADA	
Janus kinase inhibitors	Filgotinib (JAK1) Tofacitinib (JAK1,2,3) Upadacitinib (JAK1)	Oral Filgotinib EU only	Targeted Synthetic Small Molecules
S1P receptor modulators	Etrasimod ($S1P_{1,4,5}$) Ozanimod ($S1P_{1,5}$)	Oral	

Slide taken from Rubin DT, ACG VGR 2025

Rubin DT, et al. Am J Gastroenterol 2025;120(6):1187-1224

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 (MES)	0–1	1	2–3	3
Endoscopy (UCEIS)	0–1	2–4	5–8	7–8
Intestinal ultrasound	Colonic BWT≤3 mm Rectal BWT ≤4 mm mLimberg = 0		Colonic BWT >3 mm Rectal BWT >4 mm mLimberg >0	

Rubin DT, et al. Am J Gastroenterol 2025;120(6):1187-1224

Back to Our Patient…

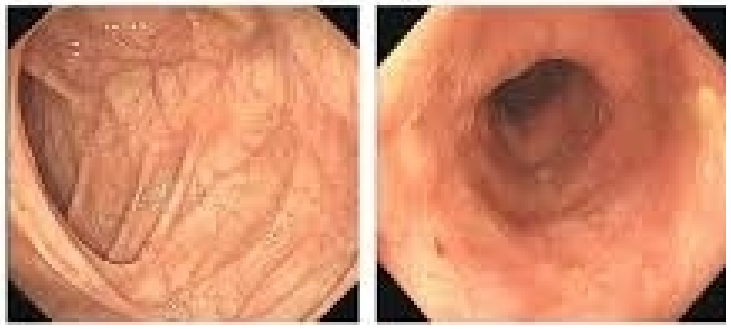
26-year-old female presents with intermittent bloody diarrhea, mild fecal urgency for the past 3 months

Labs:

Fecal calprotectin 350 ug/g

CBC, iron panel normal

Colonoscopy:



Proctosigmoiditis Mayo 1; remainder of colon and terminal ileum normal

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Rubin DT, et al. Am J Gastroenterol 2025;120(6):1187-1224

General Considerations for 5-ASA Therapies

- Good choice for induction of mild-moderate UC (15-40%)
- Maintenance of mild-moderate UC (58-78%)
- Understand delivery-response relationship
  - Drug to location of disease (moisture delivery vs pH vs topical)
  - Rectal + Oral 5-ASA therapy better than either alone
- Very safe
  - Monitor renal function (rare, interstitial nephritis); paradoxical reaction
- Use of 5-ASA in UC patients that have escalated to advanced therapy does not change outcomes

Van Staa TP, et al. Gastroenterology 2004; Ham M et al Expert Rev Clin Pharmacol 2012

Mild-Moderate UC

Ulcerative Proctitis

- Induction
  - Topical 5-ASA
  - (No response: tacrolimus or beclomethasone suppository)
- Maintenance
  - Topical 5-ASA (at least 1g/d)

Left-Sided Colitis

- Induction
  - Oral 5-ASA (2-2.4g/d) AND topical 5-ASA
- Maintenance
  - Oral 5-ASA once daily (1.5g/d)

Extensive Colitis

- Induction
  - Oral 5-ASA (2-2.4g/d)
- Maintenance
  - Oral 5-ASA once daily (1.5g/d)

- ✓ If no response to 5-ASA, add Budesonide MMX to induce remission, but not for maintenance
- ✓ If no response to oral 5-ASA, consider alternative therapeutic class vs change to alternate 5-ASA

Limitations of “Conventional Therapies” (5-ASAs)

In a European observational study, **~50%** of patients with moderate-to-severe UC **on conventional therapy reported ongoing symptoms** of rectal bleeding[1]

~37% of patients on **5-ASA** maintenance therapy **relapsed** within 6 to 12 months[2]

Even in patients who achieve remission, **bothersome symptoms** such as **fatigue** often **persist**, limiting patient quality of life[3]

1. Peyrin-Biroulet L, et al. Dig Liver Dis 2016; 2. Murray A, et al Cochrane Database Syst Rev 2020;
3. Reves J, et al. Curr Res Pharmacol Drug Discov 2021

Back to Our Patient…(another scenario)

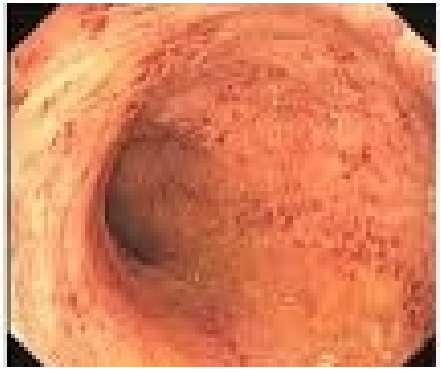
26-year-old female presents with bloody diarrhea (6-8BMs/d), fecal urgency, tenesmus and abdomen pain for the past 1 month

Labs:

Fecal calprotectin 750 ug/g

CBC, iron panel remarkable for iron deficiency anemia

Colonoscopy:



Extensive pancolitis, Mayo 2; terminal ileum normal

ACG UC Activity Index

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Rubin DT, et al. Am J Gastroenterol 2025;120(6):1187-1224

Moderate-Severe UC

Induction

Budesonide MMX

Oral corticosteroids

S1P modulator: Etrasimod, Ozanimod

Vedolizumab

IL12/23: Ustekinumab

IL-23: Guselkumab, Mirikizumab, Risankizumab

Anti-TNF: (+IMM) IFX[+], ADA, GOL

*JAK inhibitor: Upadacitinib, Tofacitinib

Maintenance

Continue advanced therapy

Thiopurine monotherapy (over steroids)

- No continuation of budesonide/steroids
- No concomitant 5-ASA needed
- Monotherapy thiopurine (or methotrexate) not recommended

[+] Infliximab is preferred anti-TNF * Prior intolerance/non-response to anti-TNF

Considerations for S1P Agonists

- Etrasimod (no titration, 2mg PO daily)
- Ozanimod (titration then 1mg PO daily)
- Consider after 5-ASA
- Better in advanced therapy naïve
- Safety:
  - Contraindicated in patients with second degree heart block
  - Eye and skin examination

Sandborn WJ, et al. Lancet 2023; Sandborn WJ et al. N Eng J Med 2021

Positioning Considerations for Moderate-Severe UC

- ✓ First therapy achieves higher rates of response, remission
- ✓ No step therapy approach
- ✓ Make distinction between primary nonresponse and secondary LOR
  - ✓ TDM for patient on anti-TNF

- ✓ Vedolizumab preferred over adalimumab
- ✓ Infliximab is preferred anti-TNF
- ✓ Consider non-anti-TNF for high infectious risk patients
- ✓ Consider EIMs

Problem with Anti-TNFs

1/3

will not respond to induction therapy with TNF inhibitors (primary non-response)

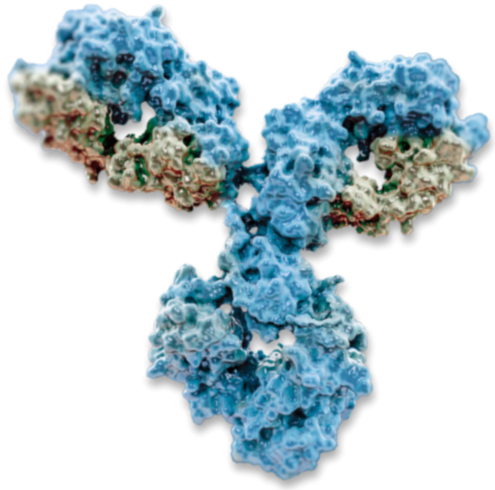
≈50%

of patients who initially respond lose response within a few years

Why?

- Neutralizing anti-drug **antibodies**
- Inadequate serum **drug** levels
- Inadequate **tissue** levels
- Other **immune pathways** are driving inflammation?

Newer Biologics (non-TNFs) Are Less Immunogenic

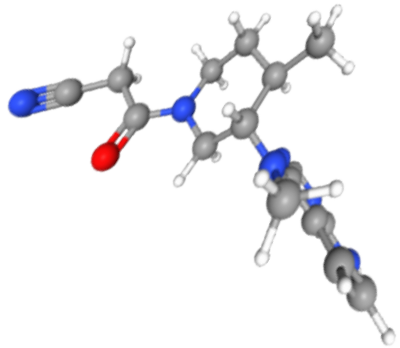


2.3%

Ustekinumab

0.77%

Vedolizumab



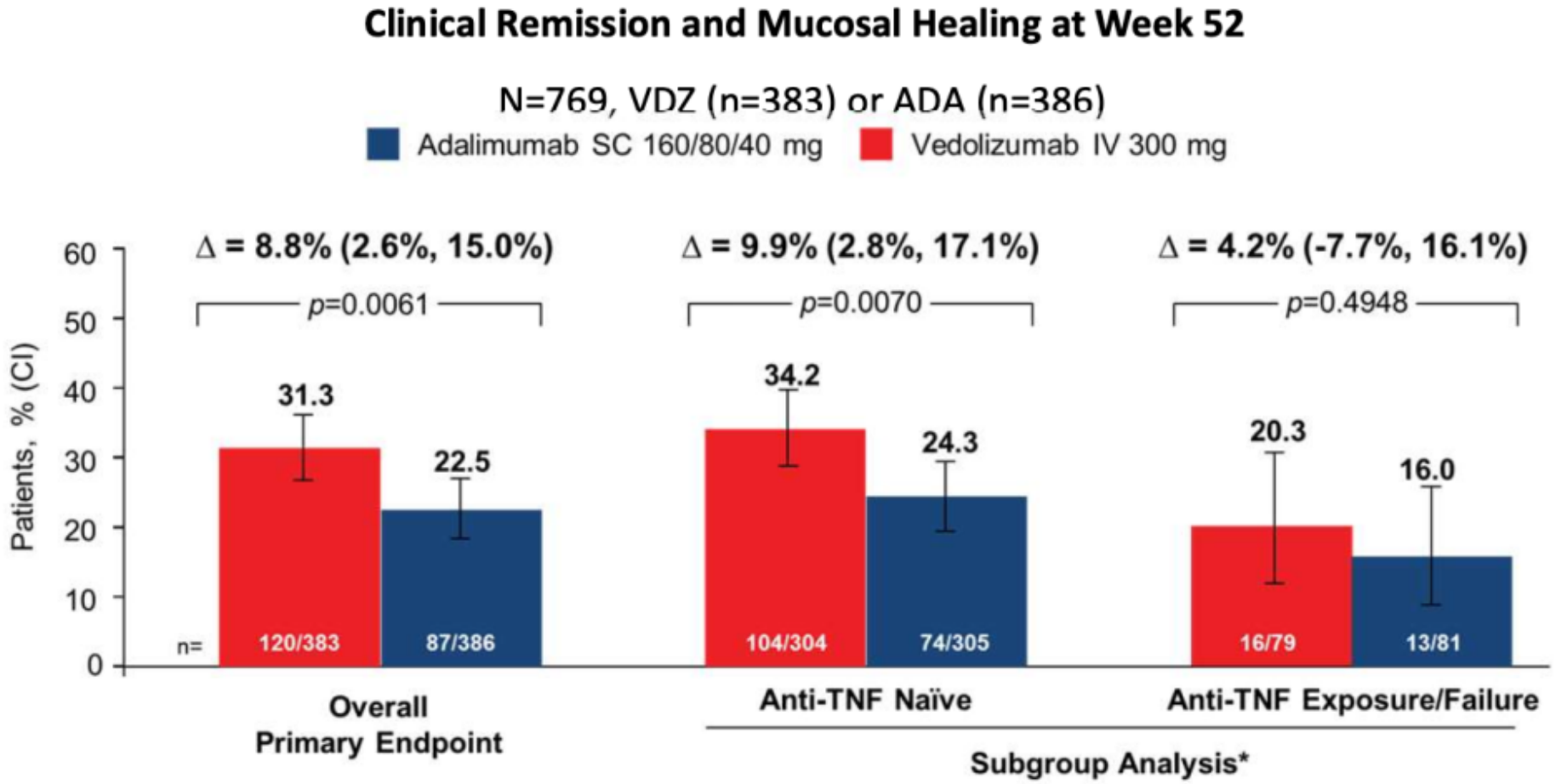
~3-4%

p19 Inhibitors

Small molecules are not immunogenic

Feagan BG, et al. *N Engl J Med*. 2016;375(20):1946-1960. Yzet C, et al. *Clinical Gastroenterol Hepatol*. 2021;19(4):668-679.e8. Adedokun OJ, et al. *Gastroenterology*. 2018;154(6):1660-1671.

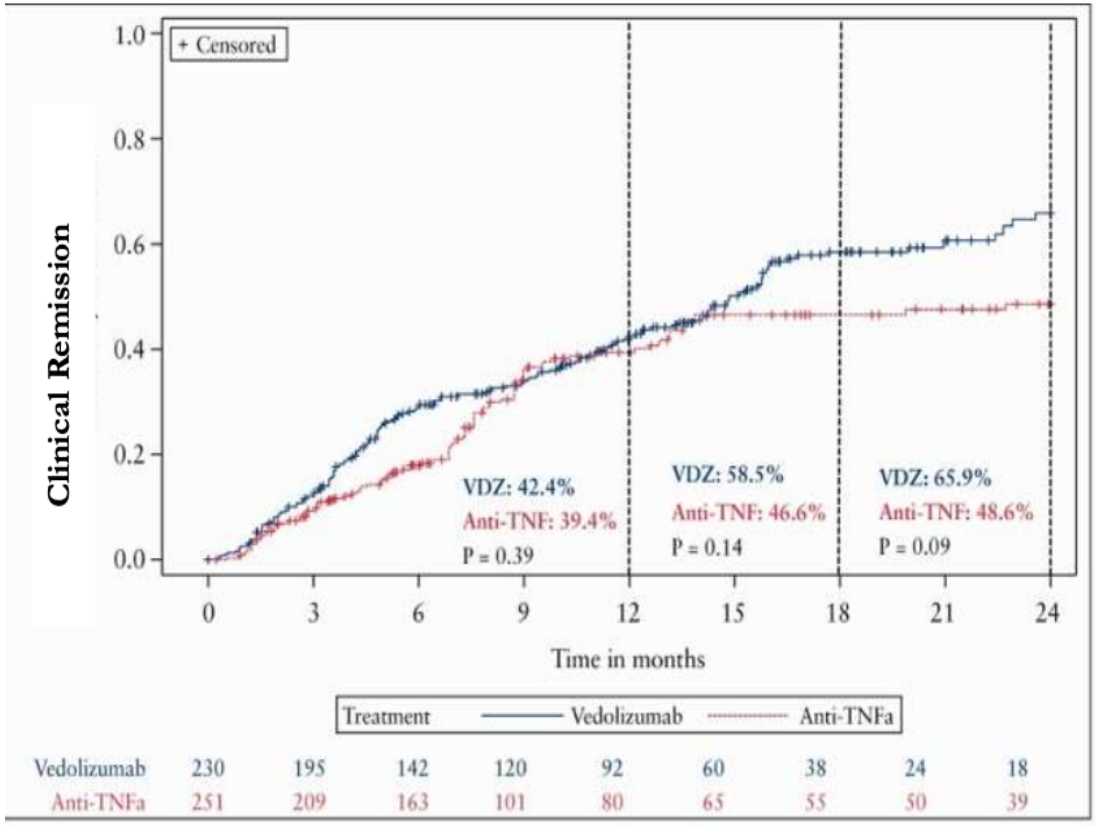
Ulcerative Colitis Head-to-Head Vedolizumab vs Adalimumab (VARSITY)

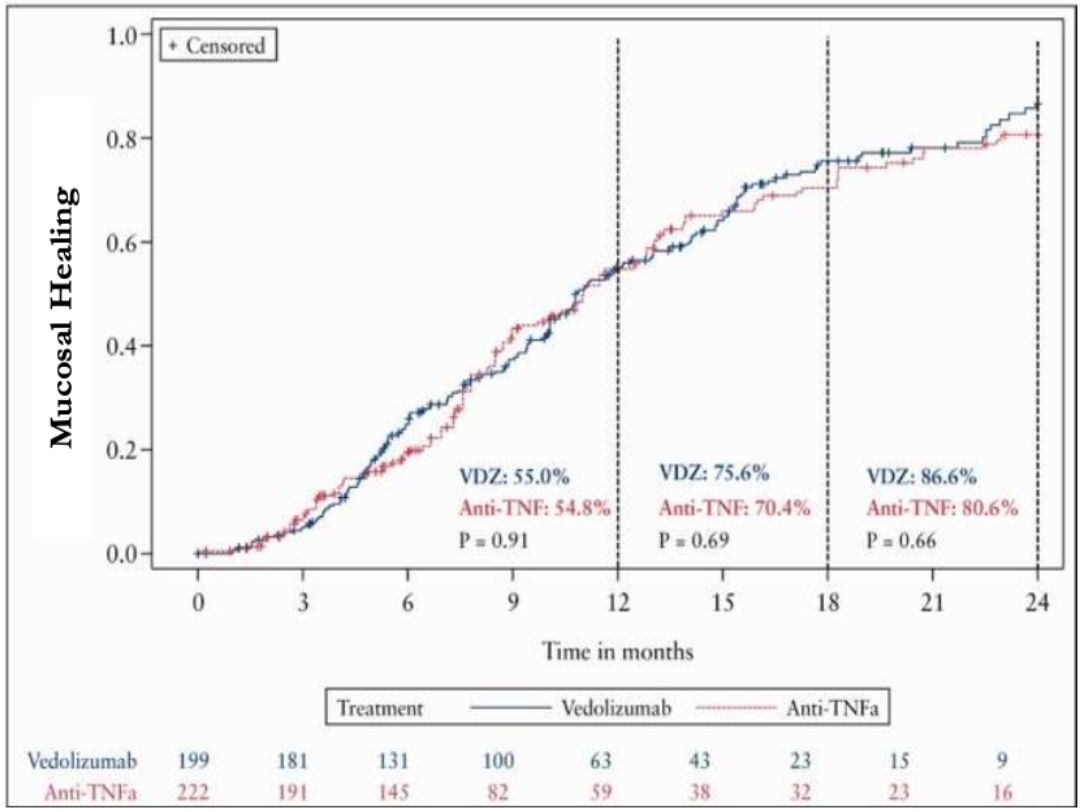


Sands BE, et al. N Engl J Med 2019;381:1215-26

Vedolizumab vs Infliximab (EVOLVE)

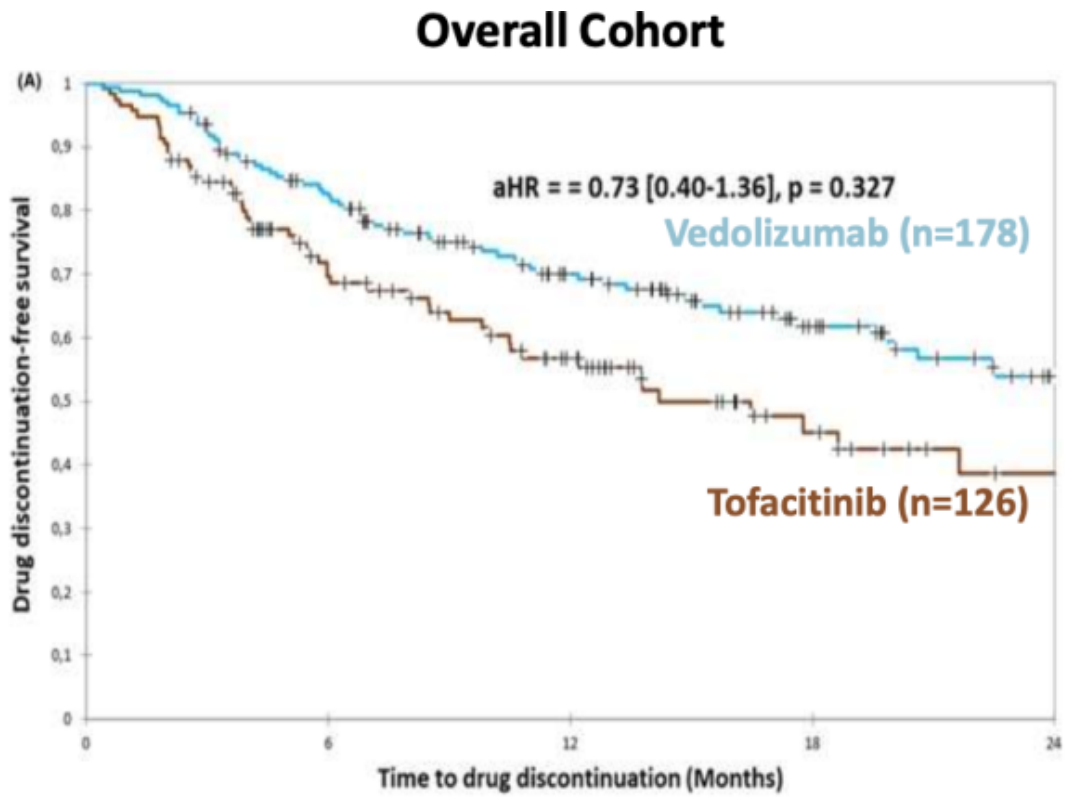
Real World Observational Study

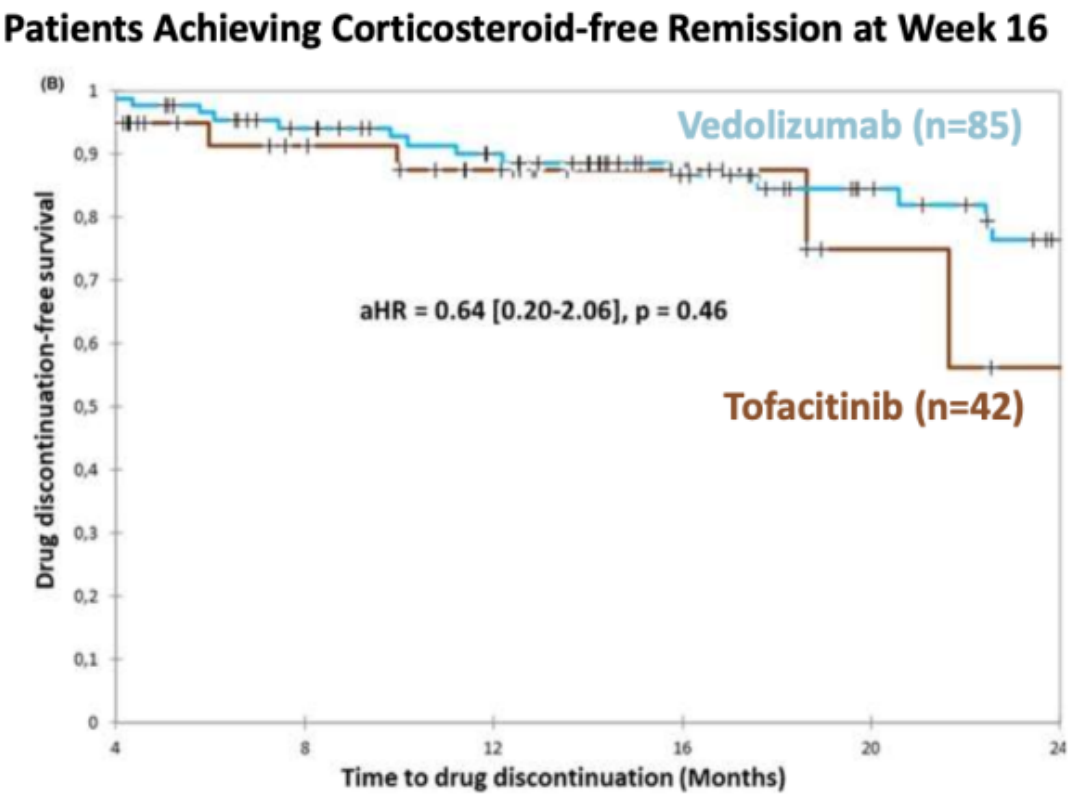




Bressler B, et al. J Crohn's Colitis. 2021;15(10):1694–1706

Second Line Advanced Therapy
Tofacitinib v Vedolizumab *after* Anti-TNF
Real World Observational Study





Buisson A, et al. Aliment Pharmacol Ther 2023;57:676-88

Considerations for IL-12/23 & IL-23 Inhibitors

- Excellent for concomitant skin (psoriasis, possible pyoderma gangrenosum)
- Safety:
  - Very safe (no risk for TB)
- Unclear if p19s superior to ustekinumab in UC
  - (SEQUENCE – CD)
- Likely can cycle (based on psoriasis data and CD experience)

Sandborn WJ, et al. N Engl J Med 2017; Danese S et al. Lancet 2022

Considerations for JAK-inhibitors

- Induction and maintenance dosing:
  - Upadacitinib: 45mg PO QD (8 wks) → 30mg or 15mg QD
    [30mg QD preferred if previously on AT]
  - Tofacitinib: 10mg PO BID (8 wks) → 10mg or 5mg BID
    [10mg BID preferred if previously on AT]
- Labeled after anti-TNFs
- EIM: arthropathy
- Safety:
  - Prior VTE or CAD
  - Older age (>65yrs)
  - Vaccinate against zoster
  - Monitor lipids

Sandborn WJ, et al. N Engl J Med 2017; Danese S, et al. Lancet 2022; Friedberg S, et al. Clin Gastroenterol Hepatol 2023

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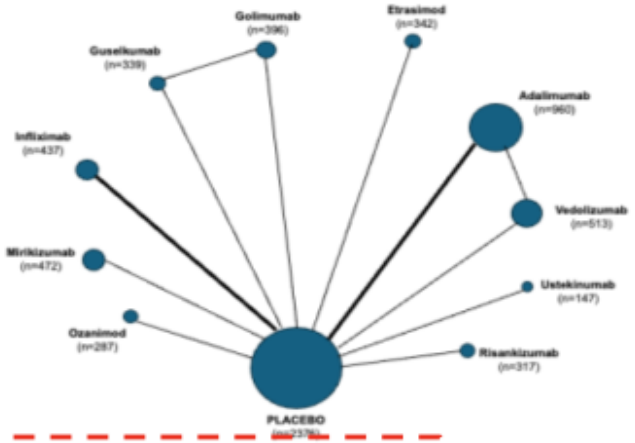
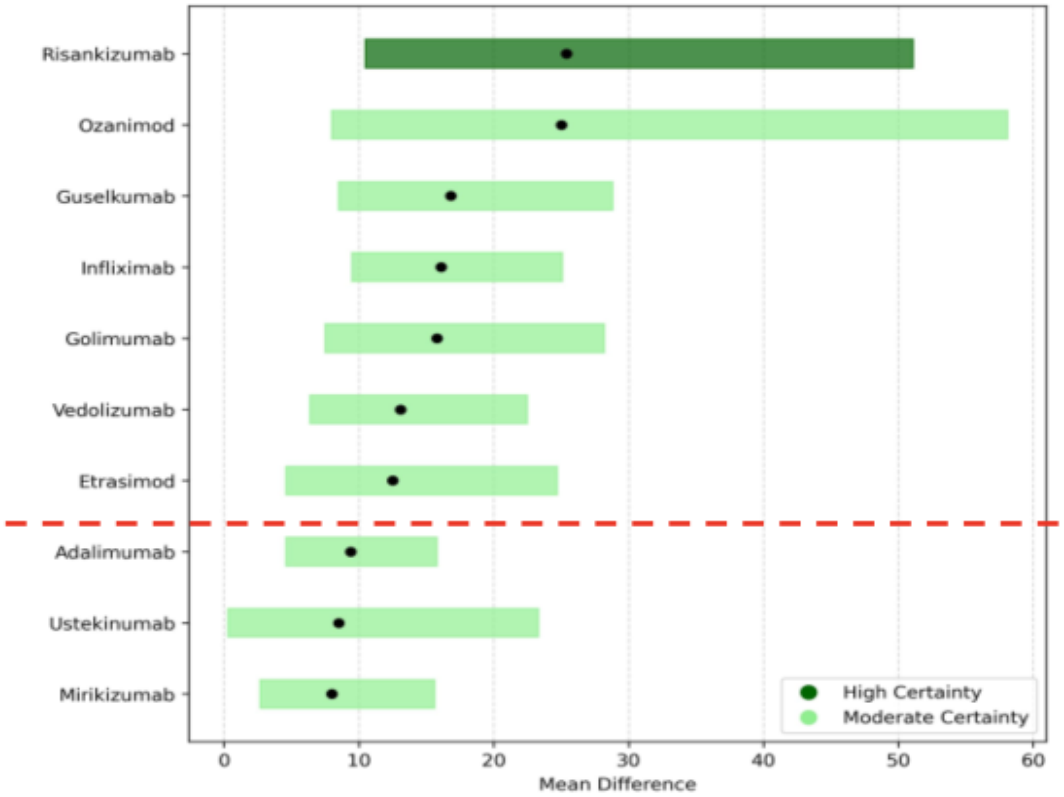
Rubin DT, et al. Am J Gastroenterol 2025;120(6):1187-1224

Comparative Efficacy of Advanced Therapies for Management of Moderate-to-Severe Ulcerative Colitis: 2024 AGA Evidence Synthesis



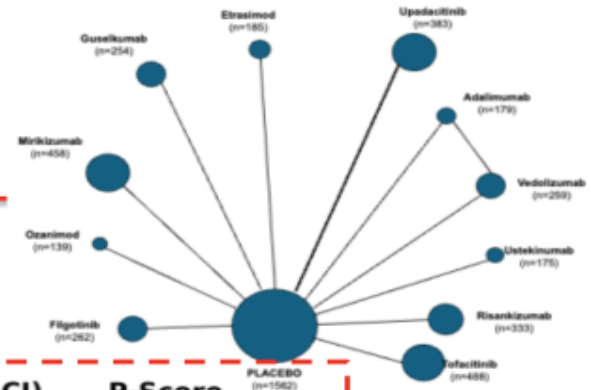
Biologic-naïve patients



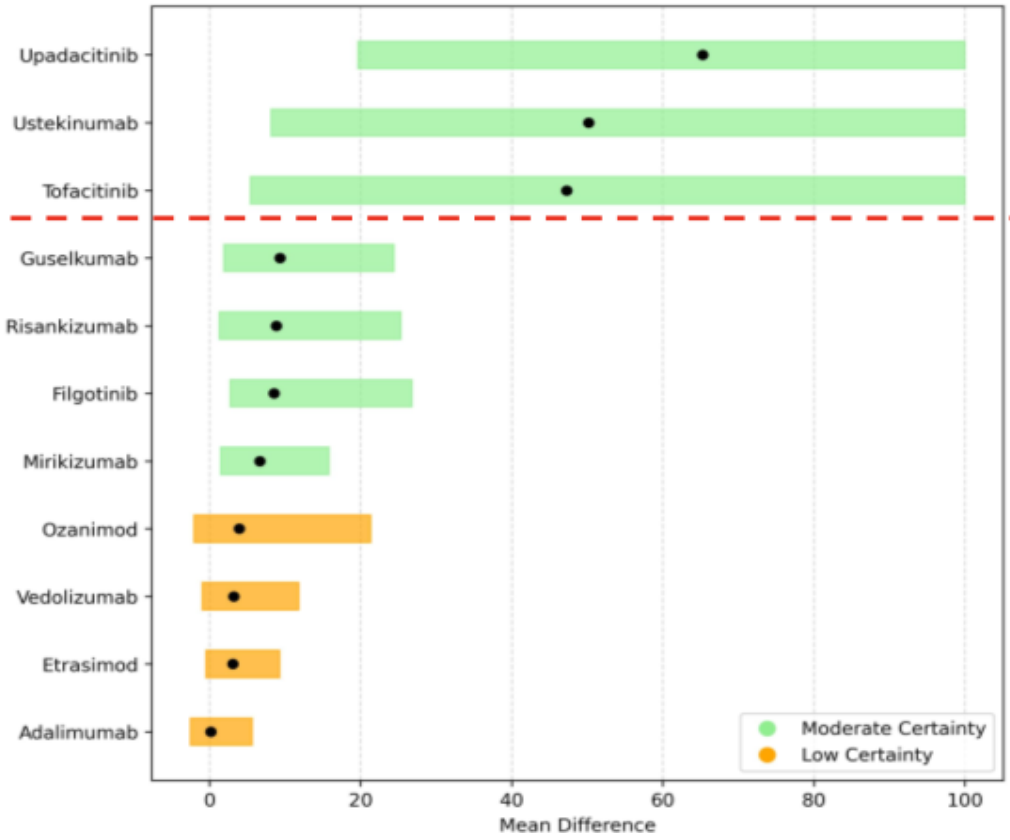
	Risk Difference (95% CI)	Relative Risk (95% CI)	P-Score
Risankizumab	25.4 [10.5 - 51.1]	3.54 [2.05 - 6.11]	0.83
Ozanimod	25.0 [8.0 - 58.1]	3.5 [1.8 - 6.81]	0.81
Guselkumab	16.8 [8.5 - 28.8]	2.68 [1.85 - 3.88]	0.66
Infliximab	16.1 [9.5 - 25.1]	2.61 [1.95 - 3.51]	0.64
Golimumab	15.8 [7.5 - 28.2]	2.58 [1.75 - 3.82]	0.62
Vedolizumab	13.1 [6.4 - 22.5]	2.31 [1.64 - 3.25]	0.52
Etrasimod	12.5 [4.6 - 24.7]	2.25 [1.46 - 3.47]	0.49
Adalimumab	9.4 [4.6 - 15.8]	1.94 [1.46 - 2.58]	0.32
Ustekinumab	8.5 [0.3 - 23.3]	1.85 [1.03 - 3.33]	0.33
Mirikizumab	8.0 [2.7 - 15.6]	1.8 [1.27 - 2.56]	0.27

Ananthakrishnan A, et al. Gastroenterology 2024; 167:1460-82

Comparative Efficacy of Advanced Therapies for Management of Moderate-to-Severe Ulcerative Colitis: 2024 AGA Evidence Synthesis



Biologic-exposed patients



	Risk Difference (95% CI)	Relative Risk (95% CI)	P-Score
Upadacitinib	65.25 [19.7 - 100.0]	14.05 [4.94 - 43.94]	0.93
Ustekinumab	50.2 [8.2 - 100.0]	11.04 [2.64 - 46.1]	0.88
Tofacitinib	47.25 [5.45 - 100.0]	10.45 [2.09 - 52.22]	0.87
Guselkumab	9.3 [1.95 - 24.4]	2.86 [1.39 - 5.88]	0.58
Risankizumab	8.85 [1.3 - 25.35]	2.77 [1.26 - 6.07]	0.56
Filgotinib	8.55 [2.8 - 26.8]	2.71 [1.56 - 6.36]	0.55
Mirikizumab	6.65 [1.5 - 15.8]	2.33 [1.3 - 4.16]	0.49
Ozanimod	3.9 [-2.0 - 21.3]	1.78 [0.6 - 5.26]	0.36
Vedolizumab	3.2 [-0.9 - 11.8]	1.64 [0.82 - 3.36]	0.33
Etrasimod	3.05 [-0.45 - 9.25]	1.61 [0.91 - 2.85]	0.3
Adalimumab	0.15 [-2.5 - 5.65]	1.03 [0.5 - 2.13]	0.1

Ananthakrishnan A, et al. Gastroenterology 2024; 167:1460-82

AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis

Siddharth Singh [1,2] · Edward V. Loftus, Jr [3] · Berkeley N. Limketkai [4] · ... · Frank I. Scott [9] · Ashwin N. Ananthakrishnan [10,11] on behalf of the AGA Clinical Guidelines Committee... Show more

ADVANCED THERAPY-NAÏVE PATIENTS (FIRST-LINE THERAPY)

SUGGEST using a HIGHER efficacy, or INTERMEDIATE efficacy medication, rather than a lower efficacy medication.

(Conditional recommendation, low certainty of evidence)

HIGHER EFFICACY MEDICATIONS: Infliximab, Vedolizumab, Ozanimod, Etrasimod, Upadacitinib*, Risankizumab, Guselkumab

INTERMEDIATE EFFICACY MEDICATIONS: Golimumab, Ustekinumab, Tofacitinib*, Filgotinib*, Mirikizumab

LOWER EFFICACY MEDICATIONS: Adalimumab

Singh S, et al. Gastroenterology 2024

AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis

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PRIOR EXPOSURE TO ONE OR MORE ADVANCED THERAPIES, PARTICULARLY TNF ANTAGONISTS

SUGGEST using a HIGHER efficacy, or INTERMEDIATE efficacy medication, rather than a lower efficacy medication.

(Conditional recommendation, low certainty of evidence)

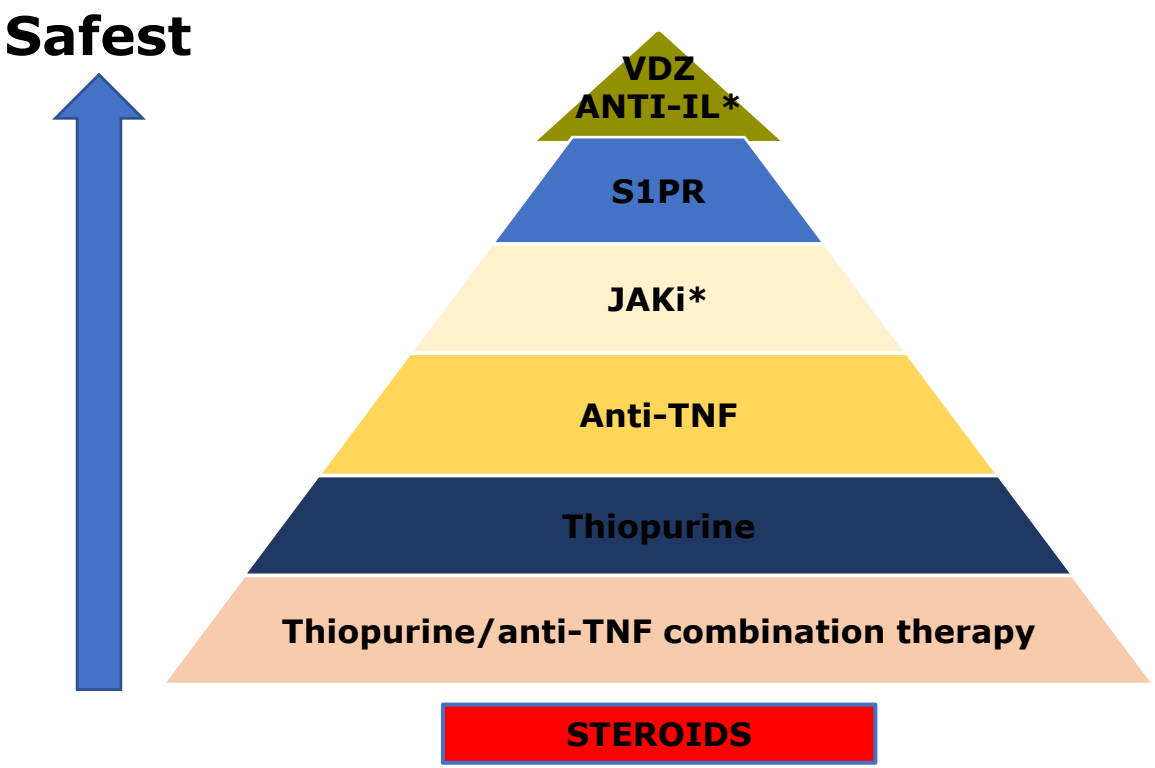
HIGHER EFFICACY MEDICATIONS: Tofacitinib, Upadacitinib, Ustekinumab

INTERMEDIATE EFFICACY MEDICATIONS: Filgotinib, Mirikizumab, Risankizumab, Guselkumab

LOWER EFFICACY MEDICATIONS: Adalimumab, Vedolizumab, Ozanimod, Etrasimod

Singh S, et al. Gastroenterology 2024

Safety Pyramid in IBD based on RCT, RWE



Patient-specific considerations influencing safety profile

- Age
- Disease classification
- Disease presentation
- Disease phenotype and inflammatory burden
- Comorbidities
- Concurrent medications (drug-interactions)
- Conception plans

Inadequate treatment of UC is an adverse event and should be balanced with risks of therapies on an individual basis

Bhat S, et al. Inflamm Bowel Dis 2023

Risks of Adverse Events, Serious Infections

Meta analysis of 20 head-to-head studies

Ustekinumab vs. TNFα antagonists
(5 cohorts; 23,232 patients)

- **CD**: **51% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Vedolizumab vs. TNFα antagonists
(17 cohorts; 51,596 patients)

- **CD**: **No difference** in risk of serious infections (OR, 1.03)
- **UC**: **32% lower risk** of serious infections with vedolizumab

Ustekinumab vs. vedolizumab
(5 cohorts; 1,420 patients)

- **CD**: **60% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

❖**Vedolizumab** may offer net benefit over TNFs in UC, but not in CD

❖**Ustekinumab** may offer net benefit over TNFs and vedolizumab in CD

Variable safety profile of AT based on treatment effectiveness and intrinsic immune suppression

Solitano V, et al. Clin Gastroenterol Hepatol 2023; 907-21

Treatment Options for Patients with Moderate-to-Severe Ulcerative Colitis

Disease severity *(Risk of disease-related complications)*

High structural damage
High inflammatory burden
Significant impact on QOL

Patient-centered approach

Lifestyle, values/preference, speed of onset, costs

Risk-Benefit Assessment *(Risk of treatment-related complications)*

Prior serious infections
Prior malignancy
Advanced age
Multiple comorbidities

First-line therapy

Vedolizumab monotherapy (moderate disease)	Infliximab (severe disease, extra-intestinal manifestation, combo with IMM)	IL-23 or IL 12-23 (for patients with significant comorbidities, or contraindication for anti-TNFs)	S1P Modulator - Etrasimod (mild-moderate disease, as oral alternative)

Second-line therapy

Prior failure of Vedolizumab	Prior failure of infliximab	Prior intolerance to infliximab
Infliximab > IL-23 or IL 12-23	Upadacitinib > IL-23 or IL 12-23	Vedolizumab

IBD_Afzali

First-line therapy

Vedolizumab monotherapy	Guselkumab, Risankizumab Mirikizumab, Ustekinumab

Second-line therapy

Infliximab monotherapy	Upadacitinib

Adapted based on Singh S, et al. Nat Rev Gastroenterol Hepatol 2023; Fudman D, et al. Clin Gastroenterol Hepatol 2025

Questions

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